# Apoptotic cell death in disease

# – Current understanding of the NCCD 2023

**Ilio Vitale[1,2,*], Federico Pietrocola[3], Emma Guilbaud[4], Stuart A. Aaronson[5], John M. Abrams[6], Dieter Adam[7], Massimiliano Agostini[8], Patrizia Agostinis[9,10], Emad S. Alnemri[11], Lucia Altucci[12,13], Ivano Amelio[14], David W. Andrews[15,16], Rami I. Aqeilan[17], Eli Arama[18], Eric H. Baehrecke[19], Siddharth Balachandran[20], Daniele Bano[21], Nickolai A. Barlev[22], Jiri Bartek[23,24], Nicolas G. Bazan[25], Christoph Becker[26], Francesca Bernassola[8], Mathieu J.M. Bertrand[27,28], Marco Emilio Bianchi[29], Mikhail V. Blagosklonny[30], J. Magarian Blander[31,32,33], Giovanni Blandino[34], Klas Blomgren[35,36], Christoph Borner[37], Carl D Bortner[38], Pierluigi Bove[8], Patricia Boya[39], Catherine Brenner[40], Petr Broz[41], Thomas Brunner[42], Rune Busk Damgaard[43], George A. Calin[44,45], Michelangelo Campanella[46,47,48], Eleonora Candi[8], Michele Carbone[49], Didac Carmona-Gutierrez[50], Francesco Cecconi[51,52,53], Francis Ka-Ming Chan[54], Guo-Qiang Chen[55], Quan Chen[56], Youhai H. Chen[57], Emily H. Cheng[58], Jerry E. Chipuk[59], John A. Cidlowski[38], Aaron Ciechanover[60], Gennaro Ciliberto[34], Marcus Conrad[61], Juan R. Cubillos-Ruiz[62], Peter Edward Czabotar[63,64], Vincenzo D'Angiolella[65], Mads Daugaard[66], Ted M. Dawson[67], Valina L. Dawson[67], Ruggero De Maria[52,53], Bart De Strooper[68,69,70,71], Klaus-Michael Debatin[72], Ralph J. Deberardinis[73], Alexei, Degterev[74], Giannino Del Sal[75,76,77], Mohanish Deshmukh[78], Francesco Di Virgilio[79], Marc Diederich[80], Scott J. Dixon[81], Brian David Dynlacht[82], Wafik S. El-Deiry[83,84,85], John W. Elrod[86], Kurt Engeland[87], Gian Maria Fimia[88,89], Claudia Galassi[4], Carlo Ganini[8,90], Ana J. Garcia-Saez[91], Abhishek D. Garg[9], Carmen Garrido[92,93,94], Evripidis Gavathiotis[95,96,97,98,99], Motti Gerlic[100], Sourav Ghosh[101], Douglas R. Green[102], Lloyd A. Greene[103], Hinrich**

**Gronemeyer[104,105,106,107], Georg Häcker[108,109], György Hajnóczky[110], J. Marie Hardwick[111,112], Ygal Haupt[113,114], Sudan He[115,116], David M Heery[117], Michael O. Hengartner[118], Claudio Hetz[119,120,121,122], David Hildeman[123], Hidenori Ichijo[124], Satoshi Inoue[125], Marja Jäättelä[126,127], Ana Janic[128], Bertrand Joseph[129], Philipp J. Jost[130], Thirumala-Devi Kanneganti[103], Michael Karin[131], Hamid Kashkar[132], Thomas Kaufmann[133], Gemma L. Kelly[63,64], Oliver Kepp[134,135], Adi Kimchi[18], Richard N. Kitsis[95,96,97,98,136,137], Daniel J. Klionsky[138], Ruth Kluck[63,64], Dmitri V. Krysko[139,140], Dagmar Kulms[141,142], Sharad Kumar[143,144], Sergio Lavandero[145,146], Inna N. Lavrik[147], John J. Lemasters[148], Gianmaria Liccardi[149], Andreas Linkermann[150,151], Stuart A. Lipton[152,153,154], Richard A Lockshin[155,156], Carlos López-Otín[157], Tom Luedde[158], Marion MacFarlane[159], Frank Madeo[50,160,161], Walter Malorni[162], Gwenola Manic[1,2], Roberto Mantovani[163], Saverio Marchi[164], Jean-Christophe Marine[10,165], Seamus J. Martin[166], Jean-Claude Martinou[167], Pier G. Mastroberardino[168,169,170], Jan Paul Medema[171], Patrick Mehlen[172], Pascal Meier[173], Gerry Melino[8], Sonia Melino[174], Edward A. Miao[54], Ute Martha Moll[175], Cristina Muñoz-Pinedo[176], Daniel James Murphy[177,178], Maria Victoria Niklison-Chirou[179], Flavia Novelli[49], Gabriel Núñez[180], Andrew Oberst[181], Dimitry Ofengeim[182], Joseph T. Opferman[183], Moshe Oren[184], Michele Pagano[185], Theocharis Panaretakis[186,187], Manolis Pasparakis[91], Josef M. Penninger[188,189], Francesca Pentimalli[190], David M. Pereira[191], Shazib Pervaiz[192,193,194,195], Marcus E. Peter[196], Paolo Pinton[79], Giovanni Porta[197], Jochen H. M. Prehn[198], Hamsa Puthalakath[199], Gabriel A. Rabinovich[200], Krishnaraj Rajalingam[201], Kodi S. Ravichandran[27,202,203], Markus Rehm[204], Jean-Ehrland Ricci[205], Rosario Rizzuto[206], Nirmal Robinson[142], Cecilia M. P. Rodrigues[207], Barak Rotblat[208,209], Carla V. Rothlin[210], David C. Rubinsztein[211,212], Thomas Rudel[213], Alessandro Rufini[163,214], Kevin M. Ryan[178,179], Kristopher A. Sarosiek[215,216,217], Akira Sawa[218], Emre Sayan[219], Kate Schroder[220], Luca Scorrano[221,222], Federico Sesti[223], Feng Shao[224], Yufang Shi[8,225,226], Giuseppe S. Sica[227], John Silke[63,64], Hans-Uwe Simon[133,228], Antonella Sistigu[229], Anastasis Stephanou[230], Brent R.**

**Stockwell[231], Flavie Strapazzon[232,233], Andreas Strasser[63,64], Liming Sun[234], Erwei Sun[235], Qiang Sun[236,237], Gyorgy Szabadkai[206,238], Stephen W. G. Tait[178,179], Daolin Tang[239], Nektarios Tavernarakis[240,241], Carol M. Troy[242], Boris Turk[243,244], Nicoletta Urbano[8], Peter Vandenabeele[27,28,245], Tom Vanden Berghe[27,28,246], Matthew G Vander Heiden[247,248,249], Jacqueline L. Vanderluit[250], Alexei Verkhratsky[251,252,253,254], Andreas Villunger[255,256,257], Silvia von Karstedt[258,259,260], Anne K. Voss[63,64], Karen H. Vousden[70], Domagoj Vucic[261], Daniela Vuri[8], Erwin F. Wagner[262,263], Henning Walczak[149,257,264], David Wallach[265], Ruoning Wang[266], Ying Wang[267], Achim Weber[268,269], Will Wood[270], Takahiro Yamazaki[4], Huang-Tian Yang[267], Zahra Zakeri[271], Joanna E. Zawacka-Pankau[272,273], Lin Zhang[274], Haibing Zhang[275], Boris Zhivotovsky[129,276], Wenzhao Zhou[236,237], Mauro Piacentini[48,277,**], Guido Kroemer[134,135,278,**] and Lorenzo Galluzzi[4,279,280,*,**].**

*Correspondence to: Lorenzo Galluzzi (deadoc80@gmail.com) or Ilio Vitale (iliovit@gmail.com)

**Shared senior co-authorship

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[1]IIGM - Italian Institute for Genomic Medicine, c/o IRCSS Candiolo, Torino, Italy; [2]Candiolo Cancer Institute, FPO - IRCCS, Candiolo, Italy; [3]Department of Biosciences and Nutrition, Karolinska Institute, Huddinge, Sweden; [4]Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA; [5]Department of Oncological Sciences Icahn School of Medicine at Mount Sinai, New York City, NY, USA; [6]Department of Cell Biology, University of Texas

Southwestern Medical Center, Dallas, TX, USA; [7]Institut für Immunologie, Kiel University, Kiel, Germany; [8]Department of Experimental Medicine, University of Rome Tor Vergata, TOR, Rome, Italy; [9]Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium; [10]VIB Center for Cancer Biology, Leuven, Belgium; [11]Department of Biochemistry and Molecular Biology, Thomas Jefferson University, Philadelphia, PA, USA; [12]Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples, Italy; [13]BIOGEM, Avellino, Italy; [14]Division of Systems Toxicology, Department of Biology, University of Konstanz, Konstanz, Germany; [15]Sunnybrook Research Institute, Toronto, ON, Canada; [16]Departments of Biochemistry and Medical Biophysics, University of Toronto, Toronto, ON, Canada; [17]Hebrew University of Jerusalem, Lautenberg Center for Immunology & Cancer Research, Institute for Medical Research Israel-Canada (IMRIC), Faculty of Medicine, Jerusalem, Israel; [18]Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel; [19]Department of Molecular, Cell and Cancer Biology, University of Massachusetts Chan Medical School, Worcester, MA, USA; [20]Blood Cell Development and Function Program, Fox Chase Cancer Center, Philadelphia, PA, USA; [21]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Bonn, Germany; [22]Department of Biomedicine, Nazarbayev University School of Medicine, Astana, Kazakhstan; [23]Department of Medical Biochemistry and Biophysics, Science for Life Laboratory, Karolinska Institute, Stockholm, Sweden; [24]Danish Cancer Society Research Center, Copenhagen, Denmark; [25]Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA; [26]Department of Medicine 1, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany; [27]VIB-UGent Center for Inflammation Research, Ghent, Belgium; [28]Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium; [29]Universita' Vita-Salute San Raffaele, School of Medicine, Milan, Italy and Ospedale San Raffaele IRCSS, Milan, Italy; [30]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [31]Department of Medicine, Jill Roberts Institute for Research in Inflammatory Bowel Disease, Weill Cornell Medicine, New York, NY, USA; [32]Department of Microbiology and Immunology, Weill Cornell Medicine, New York, NY, USA; [33]Sandra and Edward Meyer Cancer Center, New York, NY, USA; [34]IRCSS Regina Elena National Cancer Institute, Rome, Italy; [35]Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden; [36]Pediatric Hematology and Oncology, Karolinska University Hospital, Stockholm, Sweden; [37]Institute of Molecular Medicine and Cell Research, Medical Faculty, Albert Ludwigs University of Freiburg, Freiburg, Germany; [38]Signal Transduction Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, Durham, NC, USA; [39]Centro de Investigaciones Biologicas Margarita Salas, CSIC, Madrid Spain; [40]Université Paris-Saclay, CNRS, Institut Gustave Roussy, Aspects métaboliques et systémiques de l'oncogénèse pour de nouvelles approches thérapeutiques, Villejuif, France; [41]Department of

Immunobiology, University of Lausanne, Epalinges, Vaud, Switzerland; [42]Department of Biology, University of Konstanz, Konstanz, Germany; [43]Department of Biotechnology and Biomedicine, Technical University of Denmark, Kongens Lyngby, Denmark; [44]Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [45]Center for RNA Interference and Non-Coding RNAs, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [46]Department of Comparative Biomedical Sciences, The Royal Veterinary College, University of London; [47]UCL Consortium for Mitochondrial Research, London, UK; [48]Department of Biology, University of Rome Tor Vergata, Rome, Italy; [49]Thoracic Oncology, University of Hawaii Cancer Center, Honolulu, HI, USA; [50]Institute of Molecular Biosciences, NAWI Graz, University of Graz, Graz, Austria; [51]Cell Stress and Survival Unit, Center for Autophagy, Recycling and Disease (CARD), Danish Cancer Society Research Center, Copenhagen, Denmark; [52]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [53]Università Cattolica del Sacro Cuore, Rome, Italy; [54]Zhejiang University Medical Center, Hangzhou, China; [55]State Key Lab of Oncogene and its related gene, Ren-Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [56]College of Life Sciences, Nankai University, Tianjin, China;[57]Shenzhen Institute of Advanced Technology (SIAT), Shenzhen, Guangdong, China; [58]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [59]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [60]The Technion-Integrated Cancer Center, The Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [61]Helmholtz Munich, Institute of Metabolism and Cell Death, Neuherberg, Germany; [62]Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, USA; [63]The Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia; [64]Department of Medical Biology, The University of Melbourne, Melbourne, Victoria, Australia; [65]Department of Oncology, University of Oxford, Oxford, UK; [66]Department of Urologic Sciences, Vancouver Prostate Centre, Vancouver, BC, Canada; [67]Institute for Cell Engineering and the Departments of Neurology, Neuroscience and Pharmacology & Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD USA; [68]VIB Centre for Brain & Disease Research, Leuven, Belgium; [69]Department of Neurosciences, Leuven Brain Institute, KU Leuven, Leuven, Belgium; [70]The Francis Crick Institute, London, UK; [71]UK Dementia Research Institute at UCL, University College London, London, UK; [72]Department of Pediatrics and Adolescent Medicine, Ulm University Medical Center, Ulm, Germany; [73]Howard Hughes Medical Institute and Children's Medical Center Research Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA; [74]Department of Developmental, Molecular and Chemical Biology, Tufts University School of Medicine, Boston, MA, USA; [75]Department of Life Sciences, University of Trieste, Trieste, Italy; [76]International Centre for Genetic Engineering and Biotechnology (ICGEB), Area Science Park-Padriciano,Trieste, Italy; [77]IFOM ETS, the AIRC Institute of

Molecular Oncology, Milan, Italy; [78]Department of Cell Biology and Physiology, University of North Carolina Chapel Hill, NC, USA; [79]Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [80]College of Pharmacy, Seoul National University, Seoul, South Korea; [81]Department of Biology, Stanford University, Stanford, USA; [82]Department of Pathology and Cancer Institute, Smilow Research Center, New York University School of Medicine, New York, NY, USA; [83]Division of Hematology/Oncology, Brown University and the Lifespan Cancer Institute, Providence, RI, USA; [84]Legorreta Cancer Center at Brown University, The Warren Alpert Medical School, Brown University, Providence, RI, USA; [85]Department of Pathology and Laboratory Medicine, The Warren Alpert Medical School, Brown University, Providence, RI, USA; [86]Cardiovascular Research Center, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA; [87]Molecular Oncology, University of Leipzig, Leipzig, Germany; [88]Department of Epidemiology, Preclinical Research and Advanced Diagnostics, National Institute for Infectious Diseases 'L. Spallanzani' IRCCS, Rome, Italy; [89]Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy; [90]Biochemistry Laboratory, Dermopatic Institute of Immaculate (IDI) IRCCS, Rome, Italy; [91]CECAD, Institute of Genetics, University of Cologne, Cologne, Germany; [92]INSERM, UMR 1231, Dijon, France; [93]Faculty of Medicine, Université de Bourgogne Franche-Comté, Dijon, France; [94]Anti-cancer Center Georges-François Leclerc, Dijon, France; [95]Department of Biochemistry, Albert Einstein College of Medicine, New York, NY, USA; [96]Department of Medicine, Albert Einstein College of Medicine, New York, NY, USA; [97]Albert Einstein Cancer Center, Albert Einstein College of Medicine, New York, NY, USA; [98]Institute for Aging Research, Albert Einstein College of Medicine, New York, NY, USA; [99]Wilf Family Cardiovascular Research Institute, Albert Einstein College of Medicine, New York, NY, USA; [100]Department of clinical microbiology and Immunology, Sackler school of medicine, Tel Aviv university, Tel Aviv, Israel; [101]Department of Neurology and Department of Pharmacology, Yale School of Medicine, New Haven, CT USA; [102]Department of Immunology, St Jude Children's Research Hospital, Memphis, TN, USA; [103]Department of Pathology and Cell Biology, Columbia University, New York, NY,USA; [104]Department of Functional Genomics and Cancer, Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch, France; [105]Centre National de la Recherche Scientifique, UMR7104, Illkirch, France; [106]Institut National de la Santé et de la Recherche Médicale, U1258, Illkirch, France; [107]Université de Strasbourg, Illkirch, France; [108]Faculty of Medicine, Institute of Medical Microbiology and Hygiene, Medical Center, University of Freiburg, Freiburg, Germany; [109]BIOSS Centre for Biological Signalling Studies, University of Freiburg, Freiburg, Germany; [110]MitoCare Center, Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA; [111]Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [112]Departments of Molecular Microbiology and Immunology, Pharmacology, Oncology and Neurology, Johns Hopkins Bloomberg School

of Public Health and School of Medicine, Baltimore, MD, USA; [113]VITTAIL Ltd, Melbourne, Vic, Australia; [114]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [115]Institute of Systems Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [116]Suzhou Institute of Systems Medicine, Suzhou, Jiangsu, China; [117]School of Pharmacy, University of Nottingham, Nottingham, UK; [118]ETH Board, Zurich, Switzerland; [119]Biomedical Neuroscience Institute, Faculty of Medicine, University of Chile, Santiago, Chile; [120]Center for Geroscience, Brain Health and Metabolism, Santiago, Chile; [121]Center for Molecular Studies of the Cell, Program of Cellular and Molecular Biology, Institute of Biomedical Sciences, University of Chile, Santiago, Chile; [122]Buck Institute for Research on Aging, Novato, California, USA; [123]Division of Immunobiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [124]Laboratory of Cell Signaling, The University of Tokyo, Tokyo, Japan; [125]National Cancer Center Research Institute, Tokyo, Japan; [126]Cell Death and Metabolism, Center for Autophagy, Recycling and Disease, Danish Cancer Society Research Center, Copenhagen, Denmark; [127]Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark; [128]Department of Medicine and Life Sciences, Pompeu Fabra University, Barcelona, Spain; [129]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [130]Clinical Division of Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [131]Departments of Pharmacology and Pathology, School of Medicine, University of California San Diego, San Diego, CA, USA; [132]CECAD Research Center, Institute for Molecular Immunology, University of Cologne, Cologne, Germany; [133]Institute of Pharmacology, University of Bern, Bern, Switzerland; [134]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Center, Université Paris Saclay, Villejuif, France; [135]Centre de Recherche des Cordeliers, Equipe labellisée par la Ligue contre le cancer, Université de Paris, Sorbonne Université, Inserm U1138, Institut Universitaire de France, Paris, France; [136]Department of Cell Biology, Albert Einstein College of Medicine, New York, NY, USA; [137]Einstein-Mount Sinai Diabetes Research Center, Albert Einstein College of Medicine, New York, NY, USA; [138]Life Sciences Institute, University of Michigan, Ann Arbor, MI, USA; [139]Cell Death Investigation and Therapy Lab, Department of Human Structure and Repair, Ghent University, Ghent, Belgium; [140]Cancer Research Institute Ghent (CRIG), Ghent, Belgium; [141]Department of Dermatology, Experimental Dermatology, TU-Dresden, Dresden, Germany; [142]National Center for Tumor Diseases Dresden, TU-Dresden, Dresden, Germany; [143]Centre for Cancer Biology, University of South Australia, Adelaide, SA, Australia; [144]Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, SA, Australia; [145]Universidad de Chile, Facultad Ciencias Quimicas y Farmaceuticas & Facultad Medicina, Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile; [146]Department of Internal Medicine, Cardiology Division, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [147]Translational Inflammation Research, Medical Faculty, Otto von Guericke University, Magdeburg, Germany;

[148]Departments of Drug Discovery & Biomedical Sciences and Biochemistry & Molecular Biology, Medical University of South Carolina, Charleston, SC, USA; [149]Center for Biochemistry, Medical Faculty, University of Cologne, Cologne, Germany; [150]Division of Nephrology, Department of Internal Medicine 3, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [151]Biotechnology Center, Technische Universität Dresden, Dresden, Germany; [152]Neurodegeneration New Medicines Center and Department of Molecular Medicine, The Scripps Research Institute, La Jolla, CA,USA; [153]Department of Neurosciences, University of California, San Diego, School of Medicine, La Jolla, CA, USA; [154]Department of Neurology, Yale School of Medicine, New Haven, CT, USA; [155]Department of Biology, Queens College of the City University of New York, Flushing, NY, USA; [156]St. John's University, Jamaica, NY, USA; [157]Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Instituto Universitario de Oncología (IUOPA), Universidad de Oviedo, Oviedo, Spain; [158]Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital Duesseldorf, Heinrich Heine University, Duesseldorf, Germany; [159]Medical Research Council Toxicology Unit, University of Cambridge, Cambridge, UK; [160]BioTechMed Graz, Graz, Austria; [161]Field of Excellence BioHealth - University of Graz, Graz, Austria; [162]Center for Global Health, Università Cattolica del Sacro Cuore, Rome, Italy; [163]Dipartimento di Bioscienze, Università degli Studi di Milano, Milano, Italy; [164]Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy; [165]Department of Oncology, KU Leuven, Leuven, Belgium; [166]Department of Genetics, Trinity College, Dublin 2, Ireland; [167]Department of Cell Biology, Faculty of Sciences, University of Geneva, Geneva, Switzerland; [168]Department of Molecular Genetics, Rotterdam, the Netherlands; [169]IFOM-ETS The AIRC Institute for Molecular Oncology, Milan, Italy; [170]Department of Life, Health, and Environmental Sciences, University of L'Aquila, L'Aquila, Italy; [171]Laboratory for Experimental Oncology and Radiobiology, Center for Experimental and Molecular Medicine, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [172]Apoptosis, Cancer, and Development Laboratory, Equipe labellisée 'La Ligue', LabEx DEVweCAN, Centre de Recherche en Cancérologie de Lyon, INSERM U1052-CNRS UMR5286, Centre Léon Bérard, Université de Lyon, Université Claude Bernard Lyon1, Lyon, France; [173]The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, UK; [174]Department of Chemical Science and Technologies , University of Rome Tor Vergata , Rome, Italy; [175]Department of Pathology and Stony Brook Cancer Center, Renaissance School of Medicine, Stony Brook University, Stony Brook, New York, USA; [176]Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Spain; [177]School of Cancer Sciences, University of Glasgow, Glasgow, UK; [178]Cancer Research UK Beatson Institute, Glasgow, UK; [179]Department of Pharmacy & Pharmacology, Centre for Therapeutic Innovation, University of Bath, Bath, UK; [180]Department of Pathology and Rogel Cancer Center, The

University of Michigan, Ann Arbor, Michigan, USA; [181]Department of Immunology, University of Washington, Seattle, WA, USA; [182]Rare and Neuroscience Therapeutic Area, Sanofi, Cambridge, MA, USA; [183]Department of Cell and Molecular Biology, St. Jude Children's Research Hospital, Memphis, TN, USA; [184]Department of Molecular Cell Biology, The Weizmann Institute, Rehovot, Israel; [185]Department of Biochemistry and Molecular Pharmacology, New York University Grossman School of Medicine and Howard Hughes Medical Institute, New York, NY, USA; [186]Department of GU Medical Oncology, MD Anderson Cancer Center, Houston, Texas, USA; [187]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [188]IMBA, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria; [189]Department of Medical Genetics, Life Sciences Institute, University of British Columbia, Vancouver, Canada; [190]Department of Medicine and Surgery, LUM University, Casamassima, Bari, Italy; [191]REQUIMTE/LAQV, Laboratório de Farmacognosia, Departamento de Química, Faculdade de Farmácia, Universidade do Porto, Portugal; [192]Department of Physiology, YLL School of Medicine, National University of Singapore, Singapore; [193]NUS Centre for Cancer Research (N2CR), National University of Singapore, Singapore; [194]National University Cancer Institute, NUHS, Singapore; [195]ISEP, NUS Graduate School, National University of Singapore, Singapore; [196]Department of Medicine, Division Hematology/Oncology, Northwestern University, Chicago, IL, USA; [197]Center of Genomic Medicine, Department of Medicine and Surgery, University of Insubria, Varese, Italy; [198]Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland (RCSI) University of Medicine and Health Sciences, Dublin 2, Ireland; [199]Department of Biochemistry and Chemistry, La Trobe Institute for Molecular Science, La Trobe University, Melbourne, Victoria, Australia; [200]Laboratorio de Glicomedicina. Instituto de Biología y Medicina Experimental (IBYME), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina; [201]Cell Biology Unit, University Medical Center Mainz, Mainz, Germany; [202]Division of Immunobiology, Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA; [203]Center for Cell Clearance, Department of Microbiology, Immunology, and Cancer Biology, University of Virginia, Charlottesville, VA, USA; [204]Institute of Cell Biology and Immunology, University of Stuttgart, Stuttgart, Germany; [205]Université Côte d'Azur, INSERM, C3M, Equipe labellisée Ligue Contre le Cancer, Nice, France; [206]Department of Biomedical Sciences, University of Padua, Padua, Italy; [207]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal; [208]Department of Life sciences, Ben Gurion University of the Negev, Beer Sheva, Israel; [209]The NIBN, Beer Sheva, Israel; [210]Department of Immunobiology and Department of Pharmacology, Yale School of Medicine, New Haven, CT USA; [211]Department of Medical Genetics, Cambridge Institute for Medical Research, Cambridge, UK; [212]UK Dementia Research Institute, University of Cambridge, Cambridge Institute for Medical Research, Cambridge, UK; [213]Microbiology Biocentre,

University of Würzburg, Würzburg, Germany; [214]University of Leicester, Leicester Cancer Research Centre, Leicester, UK; [215]John B. Little Center for Radiation Sciences, Harvard School of Public Health, Boston, MA, USA; [216]Department of Systems Biology, Lab of Systems Pharmacology, Harvard Program in Therapeutics Science, Harvard Medical School, Boston, MA, USA; [217]Department of Environmental Health, Molecular and Integrative Physiological Sciences Program, Harvard School of Public Health, Boston, MA, USA; [218]Johns Hopkins Schizophrenia Center, Johns Hopkins University, Baltimore, MD, USA; [219]Faculty of Medicine, Cancer Sciences Unit, University of Southampton, Southampton, UK; [220]Institute for Molecular Bioscience, The University of Queensland, St Lucia, Australia; [221]Department of Biology, University of Padua, Padua, Italy; [222]Veneto Institute of Molecular Medicine, Padua, Italy [223]Department of Neuroscience and Cell Biology, Robert Wood Johnson Medical School, Rutgers University, NJ, USA; [224]National Institute of Biological Sciences, Beijing, PR China; [225]The Third Affiliated Hospital of Soochow University and State Key Laboratory of Radiation Medicine and Protection, Institutes for Translational Medicine, Soochow University, Jiangsu, China; [226]CAS Key Laboratory of Tissue Microenvironment and Tumor, Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai, China; [227]Department of Surgical Science, University Tor Vergata, Rome, Italy; [228]Institute of Biochemistry, Brandenburg Medical School, Neuruppin, Germany; [229]Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; [230]European University Cyprus, School of Medicine, Nicosia, Cyprus; [231]Department of Biological Sciences and Department of Chemistry, Columbia University, New York, NY USA; [232]IRCCS Fondazione Santa Lucia, Rome, Italy; [233]Univ Lyon, Univ Lyon 1, Physiopathologie et Génétique du Neurone et du Muscle, UMR5261, U1315, Institut NeuroMyogène CNRS, INSERM, Lyon, France; [234]State Key Laboratory of Cell Biology, Shanghai Institute of Biochemistry and Cell Biology, Center for Excellence in Molecular Cell Science, Chinese Academy of Sciences, Shanghai, China; [235]Department of Rheumatology and Immunology, The Third Affiliated Hospital, Southern Medical University, Guangzhou, China; [236]Laboratory of Cell Engineering, Institute of Biotechnology, Beijing, China; [237]Research Unit of Cell Death Mechanism, 2021RU008, Chinese Academy of Medical Science, Beijing, China; [238]Department of Cell and Developmental Biology, Consortium for Mitochondrial Research, University College London, London, UK; [239]Department of Surgery, The University of Texas Southwestern Medical Center, Dallas, TX 75390, USA; [240]Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, Crete, Greece; [241]Department of Basic Sciences, School of Medicine, University of Crete, Heraklion, Crete, Greece; [242]Departments of Pathology & Cell Biology and Neurology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Irving Medical Center, New York, NY USA; [243]Department of Biochemistry and Molecular and Structural Biology, J. Stefan Institute, Ljubljana, Slovenia; [244]Faculty of Chemistry and Chemical

Technology, University of Ljubljana, Ljubljana, Slovenia; [245]Methusalem Program, Ghent University, Ghent, Belgium; [246]Infla-Med Centre of Excellence, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium; [247]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA; [248]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, USA; [249]Dana-Farber Cancer Institute, Boston, MA, USA; [250]Division of BioMedical Sciences, Memorial University, St. John's, NL, Canada; [251]Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; [252]Achucarro Center for Neuroscience, IKERBASQUE, Bilbao, Spain; [253]School of Forensic Medicine, China Medical University, Shenyang, China; [254]State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania; [255]Biocenter, Institute for Developmental Immunology, Medical University of Innsbruck, Innsbruck, Austria; [256]The Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences (OeAW), Vienna, Austria; [257]The Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD), Vienna, Austria; [258]Department of Translational Genomics, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; [259]CECAD Cluster of Excellence, University of Cologne, Cologne, Germany; [260]Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, Cologne, Germany; [261]Department of Early Discovery Biochemistry, Genentech, South San Francisco,CA, USA; [262]Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria; [263]Department of Dermatology, Medical University of Vienna, Vienna, Austria; [264]Centre for Cell Death, Cancer and Inflammation, UCL Cancer Institute, University College London, London, UK; [265]Department of Biomolecular Sciences, The Weizmann Institute of Science, Rehovot, Israel; [266]Center for Childhood Cancer and Blood Diseases, Abigail Wexner Research Institute at Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA; [267]Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai, China; [268]University of Zurich and University Hospital Zurich, Department of Pathology and Molecular Pathology, Zurich, Switzerland; [269]University of Zurich, Institute of Molecular Cancer Research, Zurich, Switzerland; [270]Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, UK; [271]Queens College and Graduate Center, City University of New York, Flushing, NY,USA; [272]Department of Medicine Huddinge, Karolinska Institute, Stockholm, Sweden; [273]Department of Biochemistry, Laboratory of Biophysics and p53 protein biology, Medical University of Warsaw, Warsaw, Poland; [274]Department of Pharmacology & Chemical Biology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [275]CAS Key Laboratory of Nutrition, Metabolism and Food Safety, Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai, China; [276]Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russia; [277]National Institute for Infectious Diseases IRCCS "Lazzaro Spallanzani", Rome Italy; [278]Institut du Cancer Paris CARPEM, Department of Biology, Hôpital Européen

Georges Pompidou, AP-HP, Paris, France; [279]Sandra and Edward Meyer Cancer Center, New York, NY, USA; [280]Caryl and Israel Englander Institute for Precision Medicine, New York, NY, USA.

## COI:

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BioPharma. S.v.K. is named inventor on patent applications covering some of the therapeutic concepts pertaining to TRAIL-R blockade in disease. Y.H.C. is a member of the board of advisors for Amshenn Inc. and Binde Inc.. T.-D.K. is a consultant for Pfizer. T.V.B. and P.V. hold patents related to ferrostatin-1 analogues. W.S.E-D. is founder and shareholder (no research funding) of Oncoceutics/Chimerix, which is developing ONC201/TIC10 as cancer therapeutic. W.S.E-D. is founder and shareholder (no research funding) of p53-Therapeutics, an early-stage company developing small molecules targeting mutant p53. W.S.E-D. founder, and shareholder (no research funding) of SMURF-Therapeutics, an early-stage company developing small molecules targeting hypoxia. W.S.E-D. is Co-Chair in the Executive Committee for Precision Oncology Alliance (no research funding) of Caris Life Sciences. W.S.E-D. receives support from D&D Pharma and AACR-Novocure. W.S.E-D. is the advisory board of Ocean Biomedical. W.S.E-D. is the advisory board of RAIN Therapeutics. G.K. has been holding research contra.cts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage. G.K. has been consulting for Reithera. G.K. is on the Board of Directors of the Bristol Myers Squibb Foundation France. G.K. is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. G.K is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. G.K.'s brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. LG is/has been holding research contracts with Lytix Biopharma, Promontory and Onxeo, has received consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, OmniSEQ, Onxeo, The Longevity Labs, Inzen, Imvax, Sotio, Promontory, Noxopharm, EduCom, and the Luke Heller TECPR2 Foundation, and holds Promontory stock options. All other authors have no conflicts to declare.

## Abstract

Apoptosis is a form of regulated cell death (RCD) that involves proteases of the caspase family. Pharmacological and genetic strategies that experimentally inhibit or delay apoptosis in mammalian systems have elucidated the key contribution of this process not only to (post-)embryonic development and adult tissue homeostasis but also to the etiology of multiple human disorders. Consistent with this notion, while defects in the molecular machinery for apoptotic cell death impair organismal development and promote oncogenesis, the unwarranted activation of apoptosis promotes cell loss and tissue damage in the context of various neurological, cardiovascular, renal, hepatic, infectious, neoplastic and inflammatory conditions. Here, the Nomenclature Committee on Cell Death (NCCD) gathered to critically summarize abundant pre-clinical literature mechanistically linking the core apoptotic apparatus to organismal homeostasis in the context of disease.

## Facts

- Intrinsic and extrinsic apoptosis are forms of regulated cell death (RCD) promoting the cellular demise along with the activation of proteases of the caspase family.
- In mammalian organisms, executioner caspases are activated after cells are already committed to die.
- Apoptosis can be manipulated by genetic or pharmacological means, and multiple genetically engineered animal models and pharmacological tools to modulate apoptosis have been developed.
- Apoptosis is intimately involved in both (post-)embryonic development and adult tissue homeostasis.
- Apoptosis deregulation promotes oncogenesis and contributes to the etiology of multiple human disorders, including cardiovascular, hepatic, inflammatory and neurological conditions.
- To date, venetoclax is the only apoptosis inducer that has received regulatory approval for use in humans.

## Open Questions

- Will inhibitors of apoptotic caspases with elevated target specificity become available?
- Will agents specifically conceived to modulate apoptosis enter the clinical practice to treat solid tumors or other human disorders beyond hematological malignancies?
- Is it conceivable to design combinatorial strategies aimed at inhibiting apoptosis while interrupting compensatory activation of other RCD signaling cascades?
- Will it be possible to specifically inhibit apoptotic signaling without impacting on other processes dependent on apoptosis regulators such as differentiation, proliferation, and inflammatory reactions?

## Introduction

The health and homeostasis of multicellular organisms depend on the tight balance between cell proliferation and cell death. In this context, a large body of experimental evidence has demonstrated the existence of a form of regulated cell death (RCD) that is executed by a genetically programmed process, and hence amenable to manipulation by genetic or pharmacological means [1]. Over the past decades, multiple variants of RCD have been characterized at the genetic, biochemical, functional, and immunological level [2, 3, 4, 5, 6, 7, 8]. For instance, programmed cell death (PCD) has been functionally defined as a modality of RCD activated under purely physiological conditions (i.e., in the absence of perturbations of extracellular or intracellular homeostasis) in the context of embryonic/post-embryonic development or adult tissue homeostasis [1, 9]. Conversely, pathological RCD is invariably initiated in the context of failure to adapt to shifts in extra-cellular or intra-cellular homeostasis, constituting a *de facto* organismal program for the elimination of excessively damaged and/or potentially harmful cells, such as cells infected with pathogens [1, 10]. From a biochemical perspective, an increasing number of RCD modalities have been defined by the Nomenclature Committee on Cell Death (NCCD) based on the mechanistic involvement of specific molecular components [1, 11]. For instance, apoptotic cell death has been defined as a form of RCD that is mainly executed by proteases of the caspase family, namely caspase 3 (CASP3), CASP6 and CASP7 initiated by CASP8 and CASP9 [1, 12, 13]. However, in mammalian organisms, with the exception of CASP8, apoptotic caspases simply accelerate RCD because their activation occurs when cells are already committed to die [1, 14, 15, 16]. This means that contrarily to simpler organisms (e.g., *C. elegans*), in which apoptotic caspase elimination fully rescues cells from death, in mammals, apoptotic cell death can at most be retarded but not prevented by pharmacological or genetic strategies inhibiting the activity of these caspases. Mitochondrial permeability transition (MPT)-driven necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic cell death, NETotic cell death,

lysosome-dependent cell death, and autophagy-dependent cell death represent forms of RCD that involve precise molecular events and hence can also be manipulated with pharmacological or genetic interventions [1, 2, 3, 4, 5, 6, 17, 18, 19]. Other RCD modalities have been recently identified, such as alkaliptosis [20], cuproptosis [21] and PANoptosis (involving the simultaneous activation of pyroptosis, apoptosis, and necroptosis) [22], and their signal transduction modules are under investigation. The importance of several of these forms of RCD in health and disease is not yet known.

Along with the identification of key RCD regulators and the advent of modern tools for genetic manipulation, a great experimental effort has been devoted to elucidating the role of RCD in the physiopathology of multi-cellular organisms [23]. Thus, various studies in animals (mostly rodents) genetically altered to be deficient for or over-express components of the apoptotic apparatus (either at the whole-body level or in selected cell/tissue types) have provided formal proof of the relevance, but not always the exquisite requirement, of apoptosis for embryonic and fetal development or adult tissue homeostasis [24, 25, 26].

Along similar lines, pharmacological and genetic tools aimed at altering apoptotic signaling in pre-clinical disease models revealed the mechanistic contribution of apoptosis to the etiology of various conditions associated with the loss of post-mitotic or (in certain settings) non-post-mitotic cells, including a panel of neurological, cardiovascular, renal, hepatic, and inflammatory disorders [24]. Extensive studies over the last five decades highlighted the apoptotic machinery as a major target for the development of new therapeutic interventions [27], not only for the induction of cell death in the context of disrupted tissue homeostasis (e.g., for neoplastic diseases) [28], but also for the inhibition of cell death in the context of ischemic, degenerative and inflammatory conditions [29, 30]. However, while at least one drug designed to induce apoptosis is currently approved for use in humans, namely the BCL2 apoptosis regulator (BCL2) inhibitor venetoclax [31, 32, 33, 34] which is used alone or in combinatorial regimens for the treatment of

chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma and acute myeloid leukemia (AML) [31, 35, 36, 37, 38], no other agents specifically conceived to inhibit the apoptotic apparatus have been licensed for clinical practice so far. The broad-spectrum caspase inhibitor emricasan received fast-track designation by the US Food and Drug Administration (FDA) for the treatment of non-alcoholic steatohepatitis in 2016 but demonstrated inconsistent clinical efficacy [39, 40, 41], and – as of now– is not approved for therapy in humans.

The lack of clinically approved, selective apoptosis inhibitors and the inconclusive performance of emricasan in recent trials reflect several aspects of (apoptotic and non-apoptotic) RCD that began to emerge only recently (**Figure 1**). First, while detecting cell death as well as biomarkers of specific RCD variants *in vitro* is relatively straightforward [42], precise quantification of cell death *in vivo* in adult tissue remains challenging, at least in part because of rapid disposal of cell corpses by efferocytosis [43, 44, 45, 46]. Thus, the actual contribution of cell death to the etiology of various human disorders is difficult to quantify by observational approaches [47, 48]. Second, while for a long-time, specific forms of RCD were considered virtually independent entities, recently it became clear that the molecular machinery for RCD is composed of highly interconnected modules characterized by substantial redundancy, backup pathways and feedback loops [10, 49, 50]. Thus, molecules that inhibit one specific form of RCD may ultimately be unable to confer actual cyto- and tissue protection instead only altering the kinetic and biochemical manifestations of death by allowing the engagement of a different RCD sub-routine. For instance, while CASP8 is a major signal transducer in death receptor (DR)-driven apoptosis (see below), it intrinsically inhibits necroptosis induced by DR and certain other signaling pathways, such as Toll-like receptor (TLR) signaling [51, 52, 53], suggesting that caspase inhibition in the context of DR signaling may promote necroptotic cell death [54, 55, 56, 57]. Together with a low target specificity and selectivity within the caspase family [57], this can explain the inadequate efficacy of emricasan observed in pre-clinical and clinical studies. Third, even in the hypothetical scenario of agents capable of simultaneous inhibition of

all (known and unknown) RCD pathways, loss of cellular homeostasis due to failing adaptation to stress generally involve degenerative processes that at some stage cannot be reversed, such as widespread mitochondrial permeabilization and loss of RNA and protein synthesis [4, 58, 59, 60], i.e., even if all RCD modalities could be blocked effectively, cells might undergo uncontrolled necrotic death. In this setting, cell death may occur as a consequence of an irremediable degeneration of cellular functions that can no longer be rescued pharmacologically or even genetically [61]. Supporting these latter notions, accumulating literature indicates that, at least in mammalian systems, perhaps with the exception of CASP8, so-called apoptotic caspases mainly control the kinetics of apoptotic cell death and its immunological manifestations, but not whether cell death ultimately occurs or not, [15, 16]. This points to the caspase family as a major regulator of organismal homeostasis via control of inflammatory responses [62, 63]. The simultaneous inhibition of multiple caspases, as for instance by emricasan, may thus also impact inflammation, as was demonstrated for TNF-induced systemic inflammatory respiratory syndrome (SIRS) in vivo for the pan caspase-inhibitor zVAD-fmk [54, 64]. To complicate matters, multiple components of the core apoptotic machinery, including caspases and multiple members of the BCL2 family have been reported to regulate a variety of non-apoptotic functions beyond inflammation, such as mitochondrial energy production, $Ca^{2+}$ signaling and terminal differentiation [65, 66, 67, 68, 69, 70, 71, 72]. Structurally, distinguishing between apoptotic and non-apoptotic functions of caspases and the BCL2 family remains challenging. Finally, there is a hitherto unclarified heterogeneity in the regulation of RCD at distinct anatomical sites (possibly linked to micro-environmental features) at distinct stages of cellular differentiation, and in the context of diverse patho-physiological states (*e.g.*, in young *vs.* adult and aged individuals).

All these issues should also be kept under consideration in the context of the present review, in which the NCCD aims at critically discussing a large amount of pre-clinical data in support of a key role for the apoptotic machinery in mammalian diseases. Specifically, the interpretation of results of genetic and

pharmacological experiments presented herein should place particular attention on the aforementioned connectivity amongst different RCD variants as well as on discriminating between essential *vs.* accessory aspects of cell death [14]. Another issue to be considered is the fact that most conclusions are based on use of knockout/congenic mice which often present other passenger mutations potentially influencing the observed phenotype [73]. Our objective is not only to provide a critical summary of the existing literature, but also to offer an updated framework for interpretation of these findings in view of currently accepted models of RCD signaling.

## Intrinsic apoptosis in disease

There are substantive supporting data from genetic studies to demonstrate that the molecular machinery for intrinsic apoptosis (described in **Box 1** and **Figure 2**) is involved in embryonic and fetal development as well as in adult tissue homeostasis. Numerous preclinical studies in animal models of disease demonstrate that intrinsic apoptosis contributes to etiology in various disorders involving the loss of not only post-mitotic, but also non-post-mitotic tissues, including neurological, cardiac, renal, hepatic, autoimmune/inflammatory, oncological, and infectious conditions. However, as discussed above, the interpretation of these results should be taken with caution given the high interconnectivity of RCD pathways and the crosstalk between RCD and inflammatory response. Moreover, the activation of executioner caspases occurs after cells are already committed to intrinsic apoptosis [15, 16]. Accordingly, caspase inhibition only delays the execution of cell death. In this context, the phenotypes observed under apoptotic caspase-deleted or inhibited conditions may reflect cell-extrinsic effects of caspase activity such as the release of immunomodulatory and cytotoxic signals from dying/dead cells, including damage-associated molecular patterns (DAMPs) or cytokines (this concept is extensively discussed in [14]). These phenotypes may also stem from the lack of processes independent of intrinsic (or extrinsic) apoptosis,

as, for instance, the lack of CASP3-mediated cleavage of gasdermin E (GSDME) leading to impaired pyroptosis and associated inflammatory response [74, 75].

Below, we will provide details of the pro-apoptotic BCL2 proteins, the anti-apoptotic BCL2 proteins, the components of the apoptosome - a platform for the activation of initiator caspases composed of cytochrome c, somatic (CYCS), apoptotic peptidase activating factor 1 (APAF1) and pro-CASP9 - and effector caspases in disease. The instances of involvement encompass participation in the pathogenic mechanisms as well as experimental deletion or inhibition as a means of exploring potential utility as treatment targets. The effects of these regulators and effectors of the intrinsic apoptosis pathway on health are described in **Box 2**, **Box 3** and **Box 4.**

**Neurological disorders.** Intrinsic apoptotic factors are implicated in the pathophysiology of numerous neurological diseases (**Figure 3**). In a mouse model of amyotrophic lateral sclerosis (ALS), deletion of BCL2-associated X protein (*Bax*) reduces neuronal cell death coupled to attenuated motor dysfunction and neuromuscular degeneration [76]. Additional ablation of BCL2-antagonist/killer 1 (*Bak1*) further enhances neuroprotection, resulting in improved overall animal survival [77]. Similar protective effects were observed in mice lacking the BH3-only proteins BCL2 like 11 (BCL2L11, best known as BIM) and BCL2 binding component 3 (BBC3, best known as PUMA), as well as in transgenic mice overexpressing BCL2, X-linked inhibitor of apoptosis (XIAP) [78, 79, 80, 81, 82]. Moreover, intra-cerebroventricular administration of the broad-spectrum inhibitor Z-VAD-FMK protects mice from ALS [83], although whether such protection arises from the inhibition of intrinsic apoptosis was not proven. *Bax* deletion also attenuates neuromuscular dysfunctions in a mouse model of congenital muscular dystrophy (another neurodegenerative disease affecting motoneurons) [84], while BCL2 overexpression limits neuromuscular disease progression in some (but not all) mouse models of progressive motor neuronopathy and muscular dystrophy [85, 86, 87]. Finally, genetic or pharmacological inhibition of poly (ADP-ribose) polymerase

family, member 1 (PARP1) and PARP2 halts axonal degeneration and improves related motor phenotypes in *Caenorhabditis elegans* models of ALS [88].

Multiple components of the molecular machinery for intrinsic apoptosis, including BAX, PUMA, BH3 interacting domain death agonist (BID), Harakiri, BCL2 interacting protein (contains only BH3 domain) (HRK), were shown to drive neuronal death in Alzheimer's disease (AD) and Parkinson's disease (PD) models [89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101]. Thus, overexpression of BCL2 decreases the appearance of early pathological markers of AD, such as amyloid precursor protein (APP) and microtubule-associated protein tau (MAPT, best known as tau) cleavage, which depend on caspases [102, 103, 104], resulting in attenuated neurological defects [105, 106]. Some findings indicate a role of apoptotic caspases in the pathogenesis of AD. However, as discussed above, during intrinsic apoptosis, caspases simply accelerate the course of cell death, and, so, such effects may be linked to the release of cytotoxic and pro-inflammatory factors from dying cells. In more detail, pharmacological inhibition of CASP3 reduces early synaptic failure in mouse models of AD, ultimately improving cognitive defects [107]. Moreover, expression of a mutated form of amyloid β (an APP cleavage product) or administration of broad-spectrum caspase inhibitors attenuates synaptic defects in models of AD, an effect only partially recapitulated by CASP3-specific inhibitors [108]. Along similar lines, genetic deletion of *Casp2* was reported to provide protection from synaptic loss and cognitive decline in a mouse model of AD [109]. Such protection may be linked to the generation of a specific cleavage product (Δtau314) by CASP2, which is reported to impair cognitive and synaptic function by promoting the missorting of tau to dendritic spines [110, 111]. Accordingly, CASP2 inhibitors blocked tau truncation and restored excitatory neurotransmission in mouse models of tauopathies, including AD [112, 113]. Of note, a role for CASP4 in AD pathogenesis is also reported [114, 115]. Moreover, studies using senescence-accelerated OXY5 rat model of AD demonstrated that the treatment with mitochondria-targeted antioxidant SkQ1 improved mitochondrial fitness and slowed down the signs of Alzheimer's disease-like pathology in older rats [116]. Lack of BIM

(due to deletion of *Bcl2l11*) also confers protection to dopaminergic neurons in experimental PD imposed by inhibition of mitochondrial complex I, an effect that depends on BAX activation [117]. In addition, genetic deletion or down-regulation of *Casp3*, as well CASP3 inhibition by transgenic, neuron-restricted expression of XIAP protects mice against pharmacologically induced PD, attenuating both dopaminergic neuron alterations and behavioral deficits [118, 119, 120, 121]. Whether protection arises from the lack of cell-intrinsic or cell-extrinsic processes dependent on apoptotic caspases has not been investigated. Finally, pharmacological inhibition of CASP3 confers neuroprotection to rat model of Huntington's disease (HD) [122, 123, 124]. That said, the precise mechanisms whereby components of the molecular apparatus for intrinsic apoptosis influence neurodegeneration need to be further explored. Two studies in clear contradiction to each other reported that at sublethal doses, pharmacological inhibition of myeloid cell leukemia sequence 1 (MCL1) improved disease outcome in a mouse model of AD with a mechanism independent of apoptosis induction and involving the stimulation of mitophagy [125], but that Mcl1 haploinsufficiency accelerated the degeneration and dysfunctionality of motor neurons in mice [126]. Also, there is evidence that necroptosis or ferroptosis rather than apoptosis can be the major contributor in neuronal cell destruction during AD [127, 128]. Finally, although *Bax* deletion prevents the demise of cerebellar granule neurons in a transgenic model of inherited prion disease [129], the direct contribution of BAX to neurotoxicity during prion disorders is a matter of controversy [130].

BCL2 family proteins have also been reported to contribute to axonal degeneration and neuronal cell death in animal models of brain trauma, degeneration, or neurotoxicity [131, 132, 133]. Thus, BAX- or BID-deficient mice, as well as transgenic mice overexpressing BCL2, display increased survival of cortical or hippocampal neurons after experimental traumatic brain injury, as compared to wild-type mice [134, 135, 136, 137]. Moreover, transgenic BCL2 overexpression protects mouse neurons against the detrimental effects of transection of the sciatic nerve [138]. Likewise, BAX deficiency enhances the survival of oligodendrocytes in mice subjected to spinal cord injury [139]. Both neuroprotection and functional

improvements were observed in rat or mouse models of traumatic spinal cord injury upon local administration of Z-VAD-FMK) and other caspase inhibitors [140, 141, 142]. However, these findings need to be validated given the low selectivity of these inhibitors among caspases. Of note, in rats, post-traumatic neuroprotection can further be improved by combined inactivation of PARP1 and CASP3 [143], suggesting a potential involvement for PARP1-dependent parthanatos in the process.

Deletion of *Bax* (but not of the genes encoding BIM, PUMA or BID), as well as *Bax* haploinsufficiency, prevents the death or degeneration of retinal ganglion cells in mice subjected to optic nerve injury [144, 145, 146, 147]. Moreover, the demise of injured retinal ganglion cells is exacerbated in mice with a conditional loss of *Bcl2l1* (leading to lack of BCL-$X_L$) [148] and decreased in transgenic mice over-expressing XIAP [149] or BCL-$X_L$ [150] in the eye, or in rodents treated with an XIAP-derived cell-permeant peptide targeting CASP9 [151], or a CASP3-targeting small-interfering RNA (siRNA) [152, 153]. Moreover, transgenic or adenovirus-driven XIAP expression protects the retina in various animal models of retinal disease, degeneration, or ischemia [154, 155, 156, 157, 158, 159], while a BCL-$X_L$ inhibitor alleviated pathogenic neo-vascularization during diabetic retinopathy [160]. Genetic deletion of *Casp9* from endothelial cells protected retinal ganglion cells from ischemic death, supporting non-cell autonomous functions of CASP9 [151]. Of note, CASP7 seems to play a crucial role in retinal ganglion cell death, as demonstrated in a model of optic injury in *Casp7*$^{-/-}$ mice [161]. However, both pro-survival (BCL2) and pro-apoptotic (BAK1, BAX and BIM) BCL2 family members contribute to retinal neo-vascularization in response to experimental ischemic retinopathy [162, 163, 164]. In one of these papers, this effect is linked to an increased survival of endothelial cells in the absence of BAX and BAK1 [164]. Persistent endothelial cells promote rapid tissue re-vascularization, thus preventing the occurrence of a pathogenic excessive neovascularization. Moreover, the inhibition of the intrinsic apoptotic pathway by genetic inhibition of c-Jun N-terminal kinase 1 (*Jnk1*) or the administration of a broad-spectrum caspase inhibitor led to reduced choroidal neo-vascularization in the murine model of wet age-related macular degeneration (AMD) [165]. These

observations may indicate that factors released by dying cells regulate neo-vascularization in the retina or other eye tissues.

Deletion of *Bax*, *Hrk* or *Casp3* as well as transgenic overexpression of XIAP prevents neuronal loss and/or axon degeneration in mouse models of trophic factor deprivation including nerve growth factor (NGF) withdrawal [166, 167, 168]. Conversely, lack of BIM or PUMA does not limit hippocampal neuronal injury upon experimental excitotoxicity [169, 170]. Moreover, while *in vivo* delivery of an XIAP fusion protein protects neurons against death induced by glutamate or kainic acid [171], kainic acid-mediated neurodegeneration cannot be rescued by the CASP3 inhibitor DEVD-CHO [172]. Conversely, BIM appears to be activated during excitotoxicity [173], and *Bcl2l11*$^{-/-}$ mice (which lack BIM) display attenuated neuro-degeneration after experimental seizures induced by administration of kainic acid into the amygdala, at least in part because of decreased neuronal cell death in the hippocampus (but not in the neocortex) [174]. Moreover, data from knockout mice suggest that experimental seizure-induced neuronal death involves BCL2-associated agonist of cell death (BAD), BCL2 interacting killer (BIK), BCL2 modifying factor (BMF), or PUMA [175, 176, 177, 178] and that BCL2-like 2 (BCL2L2; best known as BCL-W) may provide neuroprotective, seizure-suppressive functions [179]. Confirming a certain degree of functional redundancy, phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1, best known as NOXA) and BID seem dispensable for RCD driven by excitotoxicity, as shown in kainic acid-treated animals [180, 181].

Intrinsic apoptosis is also involved in neuronal apoptosis post-ischemic injury in both developing and adult brains. In a mouse model of neonatal hypoxia-ischemia, neuroprotection was documented upon deletion of *Bax* [182], simultaneous absence of BIM and BAD [183], or transgenic overexpression of XIAP [184]. Conversely, *Xiap*$^{-/-}$ mice are sensitized to neonatal hypoxia-ischemia injury [185]. Apparently at odds with these findings, *Casp3*$^{-/-}$ mice display increased vulnerability to such experimental perturbation, possibly due to complementary over-activation of CASP3-independent pathways [186]. Of note, the

absence of CASP3, BAX, or PUMA (but not the absence of NOXA, BIM or HRK) also confers neuro-protection to newborn mice acutely exposed to ethanol [187, 188, 189], while loss of BAX is neuroprotective in newborn mice exposed to isoflurane [190] as well as ionizing radiation [133, 191]. At the same time, it is interesting to note that BAX-dependent neuronal RCD also contributes to reactive microgliosis during the recovery of the developing brain from acute alcohol exposure [192], pointing to an etiological role for activation of microglial cells by dead neurons.

*Bax*$^{-/-}$ mice displayed pronounced neuroprotection when subjected to distinct experimental brain injuries, including middle cerebral artery occlusion [193]. A similar protection against experimental ischemic insults has been observed in mice deficient for BMF [194], or BID [195, 196, 197]. Conversely, NOXA seems to be dispensable for neuronal damage induced by experimental ischemic stroke [194]. Moreover, the absence of BID fails to protect mice from ischemia-reperfusion, although it limits the associated inflammatory response [198]. Transgenic over-expression of BCL2, BCL-$X_L$ or XIAP as well as inhibition of apoptotic caspases or genetic deletion of *CASP6* ameliorates neuronal survival upon global ischemia, focal ischemia or stroke [199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215]. It should be noted, however, that in these settings, neuroprotection by inhibition or deletion of caspases may be related to the lack of cell-extrinsic or apoptotic-unrelated roles of caspases. Morevoer, various examples of caspase-independent neuronal death after cerebral ischemia have been reported [216, 217, 218, 219]. In thic context, it is important to note that apoptosis is dynamically regulated during lifespan in the brain [24]. Indeed, while immature brain cells express high levels of many BCL2 proteins [133, 220, 221], most of these proteins are downregulated in the adult brain, when most post-mitotic neural cells become resistant to apoptosis [131, 222]. This may help explain the divergent findings on the mechanisms of neural cell death reported above.

**Cardiovascular conditions.** While a role for RCD in non-reperfused myocardial infarction remains questionable, apoptosis and other cell death programs including necroptosis, MPT-driven necrosis,

ferroptosis, pyroptosis and autosis appear to contribute to cardiomyocyte death and tissue damage during myocardial infarction with reperfusion (also referred to as myocardial ischemia-reperfusion injury). However, the relative importance of the RCD and how they interconnect mechanistically and functionally to produce an integrated response remains poorly understood. For example, *Bak1*$^{-/-}$mice with a cardiomyocyte-specific deletion of *Bax* displayed considerably reduced infarct size as compared to their wild-type littermates when subjected to experimental myocardial ischemia-reperfusion, although it remains unclear whether these effects are attributable to reductions in apoptosis or MPT-driven necrosis [223, 224, 225], a RCD variant shown to participate in the pathogenesis of ischemic stroke [226]. Protection against myocardial ischemia-reperfusion has also been reported in transgenic mice overexpressing BCL2 [227, 228, 229] or a BCL-$X_L$-derived peptide [230]. Likewise, deletion of *Bbc3* (leading to lack of PUMA) ameliorates myocardial ischemia-reperfusion injury [231], ultimately translating into increased survival [232]. Moreover, neurotrophin-3 was reported to confer cardioprotection fromischemic and reperfusion injuries by reducing BIM levels [233]. Broad spectrum caspase inhibition [234, 235, 236] and XIAP mimicking peptides [237] were shown to modestly reduce myocardial infarct size. Finally, simultaneous deletion of *Casp3* and *Casp7* had no cardioprotective effect during reperfused myocardial infarction [238], in line with the notion that the absence of caspase only delays cell death.

In contrast to the large burst of cell death over several hours characterizing myocardial infarction, cardiomyocytes are lost gradually over months to years during heart failure with reduced ejection fraction [3]. The role of intrinsic apoptosis in these heart conditions is, however, debated. In a mouse model of cardiomyopathy based on the deletion of desmin (*Des*), the cardiomyocyte-specific over-expression of BCL2 reduces cardiac lesions and hypertrophy coupled to ameliorated cardiac functionality [239]. However, despite improved survival, these mice show increased levels of necrosis due to the activation of alternative cell death pathways [240]. Moreover, *Casp3*$^{-/-}$ mice display enhanced vulnerability to experimental cardiomyopathy, at least in part reflecting the inefficient activation of pro-survival AKT

serine/threonine kinase 1 (AKT1) signaling [241]. As an alternative explanation, the absence of CASP3 may foster RCD-driven inflammation as a consequence of increased type I interferon (IFN) release [242, 243, 244]. Indeed, experimental data linking dysregulated type I IFN release and cardiac conditions have recently emerged [245].

As for therapeutic interventions, cardioprotective effects have been achieved by inhibition of CASP3 in rodent models of myocardial dysfunction induced by endotoxin [246], burn injury [247] or hypoxia [248], although perhaps such effects can be attributed to the lack of cell-extrinsic or apoptosis-unrelated effects of caspase activity. Moreover, inhibition of BAX prevents cardiotoxicity induced by doxorubicin in zebrafish and mice without affecting the anti-neoplastic activity of doxorubicin [249]. Similarly, the endothelial cell-specific expression of B cell leukemia/lymphoma 2 related protein A1a (BCL2A1A) promotes survival in a model of allogeneic heart transplantation [250].

Finally, the mechanistic links between intrinsic apoptosis and atherosclerosis remain a matter of debate. Indeed, while *Casp3* deletion favors plaque development in mouse models of atherosclerosis [251], the absence of DNA fragmentation factor subunit beta (DFFB, best known as CAD)) [252] protects mice against the disease. Likewise, while conditional deletion of *Mcl1* in myeloid cells is pro-atherogenic [253], genetic or pharmacological inhibition of BCL-$X_L$ reduces atherosclerosis via a mechanism involving the depletion of platelets [254]. Moreover, the macrophage or leukocyte-specific deletion of the gene encoding BIM in mice has modest effects on plaque development, especially in the early phase of atherosclerosis [255, 256]. As the etiology of atherosclerosis involves a major inflammatory component, these apparently discrepant results may reflect (at least in part) the key role of some components of the apoptotic machinery in the control of inflammatory responses.

**Renal disorders.** Germline or kidney-specific deletion of *Bax* attenuates acute kidney damage in mice subjected to experimental renal ischemia/reperfusion [257]. A similar nephron-protection has been observed

718 in *Bid*$^{-/-}$ mice [258], as well as in transgenic mice specifically expressing BCL-$X_L$ in the kidney [259].
719 Moreover, the simultaneous deletion of *Bax* and *Bak1* in kidney proximal tubules limits tubular apoptosis
720 and ameliorates kidney inflammation and fibrosis in a mouse model of renal fibrosis based on unilateral
721 ureteral obstruction [260, 261]. Apoptotic caspases also appear to contribute to the etiology of renal
722 conditions, although, perhaps, this reflects cell-extrinsic effects of caspase activity. *Casp3* deletion
723 reduces microvascular rarefaction and renal fibrosis in mice subjected to experimental ischemia-
724 reperfusion injury [262], resulting in better long-term outcomes [263]. Moreover, the lack of CASP3 increases
725 the survival of mice with chronic kidney disease caused by a congenital mutation in cystin 1 (*Cys1*) [264].
726 In this setting, CASP3-deficient mice display increased CASP7 and decreased BCL2 expression, which
727 is in line with recent clinical evidence of constitutive BCL2 down-regulation in patients with polycystic
728 kidney disease [265]. Administration of broad-spectrum caspase inhibitors limits kidney damage and
729 improves renal functionality after a variety of experimental insults to kidneys, as observed in animal
730 models of renal ischemia [266, 267], polycystic kidney disease [268], glomerulonephritis [269], lupus nephritis [270]
731 and diabetic renal disease [271]. Nonetheless, the specific targeting of apoptotic caspases will reveal
732 whether this effect reflects the inhibition of intrinsic apoptosis. Indeed, these studies do not rule out the
733 involvement of non-apoptotic RCD pathways in the etiology of acute and chronic kidney injury [272, 273].
734 Moreover, some of the nephron-protective effects of broad-spectrum caspase inhibitors have been linked
735 to decreased post-RCD inflammation rather than the sole inhibition of apoptosis [266, 274]. In this context,
736 Z-VAD-FMK aggravates (rather than ameliorates) renal dysfunction in a mouse model of cisplatin
737 nephrotoxicity, by a mechanism involving the abrogation of cyto-protective autophagy [275]. Similarly, Z-
738 VAD-FMK is ineffective in mouse models of osmotic nephrosis and contrast-induced acute kidney injury
739 [276], and this may be linked to the ability of Z-VAD-FMK to inhibit CASP8 (and hence promote
740 necroptosis). Finally, acute loss of BCL-$X_L$ in all tissues of adult mice, except for hematopoietic cells,

caused severe renal tubular degeneration leading to fatal anemia due to the loss of erythropoietin production [277].

**Hepatic diseases.** Abundant evidence highlights pathogenic roles of apoptosis in acute liver injuries, as well as in alcohol-related and alcohol-unrelated chronic liver disorders. Hepatocytes express high levels of BID, which connects DR signaling to mitochondrial outer membrane permeabilization (MOMP) upon CASP8-dependent cleavage [278], and this complicates distinguishing between the intrinsic and extrinsic pathways. Here, we shall discuss studies performed on animal models of liver injury unrelated to overt signaling engaged by the Fas cell surface death receptor (FAS; also known as CD95 or APO-1) or the TNF receptor superfamily member 1A (TNFRSF1A, best known as TNF-R1) (which instead will be discussed in the next section).

Distinct preclinical models of hepatic ischemia-reperfusion injury demonstrated that deletion of *Bcl2l11* (leading to lack of BIM) and/or *Bid* as well as over-expression of BCL2 or administration of pharmacological broad-spectrum caspase inhibition mediate robust hepatoprotective effects [279, 280, 281, 282]. A similar improvement of hepatocyte survival and liver functionality was observed in rodents specifically expressing a mutated variant of BID in the liver and subjected to warm ischemia/reperfusion injury [283]. As for other models of liver injury, BIM-deficient mice are protected against viral hepatitis [284]. Moreover, deletion of the genes encoding BIM or PUMA, but not that of BCL2-related ovarian killer (*Bok*) limits liver injury in mice exposed to the hepatotoxic agent acetaminophen [285, 286, 287]. Moreover, pre-treatment with Z-VAD-FMK improves the survival of mice subjected to extensive hepatectomy [288].

There is contrasting evidence on the role of BID in the etiology of liver conditions unrelated to overt FAS and TNF-R1 signaling. In a model of alcohol-related liver disease, the lack of BID confers some protection against ethanol-induced fibrosis, although mice display persisting signs of inflammation and steatosis [289]. Moreover, mice with a hepatocyte-specific deletion of *Bid* present reduced liver

764 inflammation and fibrosis when subjected to a choline-deficient diet to cause non-alcoholic
765 steatohepatitis (NASH) [290]. Also, administration of BID-targeting antisense oligonucleotides exerted
766 significant hepatoprotective effects [291]. However, BID deficiency fails to ameliorate liver injury and
767 fibrosis upon bile duct ligation (as a model of obstructive cholestasis and chronic liver disease) [292]. Of
768 note, in the same experimental model, the liver-specific overexpression of MCL1 but not BCL2 protects
769 animals from hepatic damage [293, 294], suggesting some specificity for MCL1. To add a layer of
770 complexity, conditional deletion of *Xiap* in hepatocytes does not result in liver injury, steatosis, or
771 fibrosis, possibly due to compensatory effects of other inhibitor of apoptosis protein (IAPs) isoforms [295].
772 That said, *Xiap*$^{-/-}$ and *Casp3*$^{-/-}$ mice subjected to diet-induced hepatic steatosis and/or fibrosis, display
773 exacerbated and attenuated liver damage, respectively [296, 297]. These effects have been linked to the
774 modulation of the inflammatory response rather than apoptosis. Finally, genetic co-deletion of *Mcl1* and
775 transformation-related protein 53 (*Trp53*, best known as p53) [298] as well as conditional deletion of the
776 genes encoding BCL-$X_L$ or MCL1 promote fibrosis and/or carcinogenesis, two common final stages of
777 liver disease [299]. In this latter study, the additional deletion of *Bak1* limited hepatotoxicity, which is in
778 line with evidence indicating that deletion of *Bid* and/or *Bok* protects mice against experimentally
779 induced hepatocarcinogenesis [300, 301, 302].

780 CASP2 was found upregulated in mouse model of NASH and in NASH patients and was implicated in
781 driving lipogenesis and steatohepatitis with a mechanism involving the cleavage of the site-1-protease
782 (S1) followed by the activation of sterol regulatory element binding proteins (SREBP) [303]. In this study,
783 the ablation or pharmacological inhibition of CASP2 prevented diet-induced steatosis and NASH
784 progression. Of note, CASP2 deficiency was also reported to protect mice from diet-induced obesity and
785 metabolic syndrome [304]. Supporting the etiological contribution of caspase activation to liver disease, the
786 administration of broad-spectrum caspase inhibitors (e.g., emricasan, VX-166) reduced liver injury,
787 inflammation and fibrosis in mice fed a diet rich in fat or deficient in methionine and choline [305, 306].

Along similar lines, emricasan reportedly decreased portal pressure, fibrogenesis and hepatic inflammation, and preserved liver function in rodent models of chronic carbon tetrachloride ($CCl_4$)-mediated cirrhosis or cholestasis driven by bile duct ligation [307, 308, 309]. Preliminary anti-inflammatory effects coupled with improved liver function have also been observed in patients with NASH-related cirrhosis treated with emricasan [39, 310]. However, follow-up, randomized clinical studies failed to observe beneficial effects of this agent on portal pressure and clinical outcome [40, 41, 311]. At least in part, these findings may reflect the complex interconnection between multiple RCD variants involved in the pathogenesis of NASH. Supporting this possibility, the administration of CASP3-specific inhibitors that abrogate both pro-apoptotic and pro-pyroptotic activities of CASP3 protected mice against acute liver injury caused by bile duct ligation [312]. Additional pharmacological and genetic studies specifically targeting intrinsic apoptosis (over other RCD pathways controlled by caspases) are needed to formally ascertain the involvement of this pathway in the etiology of hepatic disorders.

**Hematological malignancies and solid cancers.** The role of the intrinsic apoptosis pathway in preventing oncogenesis has been demonstrated in multiple animal models of induced hematological and solid tumors. In particular, a wide range of evidence demonstrates that over-expression of BCL2, BCL-$X_L$ or MCL-1 accelerates the onset of leukemia and lymphoma induced by over-expression of the MYC proto-oncogene, bHLH transcription factor (MYC) [313, 314, 315, 316, 317]. Accordingly, the pharmacological inhibition of anti-apoptotic BCL2 proteins is effective against MYC-driven tumors, even when they lack p53 function [318, 319, 320, 321]. In this context p53 has been shown to exert multiple roles in RCD (e.g., [322, 323, 324]). In particular, it acts as a direct or indirect regulator of the expression of several apoptotic genes [325, 326, 327, 328] and connects apoptosis induction and cell cycle arrest [329]. One main target of p53 in this context is cyclin dependent kinase inhibitor 1A (*CDKN1A*, best known as p21). p53-induced expression of *CDKN1A* leads to the activation of DREAM and RB/E2F transcriptional repressor complexes, in turn promoting cell cycle arrest by downregulating crucial cell cycle regulators such as cyclins and cyclin-

812 dependent kinases [326, 327, 330]. However, recent finding indicates that the p53-p21-DREAM or p53-p21-
813 RB/E2F axis can also downregulate *CASP2* and CASP8-associated protein 2/FLASH (*CASP8AP2*),
814 generating a feedback loop centered on p53 that limits rather than promoting the induction of apoptosis
815 [326, 327]. Of note, when analyzing the impact of endogenous proteins, it was shown that the absence of
816 BCL-$X_L$ but not BCL2 limits the development of lymphoma in transgenic mice expressing MYC under
817 the IgH enhancer (Eμ-myc mice) [331, 332], thus supporting the therapeutic use of BCL-$X_L$ inhibitors against
818 these blood cancers. Along similar lines, MCL1 overexpression [317] or *Mcl1* ablation [318, 333, 334],
819 respectively, accelerates and suppresses MYC-driven lymphomagenesis. Lending further support to the
820 relevance of MCL1, prevalence and onset of MYC-driven lymphoma development were reduced by *Mcl1*
821 haploinsufficiency [318, 334], or B cell-specific deletion of *Mcl1* [335]. Of note, loss of one allele of *Mcl1* (but
822 not complete loss of the gene encoding BCL-$X_L$) also impairs the development of thymic lymphoma in
823 p53-deficient mice [336], which possibly explains the limited effect of the BCL-$X_L$ + BCL2 + BCL-W
824 inhibitor ABT-737 in these models of tumorigenesis [337]. The contribution of pro-survival BCL2 proteins
825 in the development of AML has been demonstrated by using mice reconstituted with genetically modified
826 bone marrow cells overexpressing MYC [338] and in human Burkitt lymphomas and diffuse large B-cell
827 lymphomas (Diepstraten, 2020,31985804). Notably, the acute genetic removal of *Mcl1* prevents the
828 sustained survival and proliferation of AML driven by diverse oncogenic fusion proteins [339].
829 Accordingly, MCL-1 specific BH3 mimetic drugs, such as S63845, are able to potently kill a diverse
830 range of lymphoid and myeloid malignant cells in culture and even in tumor transplanted mice [340].
831 Finally, ablation of *Bcl2l2* (leading to lack of BCL-W) limits the development of MYC-mediated B cell
832 lymphoma [341].

833 In support of the relevance of the intrinsic apoptosis pathway in tumorigenesis, several studies
834 demonstrated that the development of MYC-driven lymphoma and leukemia is accelerated in mice
835 lacking the genes encoding BAX [342], BIM [343, 344], BAD [345], BMF [345] or PUMA [346, 347, 348]. In particular,

these studies report that loss of only a single allele of *Bcl2l11* (encoding BIM) accelerates the development of lymphoma and this effect was reversed following full ablation of *Bcl2l1* (leading to lack of BCL-$X_L$) [344]. In this context, the presence of all prosurvival BCL2 proteins is shown to limit the impact of BIM in *Eμ-Myc* transgenic mice [349]. Instead, the combined ablation of the genes encoding BIM and p53 or PUMA and p53 accelerates MYC-driven lymphomagenesis [350]. This is in line with the evidence that loss of the genes encoding BAX or BIM augmented lymphomagenesis in p53-deficient mice [351, 352]. Of note, PUMA seems to exert a strong tumor-suppressive role in blood cancers, as shown by the evidence that *Bbc3* deletion accelerates the development of MYC-driven B-cell lymphomas and that *Eμ-Myc* lymphomas developing in PUMA-proficient mice display downregulated expression of PUMA [347, 348, 353]. On the contrary, the loss of the gene encoding NOXA does not accelerate MYC-driven lymphomagenesis, and the role of BIK in this murine lymphoma model is debated [347, 354]. Along similar lines, while CASP2 suppresses MYC-induced lymphomagenesis in mice [355], the tumor suppressive role of apoptosome components (**Box 1**) is questioned, as shown in lethally irradiated mice reconstituted with *Eμ-Myc* transgenic APAF1-deficient or CASP9-deficient fetal liver cells which showed no difference in the incidence of lymphoma compared to their wild-type counterparts [356]. This is consistent with the notion that APAF1 and caspase-9 function downstream of the commitment to cell death (MOMP) and therefore do not act as tumor suppressors [15].

Concerning other experimental animal models of induced hematological malignancies, the absence of PUMA (due to ablation of *Bbc3*) abrogated the development of both myelodysplasia, as shown in transgenic mice expressing a nucleoporin 98 (Nup98)-homeobox D13 (Hoxd13) fusion gene [357], and thymic T cell lymphoma induced by gamma radiation [358, 359]. The explanation for these surprising findings is based on the fact that the absence of PUMA prevents the extensive death of hematopoietic cells caused by gamma radiation, which causes mobilization and extensive proliferation of hematopoietic stem and progenitor cells, resulting in elevated replication stress and genetic instability and

lymphomagenesis. These findings show that inhibition of apoptosis does not only promote the development of hematological malignancies, but in certain conditions can do the exact opposite and prevent lymphoma development. The absence of NOXA, augments the development of chronic lymphocytic leukemia in T cell lymphoma breakpoint 1 (TCL1) transgenic mice [360] and accelerated the development of thymic T lymphoma induced by gamma radiation [358]. Moreover, conditional deletion of *Bcl2l11* in B cells (leading to the absence of BIM) accelerates the development of mantle cell lymphoma in mice driven by cyclin D1 (CCND1) over-expression [361]. Over-expression of MCL1 and/or BCL2 promotes the development of acute myeloid leukemia driven by lysine (K)-specific methyltransferase 2A (KMT2A, best known as MLL) fusion proteins [339, 362] and plasmacytoma driven by ABL proto-oncogene 1, non-receptor tyrosine kinase (ABL1) [363]. Conversely, the loss of one *Mcl1* allele suppresses the development of T cell lymphoma, as shown in models based on sequential low-dose irradiation or the expression of a transgene encoding an IL2 inducible T cell kinase (ITK)-spleen tyrosine kinase (SYK) fusion protein [364]. Finally, the absence of CASP2 accelerates lymphomagenesis in ataxia telangiectasia mutated (ATM)-deficient mice [365], but this may be due to the loss of the function of caspase-2 in mitotic cell division [366]. Lending support to the role of intrinsic apoptosis in hematologic malignancies, the BCL2 inhibitor venetoclax has entered clinical practice for the treatment of CLL as single agent or more effectively in combination with other therapeutic agents [31, 35, 36, 37]. Combinatorial regimens of BCL2 inhibition with epigenetic modulation have entered center stage in certain settings of AML [38, 367]. However, mechanisms of resistance of CLL and AML to venetoclax related to defects in p53 and the apoptotic network or deregulated energy metabolism have been described [368, 369, 370, 371]. Venetoclax-based regimens also display effectiveness in patients with high-risk myelodysplastic syndromes [372], thus suggesting a potential application in these syndromes [373, 374].

Significant work demonstrated a tumor suppressor role of the intrinsic apoptotic pathway in many cancers. For example, BCL2 overexpression accelerates the development of MYC-induced mammary

884 tumorigenesis [375]. A similar acceleration of tumor development has been described for the loss of genes
885 encoding BAX, BIM, CASP2 or PUMA in distinct models of breast cancer induced by expression or
886 overexpression of C3(1)/SV40 T-antigen, MYC, or erb-b2 receptor tyrosine kinase 2 (ERBB2, best
887 known as HER2) [376, 377, 378, 379]. At odds with these results, BCL2 overexpression in the mammary gland
888 suppresses the development of breast tumors driven by the administration of dimethylbenz(a)anthracene
889 [380]. This latter finding may be explained in a similar way as was mentioned for the suppression of
890 radiation-induced thymic T cell lymphoma development by over-expression of BCL-2 or loss of PUMA
891 (see above). Conditional deletion of the genes encoding BCL2 or BCL-$X_L$ in intestinal epithelial cells
892 delays the development of colorectal cancer driven by inflammation [381, 382], which is in line with the
893 evidence that the absence of PUMA (due to *Bbc3* deletion) exacerbates colorectal tumorigenesis as
894 shown in a mouse model of intestinal oncogenesis driven by colitis or APC, WNT signaling pathway
895 regulator (APC) [383]. Interestingly, doxorubicin-induced intestinal cytotoxicity requires PUMA but not
896 BIM, whereas the reverse is true for MYC-driven apoptosis in the gut, indicative of differential roles for
897 different BH3-only proteins in this tissue [384]. Intriguingly, treatment with BCL-$X_L$, but not BCL2-
898 targeting BH3 mimetics is sufficient to prevent intestinal tumorigenesis, suggesting that BCL-$X_L$ is the
899 crucial mediator of protection of early neoplastic cells in this model [385]. In agreement, earlier work
900 showed BCL-$X_L$ dependency in cell cultures derived from both colorectal and non-small cell lung
901 cancers [386, 387]. Moreover, a tumor suppressive effect is ascribed to BAX and CASP2 respectively in
902 murine models of brain cancer [388, 389] and lung cancer [390] development. In line with this evidence,
903 pharmacologic/genetic inhibition of MCL1 delayed tumor development in a mouse model of mutant
904 KRas-driven adenoma/adenocarcinoma [391]. In the same model, tumor progression was promoted by the
905 ablation of pro-apoptotic *Bok* [392]. Of note, there is evidence of a certain tissue-specificity in the epigenetic
906 regulation of *Bcl2* and *Mcl1*, such as the epigenetic mechanism centered on the deubiquitinase BRCA1
907 associated protein 1 (BAP1) [393] a tumor suppressor that is frequently mutated in certain cancers [394] and

has been associated with tumor aggressiveness and therapy resistance [395, 396]. Finally, age-related differences in the expression of pro-apoptotic members of the BCL2 family have been linked to the increased sensitivity of neonatal/childhood tissues, relative to adult counterparts, to chemotherapy and radiotherapy. This was causally linked to MYC-dependent expression of genes encoding BAX, BID and BIM, both in mice and humans [133].

Cancer-specific contributions were attributed to particular BCL2 protein family members. For example, deletion of *Bax* accelerates the development of MYC-induced pancreatic tumors [397] which was not seen with ablation of *Bak1* or *Casp3* [397, 398] but was achieved by BCL-$X_L$ overexpression [314, 399]. Likewise, BOK seems to be crucial in hepatocarcinogenesis, as demonstrated in a mouse model of diethylnitrosamine-induced liver cancer which was accelerated on a *Bok*$^{-/-}$ genetic background [300]. Using the same mouse model, enhanced hepatic cancer development was also demonstrated for the deletion of the genes encoding PUMA or CASP2 [400, 401]. Conversely, overexpression of BCL2 was shown to limit transforming growth factor-a (TGFA)-driven hepatic tumorigenesis [402, 403], perhaps because the death of certain cells in the liver causes massive mobilization and proliferation of progenitor cells, leading to acquisition of oncogenic lesions that drive tumorigenesis in a manner similar to radiation-induced thymic lymphoma development (see above). Finally, the transgenic overexpression of BCL-$X_L$ (but not BCL2) and the keratinocyte-specific deletion of *Bcl2l1* (leading to lack of BCL-$X_L$) respectively accelerates or limits chemically- and/or ultraviolet B (UVB)-induced skin tumorigenesis [404, 405, 406, 407]. It will be important to investigate and better understand why in certain settings inhibition of apoptotic cell death promotes tumorigenesis whereas it inhibits tumorigenesis in others.

**Autoimmune and inflammatory diseases.** There is substantial evidence linking intrinsic apoptosis to the development and progression of autoimmune diseases. However, the interpretation of these findings

should take into consideration the crosstalk between the apoptotic and inflammatory pathways and the fact that apoptotic caspases accelerate cell death and regulate its immunological manifestation.

The first evidence that defects in the intrinsic apoptosis pathway can cause the development of autoimmune disease was reported when over-expression of BCL-2 in B lymphocytes [408] or loss of BIM in all tissues [409] was shown to cause fatal systemic lupus erythematosus (SLE)-like disease. Consistent with a critical role for the intrinsic apoptotic pathway in preventing autoimmune disease, the combined loss of the genes encoding BAX and BAK1 in hematopoietic cells, achieved by transplantation of lethally irradiated wild-type mice with hematopoietic stem/progenitor cells from the livers of E14.5 *Bax*$^{-/-}$*Bak1*$^{-/-}$ embryos also causes fatal SLE-like disease [410]. In mouse models of rheumatoid arthritis, ablation of the genes encoding BIM, BID or BAD, but not the loss of *Bax* and *Bak1*, accelerated the emergence and increased the duration and severity of this disease [411, 412, 413]. Consistent with these findings, administration of a BIM mimetic suppressed inflammatory arthritis in mice [414]. Mice deficient for BAX as well as transgenic mice expressing XIAP display increased severity of autoimmune encephalomyelitis induced by immunization with myelin oligodendrocyte glycoprotein (MOG) [415, 416]. Similar results have been obtained in mouse models of autoimmune encephalomyelitis genetically engineered for hematopoietic cell-specific deletion of *Bcl2l11* (leading to BIM deficiency), or the neuron-specific overexpression of BCL2 [417, 418]. Consistent with the notion that inhibition of apoptosis can promote the development of auto-immune disease, inhibition of BCL-2, BCL-XL and BCL-W using the BH3 mimetic drug ABT-263 substantially reduced pathology in several mouse models of autoimmune disease, including scleroderma [419]. In apparent contrast with these results, studies using models of type 1 (autoimmune) or type 2 (non-autoimmune) diabetes revealed that deletion of *Bax* alone or combined loss of *Bax* and *Bak1* [420, 421], deletion of the gene encoding BIM, alone or together with the gene encoding PUMA [417, 422, 423, 424] or loss of BMF [425] protect pancreatic β cells from autoimmune destruction. Moreover, the absence of BIM prevented the emergence of type 1 diabetes in non-obese diabetic (NOD)

mice [417, 422], while ablation of *Trp53* in pancreatic β cells failed to halt cell death in multiple experimental models of diabetes [426].

Based on the studies described above, inhibiting or deleting pro-apoptotic proteins or genes can have conflicting effects on autoimmune disease progression. This may depend on the cell type in which the major effect on apoptosis occurs, e.g., the immune cells (attacking the target cell) or the target cell. Inhibiting cell death in the target cells would provide protection and may improve disease outcome, whereas inhibiting cell death in the immune cell may lead to an accumulation of immune cells and aggravation of the autoimmune disease. The distinction could be explored by studying tissue-specific deletion of apoptosis regulator genes.

In this context, there is evidence that inflammatory and autoimmune disorders may derive from increased survival of specific immune cell population. For instance, elevated levels of cytokines, such as GM-CSF, IL-3 and IL-5 in immune disorders have been associated with prolonged survival of neutrophils, eosinophils or basophils with a mechanism involving the upregulation of anti-apoptotic proteins MCL1, BCL-$X_L$ and Baculoviral IAP Repeat Containing 2 (BIRC2, best known as cIAP2) promoted by [427, 428, 429, 430, 431, 432, 433, 434]. Apoptosis also plays a relevant role in certain hemopathies, including beta thalassemia [435], Diamond-Blackfand anemia [436], and in the Cohen syndrome neutropenia [437]. BIM, BID and BAD have all been shown to influence survival in mouse models of septic shock , as their targeting confer protective effects from tissue damage of multiple organs [438, 439, 440], as well as in patients with severe sepsis [441]. On the contrary, the role of apoptotic caspase in septic shock is contentious [54, 73, 442, 443]. The precise impact of apoptosis in widespread inflammation during sepsis requires further investigation.

Concerning other inflammatory disease, while broad-spectrum caspase inhibition reportedly protected rats against severe acute pancreatitis [444], activation of intrinsic apoptosis appears to attenuate the severity of this disease by limiting inflammation, as shown *in vivo* in a pancreatitis mouse model lacking XIAP

977 [445]. These data reinforce the notion that inhibiting (apoptotic) cell death may exacerbate unwarranted
978 inflammatory reactions that contribute to the pathology of various autoimmune and inflammatory
979 disorders. In line with this notion, chronic colitis driven by dextran sulfate sodium in mice manifests with
980 increased (rather than decreased) severity in BID- or BIM-deficient hosts as compared to their wild-type
981 littermates, at least in part owing to immune dysregulation [446, 447]. Similarly, inhibition of BCL2 and/or
982 BCL-$X_L$ reduces inflammation and ameliorates experimental colitis [448, 449], an effect that was abrogated
983 by concomitant deletion of the gene encoding BIM [449]. PUMA-deficient mice displayed reduced levels
984 of apoptosis amongst intestinal epithelial cells but not reduced inflammation in an experimental model
985 of colitis [450]. Corroborating the specific relevance of PUMA for intestinal homeostasis, mice deficient
986 for PUMA but not *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice were protected against the gastrointestinal side effects of
987 radiotherapy, at least in part due to increased survival of intestinal stem/progenitor cells [451, 452]. Moreover,
988 the absence of PUMA conferred protection to intestinal epithelial cells in mouse models of hypertensive
989 gastropathy [453], ulcerative colitis (UC) [454] and intestinal ischemia/reperfusion [455]. In the latter model,
990 transgenic BCL2 expression limited intestinal epithelial cell death [456]. On the other hand, deficiency in
991 XIAP, an inhibitor of CASP3, CASP7, CASP9, causes X-linked lymphoproliferative syndrome 2 with
992 one-third of these patients suffering from severe and therapy-refractory inflammatory bowel disease [457,
993 458, 459, 460]. Absence of XIAP also results in enhanced TNF production and TNF-R1/TNF-R2 targeting of
994 TLR5-expressing Paneth cells and dendritic cells, leading to ileitis and dysbiosis [461]. In this context, it is
995 interesting to note that CASP3- or CASP7-deficient mice display an altered gut microbiome [462], which
996 may play a hitherto unexplored role in multiple autoimmune and inflammatory disorders beyond
997 intestinal conditions. However, recently it was found that under steady state conditions absence of
998 CASP3 and CASP7 in the intestinal epithelial cells apparently does not affect the microbiome neither
999 cause spontaneous inflammation, suggesting that apoptosis may be dispensable for intestinal epithelium
1000 turnover and homeostasis at steady state [463].

**Infectious diseases**. Activation of RCD constitutes a protective mechanism against many microbial infections by eliminating infected cells and potentiating the anti-infective immune response. Accordingly, both viruses and bacteria have developed multiple strategies to overcome or disable host intrinsic apoptosis thus improving survival of both the host cells and the infectious organisms [464, 465 Waguia Kontchou, 2022 35397654 Waguia Kontchou, 2022 35397654 Waguia Kontchou, 2022 35397654 Waguia Kontchou, 2022 35397654]. Mice with loss of one allele of the genes encoding BCL-$X_L$ displayed reduced pathology and had improved survival rates when challenged with Japanese encephalitis virus (JEV), as compared with wild-type mice. This was attributed to compromised viral propagation within JEV-infected cells succumbing to intrinsic apoptosis [466]. There is also evidence of a contribution of BAX and BAK1 to the response to murine cytomegalovirus (MCMV) infection. In particular, the MCMV genome encodes inhibitors of BAK1 (m41.1 protein) and BAX (m38.5 protein), promoting viral replication by inhibiting the induction of intrinsic apoptosis in infected cells [467 Fleming, 2013, 23468630 Fleming, 2013, 23468630 Fleming, 2013, 23468630 Fleming, 2013, 23468630, 468 Manzur, 2009, 18949000 Manzur, 2009, 18949000 Manzur, 2009, 18949000 Manzur, 2009, 18949000]. Supporting the requirement of the inhibition of intrinsic apoptosis for optimal *in vivo* MCMV dissemination, the titers of m41.1-deficient viruses were higher in salivary glands and other organs in *Bak1*$^{-/-}$ mice as compared to wild-type animals [467 Fleming, 2013, 23468630 Fleming, 2013, 23468630 Fleming, 2013, 23468630 Fleming, 2013, 23468630]. Intrinsic apoptosis also protects against bacterial infections, as demonstrated by the lethal course of disease in *Bbc3*$^{-/-}$ mice (which lack PUMA) after *Streptococcus pneumoniae* infection [469]. Such an effect has been attributed to insufficient immune-mediated bacterial clearance because of an increased neutrophil lifespan in the absence of PUMA-mediated apoptosis.

However, in certain other contexts, excessive activation of the intrinsic apoptosis pathway has been reported to drive, rather than prevent, microbial disease pathogenesis and lethality. For example, loss of *Xiap* increased the susceptibility of mice to *Shigella* infection, manifested with coalescing necrotic areas and a high bacterial burden in the liver and this was associated with an inefficient immune-mediated

resolution of the bacterial infection [470]. Although at least part of this effect may be due to the requirement for XIAP to activate NOD signaling, rather than its ability to inhibit caspases [458, 470, 471]. Moreover, mice lacking the genes encoding BIM and NOXA (*i.e.*, *Bcl2l11*$^{-/-}$*Pmaip1*$^{-/-}$ mice) displayed high resistance to the challenge with high doses of *Listeria monocytogenes*, as shown by a decreased bacterial burden and low apoptosis induction in the spleen [472]. The overexpression of BCL2 in the hematopoietic compartment increased the survival of mice infected with Ebola virus [473], while deletion of *Bok* increased resistance of lung epithelial cells to apoptosis induced by SARS-CoV-2 virus membrane (M) protein [474]. Intriguingly, this study showed that the SARS-CoV-2 M protein, induced BOK to trigger apoptosis in the absence of BAX and BAK1 [474]. In another example, conditional deletion of *Casp3* in the murine intestinal epithelium conferred protection from pathogenic *Salmonella enterica*, and this was attributed to a reduction in cell death-induced nutrients that are critical for sustaining bacterial growth [475]. Finally, *Casp3*$^{-/-}$ mice subjected to intracranial inoculation of reovirus type 3 (strain Dearing) displayed limited injuries in the central nervous system (CNS) and enhanced survival compared to wild-type mice [476]. As discussed above, the interpretation of the infection phenotypes using CASP3-, CASP7- and/or CASP9-deficient mice needs particular caution because of the crucial roles of these caspases in modulating immune and inflammatory responses [242, 243, 244]. Notably, there is evidence for a role of specific regulators of apoptosis in the response to infection with human herpes simplex virus 1 (HSV-1). Thus, on the one hand, a significant accumulation in total leukocyte and CD8$^+$ T cells was observed in mice deficient for BIM and PUMA upon infection with HSV-1 [477], which is in line with a role of these BH3-only proteins in controlling the survival of lymphoid and myeloid cells [409, 478, 479]. On the other hand, mice deficient for NOXA, BAD or BID were reported to mount a normal CD8$^+$ T cell immune response to HSV-1 infection [477]. Some of the contradictory results reported may arise from the divergent effects of inhibition or promotion of apoptosis on immune cells versus other cell types affected by the infectious disease, a distinction that cannot be addressed using mice in which apoptotic regulators have been deleted in the

germline. In this context it is noteworthy that myeloid cell-specific deletion of the gene encoding BCL-$X_L$ or its inhibition using BH3 mimetic drugs massively reduced bacterial burden in the lung and extended the survival of mice infected with Legionella bacteria [480]. This indicates that BH3 mimetic drugs might be effective for the treatment of intra-cellular bacterial infections.

**Other diseases.** Pro-apoptotic BCL2 proteins and caspases have also been implicated in disorders affecting other tissues/organs, such as skeletal muscle and lungs. For instance, the conditional ablation of *Bax* and *Bak1* protected mouse skeletal muscles against pressure-induced injury [481]. Similar results have been obtained in rats receiving Z-VAD-FMK after being subjected to muscular compression or blunt injury [482, 483]. Moreover, deletion of *Casp3* or CASP3 inhibition with Ac-DEVD-CHO limited muscular damage and atrophy in experimental models of plaster-mediated immobilization [484, 485]. In mouse models of catabolic disorders, muscle wasting due to protein degradation was decreased by lentiviral expression of XIAP [486, 487], although whether this effect reflects the inhibition of intrinsic apoptosis needs further confirmation. Finally, *Casp3*$^{-/-}$ mice were protected against denervation-induced muscular atrophy [488], while expression of a dominant-negative variant of CASP9 improved the neuromuscular activity in a transgenic mouse model of slow-channel syndrome [489].

In a mouse model of oxidant-induced lung injury, the tissue-specific ablation of *Bax* and *Bak1* but not that of the genes encoding BID, BIM, NOXA or PUMA protected lung epithelial cells from degeneration [490]. Among the anti-apoptotic BCL2 proteins, BCL2A1 (best known as A1) seems to exert a crucial role in this setting, as *Bcl2a1* deletion aggravated lung injury in mice subjected to hyperoxia [491], while lung-specific overexpression of BCL2 did not confer protection to mice exposed to excessive oxygen supply [492]. That said, no critical cytoprotective effect of A1 was seen in acute lung inflammation and peritonitis [493]. Intrinsic apoptosis has also been reported to be involved in pulmonary fibrosis [494]. *Bid*$^{-/-}$ mice displayed decreased levels of pulmonary fibrosis after intra-tracheal bleomycin administration [495]. In

apparent contradiction, in the same model of fibrotic pulmonary damage, similar protection was reported in mice deleted for *Bcl2* [496] or in animals treated with inhibitors of BCL2 [496] or caspases [497, 498]. Along similar lines, ablation of *Bid* limited acute lung injury in mice induced by exposure to lipopolysaccharide [499]. Moreover, CASP3 depletion using short-hairpin RNAs (shRNAs) protected the lungs of mice subjected to pulmonary ischemia/reperfusion [500], a protection further strengthened when necroptosis was concomitantly also suppressed [501]. BCL2 overexpression or caspase inhibition protected rodents subjected to lung transplantation [502, 503]. This is in line with the notion that delivery of the caspase inhibitor Z-VAD-FMK to rodents ameliorated lung injury developing as a consequence of severe acute pancreatitis or lipopolysaccharide administration [504, 505] but not as a result of pneumovirus infection [506]. In the latter case, lung damage was exacerbated by Z-VAD-FMK, perhaps due to increased inflammation downstream of necroptotic RCD [506].

The studies briefly summarized above illustrate that components of the intrinsic apoptosis pathway can be part of the pathogenic mechanism of disease, and, in certain cases, this may offer the opportunity for therapeutic intervention. It is important to note though that in many pathogenic processes intrinsic apoptotic cell death is the endpoint, and simply inhibiting it will not be curative. If the cells continue being exposed to the initiating insult, they will likely undergo less regulated forms of cell death. However, inhibiting the intrinsic apoptotic cell death may buy time to remediate the factors that are damaging the cells in first place. Ischemia and hypoxia, in cases where the ensuing cell death has a substantial intrinsic apoptotic component, are examples. If cells in the ischemic region were kept alive until adequate circulation was restored, therapeutic benefits might be achieved. Other examples include metabolic disorders, which may be amenable to correction, and traumatic injury, where healing might be supported by inhibiting apoptosis. It would be worth concentrating on inhibiting intrinsic apoptotic cell death in conditions where the initiating tissue insults can be (at least partially) reversed. In contrast, failure to undergo intrinsic apoptosis is the initial pathogenic step or a contributing factor in certain

malignancies. Here, the induction of apoptosis, for example by using BH3 mimetic drugs [33, 34], targets the pathogenesis directly.

## Extrinsic apoptosis in disease

The molecular apparatus for extrinsic apoptosis is described in **Box 5** and illustrated in **Figure 4.** Unlike the intrinsic apoptotic pathway, DR-induced apoptosis is not required for embryonic or fetal development but plays a critical role in adult tissue homeostasis, as detailed in **Box 6** and **Box 7**. Of note, various components of the extrinsic pathway of apoptosis are involved in the etiology of multiple human disorders, although (1) with a considerable degree of context-dependency, and (2) with an effect not necessarily linked to the activation of apoptosis but often due to the role of DR signaling in necroptosis and inflammation, as outlined below.

**Neurological diseases.** Although numerous studies investigated FAS and TNF-R1 signaling in the pathogenesis of multiple neurological diseases, the precise role of extrinsic apoptosis remains unclear (**Figure 5**). Loss-of-function mutations of FAS ligand (*Fasl*) as well as *Fas* silencing prevented moto-neuron loss in mouse models of ALS driven by defect in superoxide dismutase 1, soluble (SOD1) [507, 508]. Moreover, the lack of TNF did not affect motor neuron loss and mouse survival in this model [509], while binding of the TNF receptor superfamily member 1B (TNFRSF1B, best known as TNF-R2) appeared to mediate neuroprotective effects [510]. As an additional layer of complexity, TNF mediates neuroprotective functions in wobbler mice - another mouse model of ALS that carries a point mutation in VPS54 GARP complex subunit (*Vps54*), at least in part by promoting the upregulation of ADAM metallopeptidase domain 8 (ADAM8) [511]. CASP8 has not yet been implicated in the pathogenesis of ALS, and non-apoptotic forms of FAS-driven RCD may play a predominant role in this context. For example, FAS

stimulation reportedly triggered the demise of motoneurons in mouse models of ALS by aggravating endoplasmic reticulum stress [512]. Similarly, cleavage of BID by CASP1 (and not CASP8) appears to contribute to neurodegeneration in transgenic mice expressing a mutant form of human *SOD1* [513]. However, the precise contributions of endoplasmic reticulum stress and CASP1 in ALS and other motoneuron disorders remain to be elucidated.

The ability of TNF-R1 signaling to influence neurodegenerative conditions involves not only the induction of extrinsic apoptosis but also the activation of an inflammatory response. In distinct murine models of AD, deletion of *Tnf*, modification of its untranslated region (UTR) as well as pharmacological or genetic removal of TNF reduced plaque formation, resulting in attenuated neurological deficits [514, 515, 516, 517, 518, 519, 520, 521]. Mechanistic studies in mice and monkeys revealed that TNF-R1 activation stimulates the protein activator of interferon-induced protein kinase EIF2AK2 (PRKRA) network [522], which is linked to PD in humans [523]. Moreover, TNF-R1 signaling has been shown to favor microglial reactivity during neurodegeneration, culminating in neuronal loss [524]. Amelioration of disease was seen in mouse models of AD upon genetic or pharmacological inhibition of TNF-R1 [525, 526]. AD-associated neuroinflammation seems to depend on TNF-induced necroptosis rather than extrinsic apoptosis [527, 528]. Unexpectedly, AD pathogenesis was shown to be enhanced in mice bearing a co-deletion of the TNF receptor superfamily member genes *Tnfrsf1a* and *Tnfrsf1b* [529], a phenotype that appears to impinge on a complex network of mutual interactions between TNF-R1 and TNF-R2 signaling [530]. Such a network may also contribute to PD pathogenesis. Genetic ablation of *Tnf* or *Tnfrsf1a* plus *Tnfrsf1b* (leading to the lack of both TNF receptors), as well as pharmacological inhibition of TNF, were reported to protect dopaminergic neurons in murine models of PD following the administration of 1-metil 4-phenyl 1,2,3,6-tetraidro-piridina (MPTP) or 6-hydroxydopamine [531, 532, 533, 534]. Notably, in the above-mentioned experimental settings, TNF is thought to induce neuronal death *in vivo* by promoting microglia reactivity

[535] with a complex interaction between TNF-R1 and TNF-R2 signaling [536]. Importantly, clinical evidence from AD patients subjected to perispinal administration of the TNF blockers infliximab or etanercept suggests that the inhibition of TNF can ameliorate AD [537, 538]. In contrast, a dominant-negative variant of TNF failed to protect mice against neuronal degeneration in a model of HD [539], suggesting that this approach may not be viable in patients with HD.

TRAIL/TRAIL-R signaling has also been implicated in the onset and progression of AD [540, 541]. Specifically, in a mouse model of AD, neutralization of TNF superfamily member 10 (*TNFSF10*, best known as TRAIL) with a monoclonal antibody resulted in decreased neuroinflammation and a reduction in cognitive defects [540]. However, these findings were not extensively validated. Similarly, the impact of FASL-FAS signaling on neurodegenerative conditions is debated. Indeed, lymphoproliferative (*lpr*/*lpr*) mice, which lack FAS [542] and to a lesser extent generalized lymphoproliferative disease (*gld*/*gld*) mice, which lack FASL [542], are particularly susceptible to neuronal degeneration driven by MPTP [543]. However, contrasting results have been obtained in another study of MPTP-treated mice with FAS deficiency [544, 545]. In this context, FAS-associated factor 1 (*Faf1*, a FAS binding protein that can initiate or enhance apoptosis) was found increased in midbrain in murine models of PD [546]. Moreover, a reduction in *Faf1* expression reduced MPTP-induced dopaminergic cell loss [547]. Such an apparent discrepancy in results may originate from the pleiotropic role of FAS in apoptosis and inflammation and other pro-survival/regenerative signals.

CASP8 activation has been detected in the brain of both AD [548] and HD [549] patients as well as in dopaminergic neurons of MPTP-treated mice and PD patients, a setting in which BID cleavage has also been documented [119]. This is in line with the ability of the broad-spectrum caspase inhibitor Q-VD-OPH to inhibit BID cleavage and mediate neuroprotection in MPTP-treated mice and rats [550]. Of note, CASP8 was also reported to promote microglia reactivity potentially leading to neuronal loss [551, 552, 553]. In this

context, genetic loss or pharmacological inhibition of CASP8 attenuated neurotoxicity by reducing microglial reactivity, thus extending survival of neurons, at least in part by stimulating the necroptotic death of activated microglial cells [551, 552, 553]. Consistent with this notion, *Casp8* deletion in myeloid cells protected mice from MPTP-mediated neurotoxicity [554], suggesting that CASP8 inhibitors may be harnessed for the treatment of neurodegenerative conditions. Corroborating this idea, a pharmacological inhibitor of TNF-R1-associated death domain protein (TRADD) protected mice from disease in a model of AD-like proteinopathy driven by mutant tau [555]. However, pharmacological inhibition of CASP8 only partially prevented neuronal alterations in other models of AD [108] and even exacerbated dopaminergic neuronal necrosis in mice developing PD upon MPTP administration [556]. Moreover, rare *CASP8* loss-of-function variants have been associated with AD in a large cohort of patients [557]. Thus, the precise contribution of CASP8 signaling to neurodegenerative disorders and whether this relates to its function in driving extrinsic apoptosis, inhibiting necroptosis or promoting inflammatory cytokine production remains to be formally defined. Concerning dependence receptors, Netrin 1 (NTN1) upregulation was shown to confer neuroprotection in murine models of PD, suggesting a potential role of dependence receptors in neurodegenerative disease [558].

DR signaling has also been shown to contribute to neuronal death and inflammation in preclinical models of CNS trauma. In a compression model of spinal cord injury, mice with loss of FAS (i.e., *lpr/lpr* mice) as well as mice treated with FASL blockers displayed reduced post-traumatic neuronal degeneration and inflammation coupled to considerable functional improvement [559, 560, 561]. This beneficial effect also involved reduced engagement of the intrinsic apoptosis pathway [562]. Myeloid cell-specific deletion of *Fasl* promoted neuronal regeneration and functional recovery in mice subjected to spinal cord injury [563]. A similar functional improvement after spinal injury was observed in mice with conditional deletion of *Tnf* in macrophages and neutrophils but not in microglia [564]. Moreover, neuroprotection and limited neuroinflammation have been documented in FAS-deficient *lpr/ lpr* mice subjected to traumatic brain

injury [565] as well as in mice subjected to experimental spondylotic myelopathy and exposed to FASL-neutralizing antibodies [566]. Studies on mice with loss of *Fas* and *Tnfrsf1a* revealed at least some redundancy between FAS and TNF-R1 signaling in the context of experimental brain trauma [567, 568, 569, 570, 571]. Furthermore, TNF inhibition reduced damage in mice or rats experiencing spinal cord injury [572, 573, 574], and also reduced the appearance of signs of autonomic dysreflexia, a cardiovascular disease associated with high-level spinal cord injury [572, 575]. Interestingly, some of these studies point to a neuroprotective function for TNF-R2 [567, 569, 571], which is in line with at least some results from models of ALS [510, 530]. Moreover, several studies question a purely detrimental effect of TNF signaling in these experimental settings [576, 577, 578, 579]. In particular, TNF was reported to support, at least in part, regeneration and long-term functional recovery in mice exposed to traumatic brain injury [577, 578, 579]. Conversely, TRAIL neutralization stands out as a promising strategy to promote neuronal regeneration and functional recovery based on mice with spinal cord injuries [580, 581]. In this context, injured neurons seem to undergo Fas-associated via death domain (FADD)- and CASP8-dependent RCD [582]. Accordingly, *Casp8* deletion or transgenic expression of a FADD inhibitor (the glycoprotein P45) protected mice after spinal cord injury [583, 584]. Similarly, transgenic expression of a dominant negative mutant of FADD (FADD-DN) limited motoneuron loss in mice undergoing axotomy [585].

Components of the molecular apparatus for the extrinsic pathway are associated with disorders of the visual system, again in the context of both exacerbated cell death and inflammation. Thus, in mouse and rat models of optic nerve injury, deletion of *Tnfrsf1a* (encoding TNF-R1) or inhibition of CASP8 with Z-IETD-FMK inhibited the degeneration of retinal ganglion cells [586, 587]. Moreover, the absence of TNF-R1 (but not the absence of TNF-R2) attenuated neurodegeneration in a mouse model of retinal ischemia, despite neuronal survival not being improved [588]. Along similar lines, deletion of *Tnf* [589] as well as inhibition of FAS [590] or TNF [591, 592] protected mice against retinal ganglion cell death in a model of glaucoma. Similar neuroprotective effects were documented for the conditional deletion of *Casp8* in

astrocytes or intra-ocular Z-IETD-FMK administration [593]. In this context, the conditional inducible ablation of *Casp8* from endothelial cells reduced postnatal retinal angiogenesis and pathological neovascularization in a mouse model of oxygen-induced retinopathy [594] (note that ablation of *Casp8* in endothelial cells is embryonically lethal [595]; *see* **Box 7**). Moreover, CASP8 inhibition could prevent experimental neovascularization of the cornea [596]. Finally, TRAIL neutralization protected the retinal tissue from damage associated with AD in a mouse model [597].

Experimental models of ischemic stroke and hemorrhage revealed a role of DR signaling in the pathophysiology of brain damage. In models of focal ischemia induced by middle cerebral artery occlusion, *lpr*/*lpr* as well as *gld*/*gld* mice (deficient for FAS or FAS ligand, respectively) displayed decreased infarct size and neuroinflammation [598, 599, 600]. Robust neuroprotection was also observed in *lpr*/*lpr* mice subjected to neonatal hypoxia-ischemia [601], as well as in *lpr*/*lpr* and *gld*/*gld* mice subjected to hyperoxia [602]. Accordingly, inhibition of FAS or FASL exerted neuroprotective effects in an experimental murine model of stroke [603, 604]. Likewise, TRAIL neutralization limited brain injury in rats and mice subjected to middle cerebral artery occlusion [600, 605] or transient ischemia-reperfusion [606]. Moreover, despite some contention in this respect [607, 608, 609, 610], abrogation of TNF/TNF-R1 signaling by genetic or pharmacological means prevented brain injury in rodent models of intracerebral hemorrhage [611] and focal cerebral ischemia [612, 613, 614, 615, 616, 617, 618, 619, 620]. Further corroborating a pathogenic role of DR signaling, transgene-driven expression of dominant-negative CASP8 mutant and of FADD-like apoptosis regulator (CFLAR; best known as c-FLIP) attenuated brain damage after middle cerebral artery occlusion [621, 622]. This is in line with the ability of CASP8 to drive BID activation upon focal cerebral ischemia [196], as well as with the neuroprotective effects afforded by pharmacological CASP8 inhibitors seen in mice experiencing subarachnoid hemorrhage [623] or mice and rats subjected to focal cerebral ischemia [624, 625]. Importantly, FADD and CASP8 expression and/or activation have also been associated with ischemic stroke in humans [626, 627].

Perhaps surprisingly, TNF appears to protect mice against experimental seizures, not only through the engagement of TNF-R2 but also through TNF-R1 signaling [610, 628, 629, 630, 631, 632, 633] and consequent modulation of NF-κB [634, 635]. Conversely, *lpr*/*lpr* mice [636], mice with neuron-specific deletion of the gene encoding TNF-R1 [637] as well as mice and rats treated with Z-IETD-FMK [584, 638, 639] displayed a reduced sensitivity to experimental seizures, pointing to a detrimental role for apoptotic DR signaling in this condition. Precise mechanisms through which TNF-R1 signaling promotes anti-apoptotic and anti-inflammatory effects in the context of excitotoxic insults remain unclear.

**Cardiovascular disorders.** Data from preclinical models of ischemic and non-ischemic conditions indicate the involvement of FASL, TRAIL and TNF in the onset and progression of myocardial infarction with reperfusion and other heart diseases. In particular, both *lpr*/*lpr* mice (lacking FAS), as well as hearts isolated from these animals, displayed reduced cardiomyocyte death and infarct area upon experimental ischemia-reperfusion [640, 641]. Nonetheless, no protection against ischemia-reperfusion was found in hearts from *Fas*$^{-/-}$ or *Fasl*$^{-/-}$ mice [642]. However, supporting the therapeutic potential of the inhibition of DR signaling for the management of myocardial infarction, FASL-neutralizing antibodies conferred cardioprotection, limited inflammation, and improved cardiac function in mice experiencing cardiac ischemia-reperfusion [643, 644, 645]. Likewise, TRAIL blockade protected monkeys, pigs, and rats against experimental infarction by increasing cardiomyocyte survival and reducing inflammation [646]. This is in line with the predictive value of the levels of TRAIL as a biomarker for heart failure in patients [647, 648]. Of note, TRAIL has also been reported to exert apoptosis-independent roles in cardiomyocyte growth and heart hypertrophy [649] as well as in angiogenesis and neovascularization upon experimental hindlimb ischemia [650]. Similar to neurological conditions, while TNF-R2 signaling appears to exert cardioprotective effects, the engagement of TNF-R1 drives cardiac hypertrophy, inflammation and cardiomyocyte loss [651, 652, 653, 654, 655, 656, 657, 658]. The opposite outcome of TNF-R1 *vs* TNF-R2 signaling has been invoked to explain the clinical failure of TNF blocking agents in patients with chronic heart

failure [659], despite encouraging preliminary findings [660, 661], as well as cardiotoxic effects associated with the use of TNF blockers in patients with rheumatoid arthritis [662]. Confirming the involvement of extrinsic apoptosis in cardiac diseases, cardiomyocyte-specific deletion of *Fadd* in mice improved cardiomyocyte survival and heart function after ischemia/reperfusion [663]. Accordingly, haploinsufficiency of the gene encoding c-FLIP increased infarct area and aggravated cardiac dysfunction in mice subjected to myocardial infarction, while the cardiomyocyte-specific overexpression of c-FLIP attenuated pathology [664, 665]. Cardioprotection has been observed in a mouse model of ischemia/reperfusion upon shRNA-mediated CASP8 depletion [666] or treatment with the CASP8 inhibitor Q-LETD-OPh [667]. Moreover, transplantation of *CASP8*$^{-/-}$ cells did not increase neovascularization in wild-type mice subjected to hindlimb ischemia [668], in line with a crucial role of CASP8 in the maintenance of endothelia in healthy conditions [595] (*see* **Box 7**). That said, combined pharmacological inhibition of apoptosis and necroptosis exerted greater cardioprotection than monotherapy in myocardial ischemia-reperfusion injury [669], suggesting the involvement of multiple RCD pathways in cardiovascular disorders.

FASL neutralization has been reported to improve cardiomyocyte survival and cardiac function in a model of cirrhotic cardiomyopathy [670]. Conversely, a cardioprotective effect of TRAIL and TNF was observed in mice developing cardiomyopathy upon the deletion of apolipoprotein E (*ApoE*) [671] or desmin (*Des*) [672], respectively. Both FASL deficiency and administration of CASP8 inhibitors decrease tissue inflammation and aneurysm formation in mice subjected to $CaCl_2$-induced abdominal aortic aneurysms [673]. A potential role of extrinsic apoptosis in gradual cardiomyocyte attrition during heart failure with reduced fraction was also reported in a transgenic mouse model of inducible CASP8 overexpression [674]. Concerning TNF receptors, deletion of *Tnfrsf1b* resulted in increased cardiomyocyte death and hypertrophy induced by isoproterenol [675]. In contrast, deletion of *Tnfrsf1a* (but not *Tnfrsf1b*) was shown to be cardioprotective in murine models of vascular thrombosis [676], and heart failure based on angiotensin II administration [677]. Similar cardioprotection to angiotensin II was reported after silencing of *Tnfrsf1a*

[678]. In line with these findings, *Cflar*$^{+/-}$ mice (which lack c-FLIP) displayed increased sensitivity to cardiac injury upon angiotensin II administration [679].

FASL and TNF have also been reported to promote cardiac maladaptation and hypertrophy in models of pressure overload [680, 681, 682, 683, 684]. Consistent with this notion, TNF inhibition [685] or transgenic c-FLIP overexpression [686] limited experimental heart hypertrophy driven by hypertension. Moreover, treatment with etanercept reduced cardiac fibrosis in a diet-induced mouse model of obesity [687]. Conversely, both FAS and TNF receptor superfamily member 10b (TNFRSF10B, best known as TRAIL-R2 or mTRAIL-R) were reported to protect mice against atherosclerosis, at least in part, by modulating TNF superfamily member 11 (TNFSF11, best known as RANKL) signaling [688, 689, 690, 691, 692], while the impact of TNF on experimental atherosclerosis remains a matter of debate [693, 694, 695, 696]. Finally, pharmacological inhibition of TNF prevented cardiotoxicity induced by doxorubicin in mice [697, 698, 699]

**Renal conditions.** FASL, TNF and TRAIL have all been implicated in the development of acute kidney injury by driving the activation of both extrinsic apoptosis and inflammation. Loss-of-function mutations in *Fasl*, inhibition or depletion of FASL [700, 701, 702] as well as *Fas* [703] or *Tnf* [704] silencing, TNF neutralization [705, 706], or TRAIL blockade [707] exerted nephron-protective effects in mouse models of renal ischemia/reperfusion. Generation of chimeric mice reconstituted with spleen cells from *gld*/*gld* mice (lacking FAS ligand) revealed a particular impact of FASL signaling in the hematopoietic compartment on ischemic acute kidney injury [701]. However, some functional overlap between DRs has also been reported. Indeed, while one study suggested that FASL neutralization was more effective than *Tnfrsf1a* deletion (leading to lack of TNF-R1) in preventing renal inflammation and cell death after acute kidney injury [700], another study reported that the neutralization of TNF but not FASL prevented tubular apoptosis and renal atrophy upon ischemia/reperfusion injury [705].

TRAIL blockade reportedly protected mice against renal damage after full-thickness scald burn, burn of all layers of the skin including epidermis and dermis [708], while TNF inhibition limited nephrotoxicity, in mice treated with cisplatin [709], and acute tubulointerstitial nephritis, in cancer patients administered with immune checkpoint inhibitors [710]. TNF neutralization also reduced tubulointerstitial fibrosis and renal injury in a mouse model of unilateral urethral obstruction [711, 712]. Contesting these findings, *Tnf*$^{-/-}$ mice showed increased fibrosis at later stages of ureteral obstruction [713]. This apparent discrepancy may reflect the distinct contribution of TNF-R1 and TNF-R2 signaling to different stages of renal fibrosis driven by urethral obstruction [714]. Conversely, experiments with *lpr*/*lpr* mice subjected to unilateral urethral ligation demonstrated a limited impact of FAS signaling to pathology [715]. The involvement of CASP8 in acute kidney injury is debated. While *Casp8* and *Casp3* protected kidneys against damage induced by renal ischemia, increasing the survival of these mice [703, 716], such a nephroprotective effect was not observed after treatment with the broad-spectrum caspase inhibitor Z-VAD-FMK [717], potentially due to caspase inhibition promoting necroptosis after DR stimulation. In line with this notion, chemical inhibitors of receptor-interacting serine/threonine kinase 1 (RIPK1) as well as deletion of *Ripk3* exerted robust nephroprotection in mouse models of ischemia/reperfusion [717, 718]. However, combined deletion of *Casp8* and *Ripk3* did not extend the beneficial effects of the genetic loss of *Ripk3* and was associated with a more pronounced demise of tubular epithelial cells by intrinsic apoptosis [719].

DR activation has also been associated with chronic kidney disorders, but evidence involving CASP8-mediated apoptotic death is lacking. The conditional deletion of *Tnf* from macrophages [720], as well as the administration of TNF inhibitors [720, 721, 722, 723], were reported to mediate beneficial effects in murine models of diabetic nephropathy. Conversely, the impact of TRAIL on this renal condition remains unclear [724, 725, 726], like that of TNF on polycystic kidney disease [727, 728]. As for glomerular inflammation, *gld*/*gld* mice (lacking FAS ligand), as well as wild-type mice treated with TNF blockers, displayed

reduced tissue damage during crescentic glomerulonephritis [729, 730, 731, 732]. Indeed, balanced TNF-R1 and TNF-R2 signaling appeared to be critical for mice to resist experimentally induced glomerulonephritis [733, 734, 735, 736, 737, 738]. This may explain apparently discrepant findings obtained with TNF-targeting measures.

**Hepatic disorders.** TNF-deficient mice, as well as rodents treated with TNF inhibitors, presented with attenuated liver injury and apoptosis upon experimental ischemia/reperfusion, resulting in improved survival [739, 740, 741]. Of note, this beneficial effect could not always be recapitulated in *lpr*/*lpr* and *gld*/*gld* mice, lacking FAS or FAS ligand, respectively [741]. Similarly, FAS inhibition, FASL neutralization, as well as administration of low-dose TNF (as a pre-conditioning maneuver) have been shown to protect the liver against ischemia/reperfusion injury by reducing hepatic cell apoptosis and/or inflammation [742, 743, 744]. Protection of the liver from ischemia/reperfusion has also been observed in mice deficient for TRAIL [745], as well as upon the conditional knockdown of CASP8 or CASP3, the combined deletion of *Casp8* and *Ripk3*, and the transgenic expression of a BID mutant that cannot be cleaved by CASP8 [283, 746, 747].

*Lpr*/*lpr* mice lacking FAS [748], *Tnfsf10*$^{-/-}$ mice (which lack TRAIL) [286], as well as animals exposed to TRAIL blockers [749], were protected against acetaminophen-induced liver damage, in line with the notion that FAS signaling and TRAIL receptor exacerbate acetaminophen hepatotoxicity [750]. Along similar lines, the hepatocyte-specific deletion of the gene encoding c-FLIP enhances liver injury and fibrosis induced by treatment with $CCl_4$ or thioacetamide [751]. Moreover, a large body of evidence demonstrates that the abrogation of extrinsic apoptosis protects mice against fulminant hepatitis and hemorrhage in the liver induced by FASL and TNF. This has been achieved with strategies including (but not limited to) FADD blockade [752, 753], *Casp8* [595, 754, 755] or *Fadd* [756] ablation, and *Casp8* silencing [757]. Accordingly, hepatocyte-specific deletion of *Cflar* augmented liver damage in mouse model of acute hepatic injury

[758]. Consistent with the notion that engagement of the intrinsic apoptotic pathway is critical for DR induced cell killing in the liver, *Bid*$^{-/-}$ mice resist fatal hepatitis and hepatocytes apoptosis induced by FAS or TNF [278, 282, 759, 760], a protection enhanced by concomitant loss of BIM or CASP8 [282]. Conditional deletion of the genes encoding BAX, BAK1 or PUMA, as well as overexpression of BCL2, can also protect hepatocytes from FAS-induced killing [761, 762, 763, 764]. The impact of loss of BAD on TNF-induced hepatitis is controversial [765, 766]. Mice deficient for CASP3 or treated with CASP3 or CASP8 inhibitors have also been shown to be less sensitive to FAS-induced hepatocyte apoptosis [767, 768]. Of note, some degree of functional compensation between caspases and alternative mechanisms of caspase activation have emerged from studies in hepatocytes responding to FAS agonists [769]. Finally, FAS and TNF-R1 signaling, as well as FADD activation, are involved in liver regeneration following partial hepatectomy [770, 771, 772, 773, 774]. In this context, liver-specific deletion of *Casp8* resulted in dysregulated hepatocyte proliferation upon partial hepatectomy coupled to the initiation of an inflammatory response [775]. It has been suggested that CASP8 modulates liver regeneration by balancing NF-κB activation and necroptosis rather than by inducing apoptosis [776].

*Gld*/*gld* mice (lacking FAS ligand) chronically fed with ethanol displayed reduced liver injury, steatosis and inflammation as compared to wild-type mice, but exhibited signs of incipient fibrosis [777]. Some degree of protection against alcohol-induced liver damage has also been documented in mice deficient for the apoptosis-inducing TRAIL receptor mTRAIL-R [778] or TNF-R1 (but not TNF-R2) [779], as well as in mice receiving a TRAIL-neutralizing antibody [780]. Accordingly, the hepatocyte-specific ablation of *Casp8* limited hepatic steatosis in murine models of ethanol administration, although it failed to prevent apoptotic RCD [781]. Conversely, apoptosis driven in hepatocytes by chronic ethanol exposure could be abolished by systemic inhibition of CASP3 with Ac-DEVD-FMK [782].

The liver-restricted overexpression of FAS induces hepatic steatosis and insulin resistance in mice subjected to a high-fat diet (HFD) [783]. In the same experimental setting, hepato-protection was observed with the hepatocyte-specific ablation of *Fas* or germline deletion of *Bid* [783]. Moreover, *Tnf* deletion [784, 785], whole-body deletion of *Tnfrsf1a* (encoding TNF-R1) alone or in combination with the gene encoding TNF-R2 [786, 787] as well as inhibition of TNF [788, 789, 790] or TNF-R1 [791] significantly reduced hepatic steatosis, fibrosis, damage, and metabolic alterations in several diet-induced or genetic models of non-alcoholic fatty liver disease (NAFLD). In apparent contrast with these findings, the hepatocyte-specific deletion of *Tnfrsf1a* failed to protect mice from diet-driven NASH [792]. Moreover, *Tnfrsf1a* deletion accelerated progression of steatosis to steatohepatitis in mice on HFD [793]. Taken together, these findings underscore the pleiotropic and context-dependent effects of TNF/TNF-R signaling in NAFLD. The impact of TRAIL on NAFLD is also debated. Indeed, contrasting evidence from experiments with mice deficient for TRAIL or treated with recombinant TRAIL suggests either a detrimental or a beneficial role to TRAIL in NAFLD induced by HFD [794, 795, 796].

The absence of mTRAIL-R promoted hepatic inflammation and fibrosis in a genetic mouse model of cholestasis [797]. Similarly, *lpr*/*lpr* mice lacking FAS [798, 799, 800] as well as TNF-deficient [801, 802] and TRAIL-deficient [803, 804] mice displayed reduced hepatocyte apoptosis and fibrogenesis after experimental cholestasis induced by bile duct ligation. In line with these results, expression of a phosphorylated FADD mimicking mutant resulted in attenuated HFD-induced hepatomegaly and steatosis [805]. Experiments based on the hepatocyte-specific deletion of *Cflar* (encoding c-FLIP) or transgenic overexpression of c-FLIP revealed a role for this modulator of CASP8 activation as a suppressor of hepatic steatosis and inflammation induced by HFD [806]. Moreover, the hepatocyte-specific deletion of *Cflar* in mice resulted in enhanced cholestatic liver injury and inflammatory responses upon bile duct ligation [807]. Moreover, the hepatocyte-specific deletion of *Casp8* protected mice against liver injury in models of cholestatic hepatitis caused by the administration of 3,5-diethoxycarbonyl-1,4-dihydrocollidine [808], as well as in

models of steatosis caused by the feeding of a methionine- and choline-deficient diet [809]. A similar hepato-protection against obstructive cholestasis has been documented in mice with hepatocyte-specific *Casp8* deletion [810]. Furthermore, liver parenchymal cell-specific ablation of the gene encoding FADD prevented RIPK1-dependent but not TNF-R1-, FAS-, and TRAIL-R-independent hepatocyte apoptosis, chronic liver inflammation and hepato-carcinogenesis in mice with liver-specific deficiency in Inhibitor Of Nuclear Factor Kappa B Kinase Regulatory Subunit Gamma (IKBKG, best known as NEMO or IKKgamma) [811, 812]. Finally, decreased BID cleavage has been associated with attenuated liver injury in mouse models of chronic cholestasis [813].

**Hematologic malignancies and solid cancers.**

Human patients with autoimmune lymphoproliferative syndrome (ALPS) caused by defects in FAS are known to show abnormally increased predisposition to lymphoma development [814]. Accordingly, FAS-deficient *lpr*/*lpr* mice develop plasmacytoma-like disease in advanced age [815]. TRAIL also seems to exert a tumor suppressive function in lymphomagenesis. The ablation of the gene encoding mTRAIL-R accelerated the development of lymphoma in *Eμ-Myc* transgenic mice [816]. Moreover, deficiency in TRAIL (but not in mTRAIL-R) promoted the development of lymphoma and other tumors in mice with haploinsufficiency for *Trp53* [817, 818]. Interestingly, mice engineered to express exclusively either membrane-bound or secreted FasL showed an increased incidence of spontaneous tumor formation when expressing only soluble FasL which was unable to induce FAS-mediated apoptosis but could exert inflammatory effects [819].

The role of FAS and TRAIL-R in the development of colorectal cancer is controversial. For instance, the loss of FAS was reported to enhance APC mutation induced but not inflammation induced intestinal tumorigenesis [820, 821, 822]. Along similar lines, while the ablation of *Tnfrsf10b* (leading to lack of mTRAIL-R) in mice did not impact tumorigenesis induced by *Apc* mutations [818], the administration of TRAIL

suppressed tumorigenesis in a mouse model of colitis-associated colon cancer [823]. Despite some contention in this respect [824, 825, 826, 827], TNF seems to contribute to the development of colorectal cancer, although whether such effects depend on the apoptotic function of TNF needs further demonstration. The administration of TNF blockers [828, 829, 830, 831, 832] or ablation of *Tnf* [833] or *Tnfrsf1a* [833, 834] limited tumor development, as shown in animal models of colorectal cancer induced by colitis, chemicals, or a mutation in *Apc*. Finally, loss of the dependence receptor DCC netrin 1 receptor (*Dcc*) accelerated cancer progression in a mouse model of *Apc* mutation driven colorectal oncogenesis [835]. A tumor suppressor role in colorectal cancer is also described for the dependence neurotrophic tyrosine kinase, receptor, type 3 (Ntrk3, best known as TrkC) [836]. Of note, the association between gain of dependence receptors ligands (e.g., NTN1) with tumor progression [837], may make their targeting a promising anti-cancer approach [838] (https://clinicaltrials.gov).

With regard to other tumor types, both TNF-R1 and FAS displayed a pro-oncogenic role in hepatic and ovarian oncogenesis. Thus, conditional deletion of *Fas* in hepatocytes delayed chemically-induced hepato-carcinogenesis, while *Fas* ablation suppressed the development of ovarian tumors in phosphatase and tensin homolog (PTEN)-deficient/Kirsten rat sarcoma viral oncogene (KRAS) mutated mice [839]. Likewise, TNF neutralization limited the onset of hepatic cancer driven by experimentally induced cholestatic hepatitis [840]. Consistent with these findings, *Casp8*$^{-/-}$ mice are protected against the development of inflammation-driven liver cancer [754]. Hyperactivation of CASP8 in the context of RIPK1 and TNF receptor-associated factor 2 (TRAF2) deficiency has been implicated in the development of hepatocellular carcinoma [841] although such effects may be independent of apoptosis induction [842, 843]. In contrast, recent studies show a tumor-suppressive function of CASP8 in the liver and certain other tissues [844, 845, 846, 847]. In particular, there is evidence of a role of CAPS8 in early tumorigenesis (but not tumor progression) exerted by modulating the DNA damage response [844] or the level of chromosomal instability (CIN) [845].

Consistent with a pro-tumorigenic effect of TNF, the ablation of *Tnf* or *Tnfrsf1a* or the blockade of TNF in mice conferred some protection against chemically-induced skin cancer development [848, 849, 850, 851, 852, 853]. In contrast, the impact of genetic and pharmacological inhibition of TNF in UVB-induced skin cancer is debated [854, 855]. Of note, the comparison between TNF-R1- *vs.* TNF-R2-deficient mice revealed a primary role of TNF-R1 in chemically induced skin oncogenesis [850]. Furthermore, TNF-R1 deficiency suppressed the development of skin cancer induced by NF-κB inhibition [856]. A similar role for TNF-R1 in supporting tumorigenesis was described in murine models of N-methyl-N-nitrosourea/testosterone-induced prostate cancer [857] and methylcholanthrene (MCA)-induced fibrosarcoma [858]. As opposed to TNF-R1, TNF-R2 shows tumor-suppressive functions in mouse models of tumorigenesis, such as the development of fibrosarcoma triggered by MCA [858] and of breast cancer induced by transgenic expression of wingless-type MMTV integration site family, member 1 (*Wnt1*) [859]. Moreover, the absence of TNF impaired tumor growth in HER2-driven mammary tumorigenesis in mice [860] and TNF neutralization suppressed chemically-induced oral [861] and urethane-induced pulmonary [862] tumorigenesis. Conversely, TNF overexpression in the airway epithelium enhanced mutant KRAS-driven lung cancer development [863].

Pre-clinical evidence indicates some tumor type-specificity for the role of TRAIL and its receptor(s) in tumorigenesis. Transgenic expression of TRAIL in the skin delayed chemically induced carcinogenesis [864]. This effect was recapitulated in mice lacking TRADD [865] but, curiously, not in mTRAIL-R-deficient mice [866], with the latter actually showing enhanced lymph node metastasis. In support of an anti-tumor function for the TRAIL/TRAIL-R system, TRAIL-deficient mice as well as mice treated with TRAIL blockers displayed increased susceptibility to MCA-induced fibrosarcoma [867, 868]. In a recent study the combined treatment with recombinant TRAIL and inhibition of cyclin-dependent kinase 9 (CDK9) was effective in a wide range of cancers [869]. Yet in contrast to this and in support of a tumor-supportive role

of endogenous TRAIL, deficiency in mTRAIL-R limited tumor growth and improved survival in a mouse model of mutant KRAS-driven lung and pancreatic tumorigenesis [870]. Moreover, malignant cell-specific ablation of genes encoding mTRAIL-R or FADD reduced lung cancer growth and tumor-protective inflammation [871], while systemic ablation of *Tnfsf10* (leading to lack of TRAIL) had no impact on HER-2 driven breast oncogenesis [817]. Interestingly, KRAS mutations have been shown to promote the switch of FAS and TRAIL receptors from a predominantly death-inducing into a metastasis promoting function [872]. Since TRAIL as well as FASL can trigger either apoptosis, necroptosis, inflammatory or pro-invasive signaling, cancer-specific preferences for one or the other of these signaling outputs likely accounts for the pleiotropic effects observed in various cancer models.

**Autoimmune and inflammatory diseases.** The interpretation of results on the impact of extrinsic apoptosis in the etiology of autoimmune and inflammatory disease should consider the fact that DR engagement can also result in the initiation of an inflammatory response not related to RCD (*see* **Box 6** and **Box 7**), meaning that DR deregulation may lead to inflammatory diseases independently of the induction of extrinsic apoptosis. The notion that defects in DR signaling can cause autoimmune disease is supported by the observation that *lpr*/*lpr* as well as *gld*/*gld* mutant mice, deficient for FAS or FAS ligand, respectively, as well as humans with defects in FAS develop systemic lupus erythematosus (SLE)-like autoimmune disease accompanied by lymphadenopathy, splenomegaly and hepatomegaly [873, 874]. A critical role for loss of caspase-CASP8 mediated apoptosis in this disease was demonstrated by the observation that similar autoimmune disease is seen in mice lacking CASP8 and also RIPK3 or MLKL (to prevent necroptosis) [51, 52, 875]. However, the roles of DRs in autoimmune disease are complex. TRAIL/TRAIL-R signaling was reported to protect mice and rats against autoimmune encephalomyelitis [876, 877, 878, 879, 880, 881], autoimmune arthritis [882, 883, 884, 885, 886] and type I diabetes [689, 882, 887, 888, 889, 890]. Perhaps surprisingly, the presence of FAS and TNF-R1 is associated with the development of certain autoimmune conditions. Indeed, both *lpr*/*lpr* lacking FAS and *gld*/*gld* mice lacking FAS ligand, as well as TNF-R1-

deficient mice, were reported to be protected against experimental encephalomyelitis [891, 892, 893, 894]. Similar results were obtained in mice with *Tnf* deletion in monocytes and macrophages but not in mice lacking TNF in microglial cells [895]. Protection against experimentally induced autoimmune conditions were also found in mice subjected to neutralization of TNF or TNF-R1 inhibition [896, 897, 898, 899, 900, 901, 902, 903]. FAS-independent mechanisms also appear to support the pathogenesis of experimental autoimmune encephalomyelitis [891, 904], with some studies pointing to a protective role for FAS-induced RCD amongst lymphocytes in this disease model [905]. Moreover, FAS engagement was reported to differentially contribute to the initiation *vs.* the recovery from autoimmune encephalomyelitis [906, 907]. In particular, FASL expression in astrocytes appears to promote recovery from experimental autoimmune encephalomyelitis, as shown by persisting demyelination and paralysis of mice with an astrocyte restricted deletion of the *Fasl* gene [906]. Finally, at least in some studies, *Tnf* deletion or TNF neutralization failed to attenuate the severity of autoimmune encephalomyelitis once the disease was established [908, 909].

Mice with defects in FASL or TNF signaling are protected against arthritis induced by immunization with xenogeneic type II collagen in complete Freund's adjuvant [910, 911, 912, 913]. Similar protection was observed in mice transplanted with mesenchymal stem cells engineered to express TNF inhibitors [914]. In keeping with this evidence, the myeloid cell specific deletion of *Fas* or the administration of antibodies that target both TNF and chemokine (C-X-C motif) ligand 10 (CXCL10) resulted in accelerated disease resolution in a model of rheumatoid arthritis induced by K/BxN serum transfer [915, 916]. Genetic loss of *Fas* or pharmacological inhibition of FAS conferred protection against autoimmune diabetes in certain animal models, including NOD mice [917, 918, 919, 920, 921, 922]. However, whether the impact of FAS on the pathogenesis of autoimmune diabetes depends on its role in the death of pancreatic β-cell [917] or its role in inflammation (*e.g.*, in the context of insulitis) remains a matter of debate [920]. Conversely, other studies found no role for FAS in diabetes [923, 924, 925]. TNF neutralization is effective only in a limited sub-group of patients with inflammatory bowel disease [926, 927]. This is in line with the finding that deletion of the

gene encoding TNF-R1 exacerbated colitis in interleukin 10 (IL10)-deficient mice [928]. Similar protection was ascribed to TRAIL/TRAIL-R signaling in a dextran sodium sulfate-induced model of colitis model [929, 930]. Finally, it has been suggested that FASL and TNF signaling contribute to the pathogenesis of acute pancreatitis [931, 932]. A similar detrimental role has been proposed for TNF in autoimmune neuritis [933, 934, 935], although there is also some contention [936], as well as in spondylarthritis [937] and psoriasis [938]. Conversely, mTRAIL-R appears to mediate beneficial effects in autoimmune thyroiditis [939, 940, 941, 942, 943] At least in part, these findings reflect the pleiotropic effects of whole-body/systemic inhibition of DRs signaling, which concomitantly impacts both the target (*i.e.*, parenchymal) and the perpetrator (*i.e.*, immune cells) of damage.

Some experimental evidence links CASP8 activation to autoimmune and inflammatory disorders. In a recent study using a chemically-induced model of intestinal inflammation, the selective absence of CASP8 in intestinal epithelial cells decreased their survival, also resulting in gut barrier dysfunction and chronic inflammation [944]. Of note, in these settings, inflammation can occur via a mechanism independent of the induction of necroptosis (which is inhibited by CASP8) and involving the activation of RIPK1 and the RNA Sensor RIG-I pathway [945, 946]. Along similar lines, chronic proliferative dermatitis in mice deficient for components of the linear ubiquitin chain assembly complex (LUBAC) was associated with an increased keratinocyte apoptosis mediated by the engagement of TN-FR1 and the activation of the RIPK1- and/or FADD-CASP8 cascade [947, 948, 949, 950, 951]. Importantly in this mouse model of an inflammatory disease the relevant contributions of cell death versus inflammatory signalling from TNF-R1 were genetically dissected demonstrating that excess apoptosis/necroptosis drove different elements of the inflammatory response depending upon the affected tissue. Concerning autoimmunity, in a mouse model of autoimmune encephalomyelitis, the oligodendrocyte-specific deletion of *Fadd* reduced demyelination and this was accompanied by limited immune cell infiltration in the spinal cord [952]. Likewise, experimental autoimmune encephalomyelitis could be prevented by transgenic expression of

FADD-DN (dominant negative form of FADD) in T cells [953] but it must be noted that this kills antigen receptor activated T cells [954]. Therefore, this protective effect is due to the removal of the T cells that would cause tissue destruction. Activation of CASP8 was identified in the microglia of patients with multiple sclerosis [955]. Moreover, transgenic expression of FADD-DN or *Casp8* ablation in pancreatic β cells protected mice from autoimmune diabetes [956]. This indicates that the killing of these cells is mediated by death receptor induced apoptosis. BID appears to be dispensable for the development of diabetes in NOD mice [957].

There are also contrasting observations on the impact of DR-induced apoptosis on the development and resolution of autoimmune rheumatoid arthritis. The absence of c-FLIP (due to *Cflar* deletion) resulted in increased disease severity but limited disease resolution in mice experiencing arthritis upon intraperitoneal injection of serum from mice expressing both the T cell receptor transgene KRN and the MHC class II molecule A(g7) (K/BxN mice) [958]. In the same model, deletion of *Casp8* in all myeloid cells enhanced disease resolution, while deletion of *Casp8* selectively in dendritic cells accelerated disease onset [959]. Further experiments are required to unveil the reasons for such cell type specificity for the role of CASP8 to help more clearly understand the role of extrinsic apoptosis in this and other autoimmune disorders.

**Infectious diseases**. Extrinsic apoptosis is reported to act as an anti-infective mechanism. FAS deficient *lpr*/*lpr*, FAS ligand deficient *gld*/*gld* and *Bid*$^{-/-}$ mice exhibit delayed clearance of *Citrobacter rodentium* and increased intestinal pathology [960]. Confirming the importance of DR-induced apoptosis, this pathogen was shown to inhibit extrinsic apoptosis of infected enterocytes by expressing specific virulence proteins, such as N-acetylglucosamine transferase NleB1, which prevents FADD-mediated recruitment and activation of CASP8 [960 Li, 2013, 23955153 Li, 2013, 23955153 Li, 2013, 23955153 Li, 2013, 23955153]. Along similar lines, *Fas*$^{-/-}$ mice had shorter lifespan than wild-type mice after challenge with *Listeria*

*monocytogenes*, succumbing to neurolisteriosis. This was proposed to be promoted by an impaired loss of monocytes due to upregulated expression of c-FLIP by the bacterial protein InlB [961]. In support of this result, conditional deletion of *Cflar* in myeloid cells improved *Listeria monocytogenes* clearance and animal survival [962]. FAS signaling also conferred protection from infection with (i) human herpes simplex virus 2 (HSV-2), as demonstrated by a decrease in the loss of monocyte and immune cell recruitment at the infection site in *Fas*$^{-/-}$ and *Fasl*$^{-/-}$ mice [963], and (ii) *Citrobacter rodentium* or lymphocytic choriomeningitis virus, as demonstrated by an increased neutrophil fraction in mice with conditional deletion of *Fas* in the myeloid compartment [964].

Supporting an anti-infection role of CASP8, mice lacking RIPK1 kinase activity failed to control systemic *Yersinia* infection, rapidly dying because of excess apoptosis driven by a kinase independent function of RIPK1 [965, 966]. In line with this finding, *Ripk3*$^{-/-}$*Casp8*$^{-/-}$ but not *Ripk3*$^{-/-}$ mice died from *Toxoplasma gondii* infection due to acute toxoplasmosis, an observation supporting the anti-infection role of CASP8-mediated apoptosis [967]. Moreover, hepatocyte-specific deficiency for CASP8 facilitated liver infection of mice by *Listeria monocytogenes*, resulting in inflammation and development of necrotic lesions in the liver [775]. These results also suggest an interconnection of multiple RCD pathways in controlling infection. Accordingly, the deletion of Z-DNA binding protein 1 (*Zbp1*), an essential cytoplasmic sensor of Influenza A virus (IAV) Z-RNA required for the activation of mixed lineage kinase domain like pseudokinase (MLKL)-dependent necroptosis, RIPK1/FADD-dependent apoptosis and NLRP3 inflammasome-dependent pyroptosis, as well as co-deletion of the genes encoding MLKL and FADD, caused a defect in the control of Influenza A virus (IAV) infection, with these mutant mice succumbing to lethal respiratory failure. These findings support an essential role of apoptosis, necroptosis and pyroptosis in IAV clearance [968, 969 Oltean, 2021, 33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799 Oltean, 2021, 33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799 Oltean, 2021, 33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799 Oltean, 2021, 33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799]. Similarly, combined activation of apoptosis and other RCD

pathways contribute to the response of mice to *Burkholderia thailandensis* infection [970]. Finally, pharmacological or tissue specific genetic deletion of cIAP1 and cIAP2 results in better control of hepatitis B virus and liver stage malaria parasites due to increased TNF induced death of infected cells (Ebert, 2015 25902529; Ebert 2015, 25902530; Ebert 2020, 32234472).

Experimental evidence also suggests a detrimental role of extrinsic apoptosis during certain infections. Mice deficient for both TNF-R1 and TNF-R2 displayed decreased sensitivity to lipopolysaccharide, suggesting a critical role for TNF in tissue injury during gram-negative bacterial infection [971]. Along similar lines, TNF-R1-deficient mice were more resistant than wild-type mice to the cytopathic effects of TNF during Sindbis virus infection, as evidenced by reduced mortality and delayed paralysis [972]. Moreover, ablation of *Ripk1* protected mice from acute liver injury after infection with *Listeria monocytogenes* [973], while knockout of *Fas* or *Fasl* reduced the effect of toxin A-induced enteritis in mice infected with *Clostridium difficile*, which has been attributed to a reduction in enterocyte loss [974]. Additionally, the infectious spleen and kidney necrosis virus (ISKNV) induced tissue damage in zebrafish by activation of DR-induced apoptosis by a viral protein encoding a TRADD interactor [975]. Of note, in this study, the absence of CASP8 protected zebrafish from ISKNV infection. Finally, *Ripk3*$^{-/-}$*Casp8*$^{-/-}$ mice exhibited high levels of protection from LPS-induced septic shock [976] or a lethal cytokine shock and tissue damage driven by TNF and IFN-γ, mirroring that of SARS-CoV-2 [977]. This evidence suggests that the combination of several types of RCD can also mediate infection-associated pathogenesis, as demonstrated for infection with Salmonella [50].

**Other diseases.** TNF is reported to impair myogenesis in a mouse model of skeletal muscle regeneration after hindlimb immobilization (hindlimb suspension) [978]. Moreover, silencing of TRAIL improved muscle regeneration in mice with acute skeletal muscle injury due to local injection of BaCl2 [979]. An inhibitory role in myogenesis was also ascribed to FADD, at least in response to freezing-induced muscle

injury [980]. In apparent contrast with this result, combined deletion of the genes encoding TNF-R1 and TNF-R2 limited skeletal muscle regeneration after cardiotoxin-induced injury [981, 982], suggesting the relevance of a balance between TNF-R1 and TNF-R2 signaling in this model. TRAIL neutralization increased muscular strength in a mouse model of Duchenne muscular dystrophy [983], while other studies associated TRAIL and FASL to myositis [984, 985].

Activation of DRs has also been implicated in the pathogenesis of acute lung injury. *Fas* silencing as well as TNF neutralization protected mice from lung injury induced by ischemia-reperfusion [986, 987]. Similarly, deletion of *Tnfrsf1a* (encoding TNF-R1) or pharmacological inhibition of TNF-R1 or CASP8 attenuated pulmonary edema formation and improved alveolar epithelial function in a murine model of acute lung injury induced by acid inhalation [988, 989]. A similar protective effect was provided by pharmacological inhibition or genetic deletion of FASL or TNF in a lipopolysaccharide-induced mouse model of acute lung injury [990, 991, 992, 993, 994, 995, 996]. However, in one study FAS signaling was shown to contribute to the resolution of acute lung injury by promoting the depletion of macrophages [997]. Using distinct mouse models of acute lung damage following sepsis, it was shown that the abrogation of FAS and TNF-R1 signaling, including the silencing of *Fadd*, decreased pulmonary apoptosis and ameliorated pathology, and in some cases this led to a survival benefit for the animals (e.g., [998, 999, 1000, 1001, 1002, 1003, 1004]). Hyperoxia-induced lung injury and bleomycin-induced pulmonary fibrosis, a model for cancer therapy-induced lung injury, are also impacted by the DR pathway. FAS and TNF deficiency exacerbated hyperoxia-induced lung injury and/or inflammation in newborn mice [1005, 1006]. In contrast, TNF inhibition conferred protection against hyperoxia-induced lung damage in a murine model [1007, 1008, 1009]. Moreover, the absence of TNF-R1 (but not the absence of TNF-R2) improved survival in mice subjected to excessive oxygen supply, although without decreasing inflammation [1010]. In support of these results, specific ablation of *Fas* in murine fibroblasts or T cells exacerbated pulmonary fibrosis induced by bleomycin [1011, 1012]. However, the level of bleomycin-induced pulmonary fibrosis was diminished in FAS

deficient *lpr*/*lpr* or FAS ligand deficient *gld*/*gld* mice [1013] and remained unchanged in mice treated with FAS neutralizing agents [1014]. Likewise, contrasting findings support or refute a role for TNF [1015, 1016, 1017] and TRAIL [1018, 1019] in both the onset and resolution of pulmonary fibrosis after administration of bleomycin. TNF neutralization has been reported to attenuate and enhance interstitial pulmonary fibrosis induced by nitrogen mustard [1020] or rituximab [1021]. Finally, FASL, TNF and/or TRAIL have been implicated in infectious or non-infectious lung disorders, including (but not limited to) infection with respiratory syncytial virus (RSV) [1022, 1023, 1024, 1025, 1026, 1027, 1028], adenovirus type 1 respiratory disease [1029, 1030], allergic reaction and asthma [1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042] and idiopathic pneumonia syndrome [1043], as well as to chronic lung diseases (e.g., chronic obstructive pulmonary disease) [863, 1044, 1045].

The studies discussed above illustrate that DR-induced apoptosis is at the heart of many disorders either promoting recovery or exacerbating disease. The active involvement in disease severity and progression makes this pathway a potentially tractable target for therapeutic interventions in a wide range of diseases, typically those with an inflammatory component. However, this effect may be llinked to the role of DR signaling in other RCD pathways and in inflammation. Moreover, there is little consensus on the roles of FASL, TNF and/or TRAIL, highlighting a high complexity of the systems which needs further investigation.

## Concluding remarks

Abundant preclinical evidence demonstrates that the intrinsic and the extrinsic pathways of apoptosis not only contribute to adult tissue homeostasis and, in the case of the intrinsic pathway, to embryonic development – the implication of CASP8 in normal development is mainly linked to its role as necroptosis inhibitor (*see* **Box 6** and **Box 7**) - but also contribute to the pathogenesis of multiple diseases, including various cardiovascular, hepatic, neurological and renal disorders as well as multiple infectious,

autoimmune, inflammatory and oncological conditions. However, despite great potential as targets for therapeutic interventions and a considerable research effort dedicated to developing effective approaches, the success of intrinsic or extrinsic apoptosis-targeting agents in clinical settings is so far limited to BH3 mimetic drugs, SMAC mimetics, caspase inhibitors as well as activators or inhibitors of DR signaling, with only one compound, the BCL-2 inhibitor venetoclax (BH3 mimetic drug), approved for routine treatment of patients with CLL or AML.

Rather than mitigating the enthusiasm about the clinical potential of modulators of apoptosis, this challenge suggests the need for a substantial change in the experimental design and re-interpretation of results, at different levels (**Figure 1**). One major issue is that studies evaluating the impact of apoptotic cell death on disease have not always addressed the connections between the core components of the intrinsic and extrinsic apoptotic machinery or their potential interaction and functional overlap with other RCD pathways. Also, the potential activation of alternative RCD modalities as a mechanism to compensate for the inhibition of apoptotic RCD has not always been explored and thus it has not been tried to prevent or overcome these alternative forms of RCD to achieve superior outcomes. The importance of independent replication of findings that suggest success from targeting a pathway in the treatment of a disease cannot be emphasized enough. Only then can the costly process of clinical translation be approached with confidence and with an increased chance of success. For example, the findings that overexpression of BCL2 or its pro-survival relatives can promote tumorigenesis and can render malignant cells resistant to diverse anti-cancer therapeutics had been reproduced hundreds of times before BH3 mimetic drug development was started. This is not yet the case for many of the other studies discussed here, as best demonstrated by the fact that for certain experiments diametrically opposing results were reported by different groups. These questions must be resolved before considering drug development programs.

Moreover, certain regulators of apoptosis and signaling cascades have been reported to exert a variety of functions beyond cell death control, including (but not limited to) inflammation (*e.g.*, multiple activated caspases and IAPs), cell differentiation (*e.g.*, pro-and anti-apoptotic BCL2 proteins), cell proliferation and survival (*e.g.*, DR engagement). The relevance of these functions is often dependent on cell/tissue type (as it is related to variable expression levels and activation status of other regulators of RCD) and the intensity and duration of the initiating stimulus (as they can direct to a distinct biological outcome, as exemplified by DR ligation). Of note, some of these cell death unrelated functions of *bona fide* cell death regulators are highly controversial and much more work must be done to verify or discard these notions. On the one hand, this pleiotropy may result in a variable (even including an antagonistic protective *vs.* promoting) impact of apoptosis on distinct human diseases, also explaining the considerable degree of context-dependency (*e.g.*, effect of stromal and immune cells) observed for its experimental modulation. On the other, the pathogenic effect of core components of the apoptotic machinery is often mediated by such apoptosis-unrelated functions including inflammation, which may point to unexplored targets for the development of new therapeutic agents or approaches.

In our opinion, investigating the molecular cascade of apoptotic cell death in the context of the functional inter-connection between apoptotic and non-apoptotic pathways, for instance by interrupting some of the molecular connections between different RCD signaling cascades, may instigate new advances, ultimately leading to clinical use of specific apoptosis-modulatory agents for the treatment of many diseases.

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## Legends to Figures

***Figure 1.*** **Principal causes of the therapeutic failure of intrinsic or extrinsic apoptosis inhibitors**. The clinical development and success of agents inhibiting apoptosis is limited by multiple contributory causes, including potential non-apoptotic, accessory or even protective roles of the targeted proteins (exemplified by the involvement of certain BCL2 family members, caspases and death receptors in processes as diverse as inflammation, cell differentiation, cell proliferation and cell survival), the high interconnectivity between RCD pathway (potentially leading to the activation of compensatory RCD variants in response to the inhibition of a specific RCD type), the low specificity and selectivity of the inhibitors developed so far (exemplified by the broad-spectrum caspase inhibitors) and the difficulty to precisely determine and quantify cell death *in vivo*. RCD, regulated cell death.

***Figure 2.*** **Molecular machinery of the intrinsic apoptosis.** Intrinsic apoptosis can be activated by a range of extracellular or intracellular stimuli, including, but not limited to, DNA damage, endoplasmic reticulum (ER) or oxidative stress, growth factor withdrawal or microtubular alterations. The critical step of the intrinsic apoptosis is the activation of the pro-apoptotic effectors of the BCL2 family, BAX, BAK and possibly BOK, which drives the outer membrane permeabilization (MOMP) and commits cells to death. MOMP results in the release from the mitochondrial intermembrane space into the cytosol of proapoptotic proteins, including CYCS and SMAC. CYCS assembles with APAF1, dATP and pro-CASP9 into the apoptosome, leading to the activation of CASP9, which in turn promotes the activation of the executioner caspases CASP3 and CASP7. The activation of the executioner caspases is facilitated by SMAC, which sequesters and/or degrades members of IAP family that inhibit apoptosis.

***Figure 3.*** **Impact of intrinsic apoptosis players on neurological disorders.** Intrinsic apoptosis is directly or indirectly involved in the pathogenesis of multiple neurological disorders, including neurodegenerative diseases, such as AD and PD, in brain damage caused by traumatic injury or

neurotoxicity as well as in neuromuscular and retinal disorders. Pro- and anti-apoptotic members of the BCL2 family are depicted, respectively, in blue and green, while caspases are illustrated in pale violet.

***Figure 4.*** **Molecular machinery of the extrinsic apoptosis pathway.** Extrinsic apoptosis is initiated by the binding of FASL to FAS or TRAIL to TRAIL-R1 or TRAIL-R2, which promotes the assembly, on the cytoplasmic tail of these death receptors, of a platform known as the DISC. Extrinsic apoptosis is also triggered by the binding of TNF to TNF-R1, which promotes the assembly of the Complex II. The DISC comprises FADD, c-FLIPs and pro-CASP8. Complex II is a platform consisting of FADD and pro-CASP8 in association with either TRADD (complex IIa) or RIPK1 (complex IIb). The assembly of these complexes promotes the activation of CASP8, which mediates CASP3 and CASP7 activation either directly, by catalyzing the proteolytic activation of CASP3 and CASP7 (in type I cells) or indirectly, via the proteolytic activation of the BH3-only protein BID and the outer membrane permeabilization (MOMP) (in type II cells). Extrinsic apoptosis can also be induced by dependence receptors like DCC, NTRK3, PTCH1, or UNC5A-D, which are activated by decreased concentration of the related ligand, as illustrated in the figure. However, the role of this pathway in normal physiology and disease is not yet established.

***Figure 5.*** **Impact of extrinsic apoptosis players on neurological disorders.** Death receptor-induced apoptosis is directly or indirectly involved in the pathogenesis of multiple neurological disorders, including neurodegenerative diseases, such as AD and PD, in brain damage due to traumatic injury or neurotoxicity as well as in neuromuscular and retinal disorders.

# **Box 1.** Principle of intrinsic apoptosis.

Intrinsic apoptosis is a type of regulated cell death (RCD) initiated by perturbations of the extracellular or intracellular microenvironment including (but not limited to) DNA damage, endoplasmic reticulum or oxidative stress, growth factor withdrawal, microtubular alteration. The critical step is mitochondrial outer membrane permeabilization (MOMP) [1, 2, 3, 4]. MOMP - which involves constitutive outer membrane proteins, such as the voltage-dependent anion channel (VDAC), is modulated by the activity of multiple pro-apoptotic and anti-apoptotic members of the BCL2, apoptosis regulator (BCL2) protein family [5, 6, 7, 8, 9]. In response to apoptotic stimuli, MOMP leads to the sequential activation of the initiator caspase 9 (CASP9) and then the executioner caspases CASP3 and CASP7 [10, 11, 12, 13, 14]. Two functionally distinct classes of pro-apoptotic BCL2 proteins have been identified. The first class encompasses the apoptotic activators BCL2 associated X, apoptosis regulator (BAX), BCL2 antagonist/killer 1 (BAK1), and BCL2 family apoptosis regulator (BOK) [15]. Once activated by apoptotic stimuli, BAX, BAK1 and BOK induce MOMP by generating pores across the outer mitochondrial membrane (OMM) [16, 17, 18, 19, 20]. These pro-apoptotic factors promote the release into the cytosol of several apoptogenic factors, including cytochrome c, somatic (CYCS) and diablo IAP-binding mitochondrial protein (DIABLO; also known as second mitochondrial activator of caspases, SMAC) [21]. CYCS exerts apoptogenic activity by associating with apoptotic peptidase activating factor 1 (APAF1) and pro-CASP9 to generate a complex known as the apoptosome, leading to sequential activation of CASP9 and the executioner caspases CASP3 and CASP7[22]. DIABLO/SMAC contributes to CASP3 and CASP7 activation by associating with and inhibiting X-linked inhibitor of apoptosis (XIAP) and other members of the inhibitor of apoptosis (IAP) protein family which restrain caspase activation [23].

The second class of pro-apoptotic BCL2 proteins (known as BH3-only proteins [24]) include BCL2 associated agonist of cell death (BAD), BCL2 binding component 3 (BBC3; best known as p53-

upregulated modulator of apoptosis, PUMA), BCL2 interacting killer (BIK), BCL2 like 11 (BCL2L11; best known as BCL2-interacting mediator of cell death, BIM), Bcl2 modifying factor (BMF), BH3 interacting domain death agonist (BID), BCL2 interacting protein harakiri (HRK, also known as DP5), and phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1; best known as NOXA [25, 26]). Of these, caspase-cleaved BID (tBID), BIM, PUMA, and NOXA have been reported to also be able to promote BAX and BAK1 activation through a direct interaction with these proteins at the mitochondria [27, 28, 29, 30, 31, 32, 33]. All BH3-only proteins, including BAD, BIK, BMF and HRK activate BAX and BAK1 indirectly by associating with anti-apoptotic BCL2 family members, thereby blocking the inhibitory binding of the latter to BAX and BAK1 [5, 9, 31, 33, 34, 35]. Some BH3-only proteins, particularly BIM, PUMA and tBID, can potently bind and inhibit all anti-apoptotic BCL-2 proteins whereas others bind only some (e.g., NOXA only binds MCL1 and A1) [31, 33, 36, 37]. It is noteworthy that BAX and BAK1 can induce apoptosis in the absence of all BH3-only proteins when the anti-apoptotic BCL2 proteins are genetically removed or inhibited by BH3 mimetic drugs [33, 34]. However, BAX and BAK1 activation in the absence of BH3-only proteins occurs at slower kinetics compared to that in the presence of BH3-only proteins [33]. These findings support the existence of both BH3-dependent and BH3-independent activation of BAX and BAK1 where BH3-only proteins function as catalysts for BAX and BAK activation [33, 38].. In this context, BAX and BAK are also reported to be activated by the tumor protein p53 (TP53; best known as p53) in a fashion independent of BH3-only proteins [39, 40]. The anti-apoptotic members of the BCL2 family encompass BCL2, apoptosis regulator (BCL2), BCL2 like 1 (BCL2L1; best known as BCL-$X_L$), MCL1, BCL2 family apoptosis regulator (MCL1), BCL2 like 2 (BCL2L2; best known as BCL-W), and BCL2 related protein A1 (BCL2A1; best known as A1) [5, 6, 7, 8]. The anti-apoptotic activity of these BCL2 proteins mainly involves MOMP maintenance, although, a non-canonical, cellular redox-dependent mechanism of cytoprotection has been ascribed in cancer cells at least for BCL2 [41, 42, 43, 44]

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## Box 2. Impact of pro-apoptotic BCL2 proteins on health.

Deletion of BCL2-associated X protein (*Bax*), BCL2-antagonist/killer 1 (*Bak1*) or BCL2-related ovarian killer (*Bok*) does not significantly affect mouse development [45, 46, 47], with the exception of a mild lymphocyte and neuron accumulation in *Bax*$^{-/-}$ mice which also exhibit male infertility due to seminiferous tubule malformation [45, 48]. Of note, a recent study has demonstrated that such defects in germ cells occur in the fetal period [49], supporting the requirement for intrinsic apoptosis in testicular development [50, 51]. Subsequent studies confirmed the role of BAX in neurogenesis, in particular the development of hippocampal and cerebellar neurons, cortical interneurons and astrocytes [52, 53, 54, 55, 56, 57]. Accordingly, *Bax*$^{-/-}$ mice exhibit impaired neurological functions manifesting with increased anxiety, depression-like traits, compromised social and sexual behavior, and impaired spatial representation and olfactory system function [58, 59, 60]. These mice also show accelerated medulloblastoma formation [61], which is in line with the oncosuppressive activity of apoptotic (and non-apoptotic) regulated cell death (RCD) [62].

Ablation of *Bok* does not compromise the relatively normal development of BAK1- or BAX-deficient mice, although *Bax*$^{-/-}$*Bok*$^{-/-}$ mice exhibit an increased number of mature oocytes [63]. In contrast, co-deletion of *Bax* and *Bak1* causes perinatal death in the vast majority (more than 90%) of mice, mainly due to multiple developmental abnormalities and feeding difficulties [46, 64]. Importantly, the developmental defects of *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice are exacerbated by additional deletion of *Bok*, underscoring not only some functional redundancy between BAX, BAK1 and BOK, but also a crucial role of pro-apoptotic BCL2 family members in the development of the central nervous system (CNS) and hematopoietic compartment [64]. However, since some *Bax*$^{-/-}$*Bak1*$^{-/-}$ and *Bax*$^{-/-}$*Bak1*$^{-/-}$*Bok*$^{-/-}$ mice can reach adulthood [46, 64], additional systems must be at play to compensate for defects in apoptosis in other organs. In is worth noting that the developmental defects of *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice can be further aggravated by deletion of

autophagy related 5 (*Atg5*) [65], which is involved in autophagy as well as in non-canonical vesicular pathways like LC3-associated phagocytosis [66, 67]. However, whether autophagy-dependent cell death compensates for the apoptotic defects of *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice remains to be formally determined [68, 69].

Further corroborating the relevance of intrinsic apoptosis for proper development, the few surviving *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice and *Bax*$^{-/-}$*Bak1*$^{-/-}$*Bok*$^{-/-}$mice display phenotypes related to defective programmed cell death (PCD), including webbed feet (due to the incomplete removal of interdigital webs), imperforate vagina and midline fusion defects including facial cleft [46, 64]. CNS issues exhibited by these animals include a striking expansion of the tissue regions that harbor the neural stem cell pool [46, 64] as well as impaired function of the motor [70] and visual [71, 72] systems. Although the number of apoptotic cells were reduced to the limit of detection in embryos lacking BAX, BAK1 and BOK [64], anomalies in the urinary tract were conspicuously absent in these animals [64]. This sparked a study examining if BID, in addition to linking the death receptor (DR) pathway and the intrinsic apoptotic pathway (**Box 5**), could act in a way similar to BAX and BAK1. Indeed, while loss of BID alone did not lead to anomalies during embryonic and fetal development, additional deletion of *Bid* in *Bax*$^{-/-}$*Bak1*$^{-/-}$*Bok*$^{-/-}$mice mice revealed a redundant requirement for BID in urogenital tract development [73]. In its previously recognized role, BID in the form of tBID activates BAX and BAK1, which would not have caused additional anomalies in the absence of BAX and BAK1. Therefore, these results indicate that BID can act in parallel with BAX, BAK1 and BOK. Congruently, full-length BID [73] or tBID [74] can mediate mitochondrial permeabilization and cause cytochrome c, somatic (CYCS) release. In this context it is worth considering that BID has been reported to be structurally similar to the multi-BH domain BCL2 family proteins, such as BAX and BCL-$X_L$ [9, 75, 76, 77].

Tissue-specific ablation of *Bax* and *Bak1*, confirmed the crucial role of these proteins in the hematopoietic system, and specifically in the homeostasis and functionality of B cells [78], T cells [79], megakaryocytes [80]

and platelets [81]. Mice reconstituted with fetal liver cells from *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice display massive lymphadenopathy and defective T cell proliferation, and the severity of these defects is even more pronounced when *Bak1*$^{-/-}$*Bax*$^{-/-}$*Bok*$^{-/-}$ fetal liver cells are used for reconstitution, an experimental setting that also reveals signs of autoimmunity [82, 83, 84]. Similarly, mice reconstituted with a *Bak1*$^{-/-}$*Bax*$^{-/-}$ hematopoietic compartment develop a fatal systemic lupus erythematosus (SLE)-like autoimmune disease [85]. Moreover, the inducible co-deletion of *Bax* and *Bak1* in lymphocytes of adult mice results in the development of severe autoimmune glomerulonephritis [78]. Finally, conditional knockout mouse models reveal a crucial contribution of BAX and BAK1 to endothelial cell homeostasis [86, 87], but little impact on cardiac and intestinal functions, as shown by the absence of hyperplasia [88, 89]. These results demonstrate that the multi-BH domain pro-apoptotic BCL2 proteins play critical roles for the normal development of multiple tissues but that, surprisingly, a few mice can reach weaning or even adulthood when all of these effectors of apoptosis are removed [64].

Amongst the BH3-only proteins, BCL2 like 11 (BCL2L11, best known as BIM) appears the most critical for embryonic development and tissue homeostasis, as shown by the fact that approximately 30% of BIM-deficient mice die during embryogenesis [90]. Surviving BIM-deficient mice display severe defects in the hematopoietic system including lymphoid hyperplasia and marked splenomegaly, and on a mixed C57BL/6 x 129SV background many of these mice spontaneously develop systemic autoimmunity often resulting in fatal kidney disease [90], a condition that can be accelerated by depletion of immunosuppressive CD4+CD25+FOXP3+ regulatory T ($T_{REG}$) cells [91]. Cells from BIM-deficient mice are profoundly resistant to growth factor deprivation, glucocorticoids, deregulated calcium flux and ER stress [90, 92]. Accordingly, BIM-deficient mice also display dysregulated T cell development and homeostasis [93, 94, 95, 96, 97] and hence exhibit defective cellular [98, 99, 100] and humoral [101, 102, 103] immune responses. *Bcl2l11* deletion (loss of BIM) has also been shown to extend the survival of granulocytes [104] and to perturb the development of mammary glands [105, 106], gastric epithelium [107] and the retina [108]. Moreover, aged BIM

deficient mice show reduced adiposity [109]. Of note, systemic deletion of *Bax* or *Bak1* exacerbates the hematopoietic dysregulation of BIM-deficient mice [110]. Conditional knockout systems confirmed a key role for BIM in the hematopoietic system homeostasis [111, 112, 113, 114], and revealed a role for BIM in the survival and differentiation of hippocampal neurons [115]. Of note, myeloid cell-specific deletion of *Bcl2l11* induces a systemic lupus erythematosus (SLE)-like disease that resembles the pathology developing in mice that lack BIM in all cells [116].

Mice lacking BH3 interacting domain death agonist (BID), phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1, best known as NOXA) or BCL2 binding component 3 (BBC3, best known as PUMA) display normal embryonic development [117, 118, 119, 120]. In these studies on BID-deficient mice, substantial reduction in FAS ligand-induced apoptosis was seen in hepatocytes [117, 121], pancreatic cells [117, 122, 123] and possibly neurons [124, 125]. Moreover, *Bid*$^{-/-}$ mice display a dysregulated myeloid compartment resulting in an increased likelihood of leukemogenesis [125], as well as cardiac dysfunction [126]. Conditional gene deletion studies confirmed the relevance of BID in the homeostasis and functionality of hepatocytes and T cells [127, 128, 129].

PUMA contributes to normal ovarian development, as shown by the evidence that two-thirds of the germ cells produced during embryonic development undergo PUMA-mediated cell death shortly after formation [130]. Moreover, cells from PUMA-deficient mice are profoundly resistant to p53-induced apoptosis triggered by genotoxic drugs and lymphoid cells are also resistant to glucocorticoids, phorbol ester and growth factor deprivation [119, 120, 131, 132, 133]. Cells from NOXA-deficient mice also showed resistance to DNA damage-inducing drugs, although to a lesser extent compared to cells lacking PUMA [119, 134]. Moreover, *Pmaip1*$^{-/-}$ mice (lacking NOXA) show limited stress-induced erythropoiesis [135]. Germline deletion of the gene encoding PUMA or NOXA *also* affects humoral immune responses [136, 137] and increases the abundance of multiple cell types in the retina [138]. Interestingly, the loss of PUMA

greatly impairs radiation induced thymic lymphoma development and the formation of liver cancer [139, 140, 141, 142] (see main text), potentially reflecting the ability of apoptotic cells to secrete mitogenic and immunosuppressive molecules such as prostaglandin E2 ($PGE_2$) [143, 144]. PUMA was also shown to play a role in radiation-induced intestinal damage [145].

Co-deletion of two or more genes coding for BH3-only proteins confirmed the pronounced relevance of BIM for development and underscored some degree of functional redundancy in the system. On the one hand, mice lacking both PUMA and NOXA develop normally but their cells are profoundly resistant to genotoxic agents, as resistant as cells lacking p53 [146]. Concomitant loss of PUMA but not the additional loss of NOXA, BAD, BID or BIK increases the severity of hematopoietic defects imposed by the lack of BIM [147, 148, 149, 150]. On the other hand, *Bcl2l11*$^{-/-}$*Bbc3*$^{-/-}$*Bid*$^{-/-}$and *Bcl2l11*$^{-/-}$*Bbc3*$^{-/-}$*Bid*$^{-/-}$*Pmaip1*$^{-/-}$ mice displayed perinatal embryonic lethality and increased incidence of developmental defects, including webbed feet, imperforate vagina, and supernumerary neurons similar in extent to those seen in *Bax*$^{-/-}$ *Bak1*$^{-/-}$ mice [33, 151]. Of note, triple deficiency of BID, BIM, and PUMA completely abrogates BAX/BAK1 dependent apoptosis in cerebellar granule neurons and T lymphocytes [151], providing in vivo evidence supporting direct activation of BAX and BAK1 by the BH3-only proteins.

Mice lacking BCL2-associated agonist of cell death (*Bad*), BCL2 interacting killer (*Bik*), BCL2 modifying factor (*Bmf*) and harakiri, BCL2 interacting protein (contains only BH3 domain) (*Hrk*) are viable and develop normally [152, 153, 154, 155]. That said, BAD-deficient mice display a prolonged platelet lifespan [156], while *Bmf*$^{-/-}$ mice are characterized by mild lymphadenopathy, vaginal atresia [154, 157] as well as minor defects in mammary gland development and oogenesis [106, 158]. Interestingly, female *Bmf*$^{-/-}$ mice had significantly more primordial follicles than wild-type control animals associated with an extended fertile life span [159], while *Bmf*$^{-/-}$ mice developed an accelerated gamma irradiation-induced thymic lymphoma [154]. Combined deletion of some of the above listed BH3-only protein-coding genes does not

cause significant embryonic lethality or developmental abnormalities. Moreover, the combined absence of BIK and NOXA did not accelerate c-MYC-driven lymphoma development [160], while increased spontaneous tumorigenesis has been documented in *Bad*$^{-/-}$*Bmf*$^{-/-}$ mice [161]. Conversely, the absence of some of these BH3-only proteins aggravates the defects caused by the loss of *Bcl2l11* (the gene encoding BIM). This applies to: (1) *Bad* co-deletion with *Bcl2l11*, which enhances lymphocyte accumulation [156], (2) *Bik* co-deletion with *Bcl2l11*, which causes male infertility due to defective spermatogenesis [162], a phenotype resembling that of BAX-deficient mice, and (3) *Bmf* co-deletion with *Bcl2l11*, which considerably increases the incidence of developmental defects, vaginal atresia, lymphadenopathy, autoimmune glomerulonephritis, and spontaneous development of hematological malignancies [157, 163, 164].

## Box 3. Impact of anti-apoptotic BCL2 proteins on health.

While myeloid cell leukemia sequence 1 (*Mcl1*) deletion in mice induces embryonic lethality at the blastocyst (embryonic E3) stage prior to implantation [165, 166], embryos lacking BCL2-like 1 (BCL2L1, best known as BCL-$X_L$) die around embryonic day 13.5) with substantial cell depletion in the developing central nervous system (CNS) and erythroid progenitors [167]. Concomitant deletion of BCL2-associated X protein (*Bax*) or caspase 9 (*Casp9*) considerably limited neuronal cell death genotype caused by the absence of BCL-$X_L$ [168, 169]. Concomitant deletion of BCL2 like 11 (*Bcl2l11*, the gene encoding BIM) rescues the erythroid progenitors (but not the neuronal) cells from death in BCL-$X_L$-deficient mice [170]. *Bcl2*$^{-/-}$ mice are born but exhibit severe defects in their kidneys, alterations of the CNS, lymphoid cell depletion as well as premature graying of their hair and they succumb to polycystic kidney disease at a young age [171, 172, 173, 174, 175, 176, 177]. These defects can all be rescued by concomitant deletion of the gene encoding BIM, and, remarkably, in the case of some defects the loss of even a single allele of *Bim* is sufficient [171]. Mice with deletion of B cell leukemia/lymphoma 2 related protein A1a (*Bcl2a1a*, one of three isoforms of BCL2A1 in mice) or loss of all isoforms of BCL2A1 (best known as A1) show no developmental defects but display minor defects in the hematopoietic compartment [178, 179, 180, 181]. The absence of BCL-W results in male infertility due to defective spermatogenesis [182, 183, 184].

As opposed to homozygous deletion, haploinsufficiency for genes encoding MCL1 or BCL-$X_L$ did not result in defects in normal development [165, 167]. However, *Mcl1*$^{+/-}$ mice display significant, albeit minor decreases in certain hematopoietic cell types [185, 186], and poor hematopoietic recovery from stress, such as gamma-radiation or treatment with 5-FU, which can be rescued by deletion of BCL2 binding component 3 (*Bbc3;* the gene encoding PUMA) [186]. Moreover, the loss of one *Bcl2l1* allele (encoding BCL-$X_L$) limits male fertility due to defects in germ cell development [187] and shortens platelet lifespan [188]. Of note, while combined haploinsufficiency for *Mcl1* and *Bcl2*, for *Mcl1* and *Bcl2a1a* or for *Bcl2l1*

and *Bcl2* does not markedly affect embryonic development in mice [189, 190, 191], $Mcl1^{+/-}Bcl2l1^{+/-}$ double heterozygote mice display severe developmental defects and die during embryogenesis or early postnatally [190].Remarkably this defect that can be rescued by concomitant deletion of a single allele of the gene encoding BIM. These observations suggest that embryonic development is safeguarded by a delicate balance between pro- and anti-apoptotic BCL2 proteins.

Conditional knockout studies confirmed the importance of the different pro-survival BCL2 family members in specific tissues at precise developmental stages. These studies showed that MCL1 is critical for the development and/or maintenance of most (but not all) hematopoietic cell populations including stem and progenitor cells [192], immature as well as mature B and T lymphocytes [193, 194, 195, 196] Jain, 2017, 28972012;[197], natural killer (NK) cells [198], neutrophils [199, 200], mast cells and basophils [201], as well as Ig secreting plasma cells [202, 203]. Accumulating evidence suggests that the survival of some hematopoietic cell subsets is safeguarded by the combined activity of two or even more anti-apoptotic BCL2 family members [204]. Conditional deletion of *Bcl2l1* alone (leading to lack of BCL-$X_L$) or in combination with loss of *Mcl1* demonstrated functional redundancy between BCL-$X_L$ and MCL1 in developing lymphocytes [205, 206] and megakaryocytes [188, 207, 208, 209]. Conversely, BCL2 and A1 appear to have overlapping actions in the survival of B cells and neutrophils [189, 210, 211] but not megakaryocytes and platelets [212]. Data from hematopoietic chimeric mice confirm the role of these proteins in hematopoiesis [104, 167, 213, 214]. BCL2 is reported to contribute to the development and homeostasis of the mouse epidermis [215]. Along similar lines, MCL1 and BCL- $X_L$ play roles in the development and homeostasis of several tissues including the myocardium [216, 217], the CNS [218, 219, 220, 221, 222, 223, 224, 225, 226], the hepatic parenchyma [227, 228, 229, 230, 231], vascular endothelium [232], thymic epithelium [233], as well as the intestinal [234], mammary [235, 236], lung [237] and renal [238] epithelium.

There are substantial differences in the severity of the defects caused by the conditional deletion of different pro-survival BCL2 family genes and between distinct tissues. For instance, conditional deletion of *Mcl1* in mouse hematopoietic stem/progenitor cells [192], erythroid cells [239] or $T_{REG}$ cells [240] is lethal. In the latter case, lethality is ascribed to multiorgan autoimmunity caused by the depletion of the pool of $T_{REG}$ cells [240]. Similarly, the megakaryocyte-specific combined deletion of the genes encoding MCL1 and BCL-$X_L$ provokes embryonic or perinatal lethality [207], which can be rescued by the absence of BAK1 [80]. Similar findings have been obtained upon the ablation of *Mcl1* from the CNS or the myocardium, or the specific removal of the gene encoding BCL-$X_L$ from the respiratory epithelium, although these experiments did not include rescue approaches [217, 218, 219, 237]. The functional overlap between MCL1 and BCL-$X_L$ appears to be particularly relevant in the CNS and liver [225, 228]. Of note, the requirement of MCL1 and BCL-$X_L$ for neurogenesis appears to fluctuate between different stages of differentiation. The neurodevelopmental defects imposed by the deletion of *Mcl1* or *Bcl2l1* can be rescued by the absence of BAX [169, 225]. The detrimental effects of the hepatocyte-specific ablation of *Bcl2l1* or *Mcl1* can be rescued by deletion of *Bax* and *Bak1* as well as by that of *Bcl2l11* (encoding BIM*)* and/or BH3 interacting domain death agonist (*Bid*) [241, 242]. These observations demonstrate that organogenesis and adult tissue homeostasis depend on the balance between both anti-apoptotic and pro-apoptotic members of the BCL2 family. Further substantiating this notion, deletion of the gene encoding BCL-$X_L$ from keratinocyte precursors limits skin cancer development driven by ultraviolet B (UVB) rays and chemical carcinogens [243]. Conversely, the hepatocyte-specific deletion of *Mcl1* promotes hepatic carcinogenesis [244], as does the deletion of *Mcl1* in intestinal epithelial cells [234]. These latter findings may appear counterintuitive, as pre-malignant cells are expected to be more susceptible to succumb to environmental stress in the absence of MCL1 or BCL-$X_L$. However, both hepatic and intestinal carcinogenesis involve a robust inflammatory component that is exacerbated by tissue damage and cell death [245]. Moreover, MCL1-deficient tissues show an increased cell turnover, which results in elevated level of replicative stress and genetic

245 instability, potentially promoting carcinogenesis [231, 234]. Also, when many cells die, progenitors get
246 mobilized and must divide extensively. This increases the risk of such cells acquiring mutations that may
247 drive neoplastic transformation, as firstly shown in a murine model of radiation induced thymic T cell
248 lymphoma development [139, 140].

249

## Box 4. Impact of the apoptosome and apoptotic caspases on health

The whole-body deletion of apoptotic peptidase activating factor 1 (*Apaf1*) or caspase 9 (*Casp9*) is associated with fetal lethality around E14.5 to E16.5 [246, 247, 248]. Severe abnormalities in APAF1-deficient fetuses include webbed feet, craniofacial malformations, incomplete neural tube closure and/or excessive brain growth and exencephaly resulting in alteration of the central nervous system (CNS) including in the visual, olfactory, and auditory systems [246, 248, 249, 250, 251, 252]. Similar defects in the developing brain result from *Casp9* deletion [166, 248, 253], a phenotype that was not exacerbated by *Casp2* co-deletion [254]. The absence of CASP9 did not rescue neuronal defects due p53 hyperactivation in neural crest cells [255].

Of note, evidence linking mutations in *APAF1*, *CASP9* and *CASP3* to neural tube defects in humans has been reported [256, 257]. Mice lacking cytochrome c, somatic (CYCS) die in midgestation [258], while the deletion of cytochrome c, testis (*Cyct*), which is specifically expressed in male gonads is associated with normal development but male infertility [259]. The neuron-specific ablation of *Cycs* results in postnatal cell death [260]. Confirming that the detrimental effects of *Cycs* deletion result from impaired apoptosis, mice expressing a mutant CYCS that retains the ability to shuttle electrons as a component of the mitochondrial respiratory chain but is unable to assemble the apoptosome exhibit perinatal lethality and developmental brain defects similar to APAF1- and CASP9-deficient mice [261].

Importantly, the genetic background of the mouse strains appears to significantly influence the impact of the absence of core components of the apoptotic machinery on embryonic development. Thus, while genetic deletion of *Casp3* in 129S1/SvImJ mice results in embryonic or early postnatal lethality due to the severe defects in brain development that are only partially rescued by concomitant deletion of the gene encoding BCL-$X_L$, on a C57BL/6 background *Casp3*$^{-/-}$ mice develop normally and survive into adulthood [262, 263, 264, 265]. A similar impact of genetic background on phenotype has also been observed

for *Apaf1*$^{-/-}$ and *Casp9*$^{-/-}$ mice [266, 267]. Although *Casp3*$^{-/-}$ mice reach adulthood on a C57BL/6 background, they exhibit defects in complex brain functions including attention and (in males) social behavior [268, 269], as well as ear and vestibular dysfunction including hearing loss [270, 271, 272, 273, 274], Abnormalities were also seen in the kidney and spleen of aged *Casp3*$^{-/-}$ mice [275]. Survival of *Casp3*$^{-/-}$ mice to adulthood in C57BL/6 mice was ascribed to the compensatory activation of CASP7 [276]. The combined ablation of *Casp3* and *Casp7* causes embryonic lethality on the C57BL/6 background, although death is caused by severe cardiac rather than brain defects [277]. Such phenotypic differences may originate from some degree of substrate selectivity exhibited by CASP3 *vs.* CASP7 [278, 279, 280, 281, 282]. Moreover, a recent study performed in *Casp7*$^{-/-}$ mice indicates that CASP7 acts as a facilitator of the variants of RCD occurring in the context of pore-driven lysis rather than an apoptotic executioner [283].

Approximately 5% of APAF1-deficient mice develop normally and survive into adulthood, although males are often sterile due to defective spermatogenesis [247]; their phenotype is reminiscent of the phenotype of mice deficient for BAX, BAK1 and BOK (*i.e.*, *Bak1*$^{-/-}$*Bax*$^{-/-}$*Bok*$^{-/-}$ mice) [64]. Of note, rare adult *Apaf1*$^{-/-}$ male mice that retain fertility display expansion of the lateral brain ventricles coupled with behavioral abnormalities and growth retardation [267]. Conversely, the rare mice expressing a CYCS variant specifically deficient in apoptotic functions that survive into adulthood exhibit impaired lymphocyte homeostasis [261]. Whole-body deletion of diablo, IAP-binding mitochondrial protein (*Diablo*, coding for a pro-apoptotic factor also known as SMAC) alone or along with HtrA serine peptidase 2 (*Htra2*) does not result in developmental defects in mice [284, 285], while the *Diablo*$^{-/-}$*Casp3*$^{-/-}$ genotype accrues the perinatal lethality observed in *Casp3*$^{-/-}$ mice [286]. Mice lacking the X-linked inhibitor of apoptosis (XIAP, the main target of the pro-apoptotic activity of SMAC and HTRA2) are also viable and develop normally, possibly due to functional compensation by other members of the inhibitor of apoptosis protein (IAP) family [287, 288], but they exhibit mild defects in late pregnancy that do not compromise lactation [287]. Consistent with this SMAC-mimetic drugs that were designed to induce

apoptosis by antagonizing IAPs are quite well tolerated [289]. *Xiap*$^{-/-}$ mice also show dysregulated innate immune responses [290], most likely linked to the modulatory role of XIAP in inflammation and necroptosis [291, 292, 293], or to the inability of these animals to resolve infections [294]. Accordingly, loss-of-function mutations in *XIAP* are associated with X-linked lymphoproliferative syndrome type 2 in humans [291, 295, 296, 297].

The myocardium-specific deletion of *Casp3* and *Casp7* impairs heart development in mice resulting in myocyte hypertrophy [298]. The role of APAF1, CASP9 and CASP3 in hematopoiesis remains debated. Specific ablation of *Apaf1* or *Casp9* from the hematopoietic system using lethally irradiated wild-type mice reconstituted with hematopoietic stem/progenitor cells deficient for these factors did not expand the lymphoid or myeloid cell compartments [299]. Likewise, no hematopoietic defects emerge from the whole-body deletion of *Casp3* [277]. Moreover, mice lacking *Casp9* in the hematopoietic system display a proper generation and functionality of megakaryocytes and platelets [300]. Moreover, the clearance of *Casp9*$^{-/-}$ thymocytes seems to occur in a caspase-independent fashion [301]. In the same line, although apoptosis is widely believed to be crucial for epithelial cell death and shedding in the intestine, during steady state, executioner CASP3 and CASP7 are dispensable for intestinal epithelial cell turnover at the top of intestinal villi, intestinal tissue dynamics, microbiome, and immune cell composition, suggesting high redundancy in non-challenged conditions [302]. Apparently at odds with these observations, *Casp3*$^{-/-}$ mice were reported to have abnormally increased numbers of splenic B cells manifesting increased proliferative capacity [303], as well as a dysregulated activity in bone marrow stromal stem cells that attenuated osteogenic differentiation [304]. A similar debate revolves around the requirement for APAF1 and caspase activity in thymocyte selection and/or T cell responses [299, 305, 306, 307, 308, 309]. Mouse bone marrow chimeras deficient for APAF1 or CASP9 in their hematopoietic cells displayed a defect in hematopoietic stem/progenitor cells that is caused by the aberrant type 1 interferon production caused by the fact that hematopoietic cells undergoing normal programmed cell death do not die in a “neat” non-

inflammatory manner [310, 311]. Taken together, these findings suggest that BAX/BAK1 dependent death of hematopoietic cells does not require caspases but that caspases are needed to prevent an inflammation causing form of cell demolition [312, 313, 314, 315]. However, neither the degree of functional redundancy exhibited by CASP3, CASP6 and CASP7, nor the potential for APAF1-independent CASP3 activation has been formally excluded in these studies, most of which involved single genetic alterations.

## **Box 5.** Principles of extrinsic apoptosis.

Extrinsic apoptosis is a regulated cell death (RCD) process frequently triggered by immune effector cells expressing TNF superfamily death ligands binding the death receptor (DRs) upon binding of a cognate ligand [316, 317, 318]. The principal DRs which will be discussed in the review are the Fas cell surface death receptor (FAS; also known as CD95 or APO-1), the TNF receptor superfamily member 1A (TNFRSF1A; best known as TNF-R1), the TNF receptor superfamily member 10a (TNFRSF10A; best known as TRAIL-R1 or DR4) and the TNF receptor superfamily member 10b (TNFRSF10B; best known as TRAIL-R2 or DR5). FAS is activated by the binding of FAS ligand (FASLG; also known as CD95L or APO-1L; FASL in mice), which is primarily expressed by effector immune cells [318]. TNF-R1 is activated by tumor necrosis factor (TNF), a functionally pleiotropic cytokine expressed in cells in the spleen, thymus and certain other adult tissues [316]. Of note, while the soluble form of TNF preferentially binds to TNF-R1, the membrane-anchored form mainly interacts with the TNF receptor superfamily member 1B (TNFRSF1B, best known as TNF-R2), which does not have death domain and therefore is not a DR [319]. Finally, TRAIL-R1 and TRAIL-R2 are specifically activated by the binding of TNF superfamily member 10 (TNFSF10; best known as TRAIL), which is expressed by a variety of cell subtypes of the innate as well as adaptive system, including monocytes, macrophages and effector T cells, as either a soluble or membrane-bound version [320]. Of note, mice express only one TRAIL receptor (TRAIL-R2, referred in this article as mTRAIL-R) which is equally homologous to human TRAIL-R1 and TRAIL-R2.

Upon ligand binding and trimerization and in certain instances formation of higher order complexes, the engagement of DRs promotes the assembly of multi-protein complexes, such as the death-inducing signaling complex (DISC) and complex II, resulting in the activation of caspase 8 (CASP8) and apoptosis [321, 322, 323, 324]. The DISC, which is assembled on the cytoplasmic tail of ligated FAS, TNF-R1, TRAIL-R1 or TRAIL-R2, is comprised of the molecular adaptor Fas-associated death domain protein (FADD),

Fas (TNFRSF6)-associated via death domain (FADD), CASP8, and (FADD-like IL-1β-converting enzyme)-inhibitory protein distinct isoforms of CASP8 and FADD like apoptosis regulator (CFLAR; best known as c-FLIP), including the alternative splicing variants, the long form c-FLIP$_L$ and the short form c-FLIP $_S$ and (in human) c-FLIP$_R$ [325, 326, 327, 328, 329, 330]. Of note, c-FLIPs are catalytically inactive CASP8-like molecules acting as a modulator of CASP8 activation. Unlike FAS- and TRAIL-R-associated DISCs, complex II is a cytosolic complex assembled secondarily upon TNF-R1 ligation, in conditions of reduced pro-survival signaling and protein synthesis as for instance upon administration of inhibitors of inhibitor of apoptosis proteins (IAPs) and cycloheximide [331]. Complex II consists of FADD and CASP8 in association with either TNF-R1-associated death domain protein (TRADD) (complex IIa) or receptor interacting serine/threonine kinase 1 (RIPK1) (complex IIb), which is involved in the modulation of apoptosis and necroptosis [332]. Upon the recruitment to the DISC (complex I), CASP8 is activated by a process involving CASP8 oligomerization and autoproteolysis. CASP8 then acts as the executor of extrinsic apoptosis by favoring the proteolytic activation of the effector caspases CASP3 and CASP7 [333]. This direct pathway is sufficient for FAS ligand induced killing thymocytes and mature lymphocytes (so-called type 1 cells), but the efficient killing of hepatocytes, pancreatic β cells, and most cancer cells (so-called type 2 cells) requires pathway amplification through caspase-8 mediated proteolytic activation of the BH3-only protein BID, leading to engagement of the intrinsic apoptotic pathway [117, 334, 335, 336, 337, 338, 339 PMID: 9501089 PMID: 9501089 PMID: 9501089 PMID: 9501089]. Of note, the absence of XIAP converts type 2 cells into type 1 cells [123], indicating that a limited amount of caspase activity is needed for cell killing.

Once activated, CASP8 also cleaves RIPK1 leading to the inhibition of necroptosis and the maintenance of inflammatory homeostasis [340]. As a further layer of complication, the engagement of DRs by their respective ligands does not necessarily culminate in the activation of the extrinsic apoptosis signaling

pathway. Indeed, the engagement of FAS, TRAIL-Rs and TNF-R1 can also result in the activation of pro-survival pathways which is often but not always dependent on NF-κB signaling [320, 341], or, alternatively, in the initiation of inflammatory responses, the promotion of processes including cell differentiation/activation (as is the case of lymphocytes), and the activation or inhibition of other RCD variants, particularly necroptosis and pyroptosis [342]. The induction of inflammatory chemokines and cytokines downstream of the activation of FAS and TRAIL-Rs is mediated by FADD and CASP8 by a mechanism that can be independent of apoptosis induction [343, 344].

Extrinsic apoptosis can be activated by another class of cell surface receptors known as dependence receptor. In this case, cell death is ignited by the decrease in the availability of a specific ligand on which these receptors depend, while the latter through the binding of a cognate ligand [345, 346]. The dependence receptors include (but are not limited to) the DCC netrin 1 receptor (DCC) and distinct types of unc-5 netrin receptors (UNC5A, UNC5B, UNC5C, and UNC5D), all of which are bound by netrin 1 (NTN1), and the neurotrophic receptor tyrosine kinase 3 (NTRK3) and patched 1 (PTCH1), which are, respectively, ligated by neurotrophin and sonic hedgehog (SHH). The activation of dependence receptors stimulates hitherto poorly characterized signaling cascade often dependent on caspase activation, leading to the induction of cell death [347, 348]. It is noteworthy that the relevance of the dependence receptor-induced apoptosis for normal physiology and disease is not established.

## **Box 6.** Impact of death receptors on health.

A large body of data demonstrates that death receptor (DR) signaling is crucial for the maintenance of adult tissue homeostasis but nor for embryonic development as demonstrated by the normal appearance of mice double knockout for caspase 8 and mixed lineage kinase domain like pseudokinase (*Casp8*$^{-/-}$ *Mlkl*$^{-/-}$ mice) or CASP8 and receptor-interacting serine-threonine kinase 3 (*Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice) (before they develop lymphadenopathy and splenomegaly) [349, 350, 351, 352, 353, 354]. Mouse strains with spontaneous mutations in TNF receptor superfamily member 6 (*Fas*) - the so-called *lpr*/*lpr* mice – or Fas ligand (TNF superfamily, member 6) (*Fasl*) - the so-called *gld*/*gld* mice - are viable but develop progressive lymphoproliferative and systemic lupus erythematosus (SLE)-like disorders [355, 356, 357, 358, 359]. The severity of these pathologies is greatly influenced by genetic background: fairly mild on a C57BL/6 background but very severe on the MRL or NOD backgrounds. Mice with heterozygous *Fas* or *Fasl* mutations are normal [359]. These lymphoproliferative and autoimmune disorders are not accompanied by impaired thymocyte development [360]. Transgenic overexpression of BCL2 [335] or MCL1 [361] in the lymphocyte compartment of *lpr*/*lpr* mice or the absence of BIM [362] massively exacerbate lymphadenopathy. This is consistent with the notion that intrinsic apoptosis and DR-induced apoptosis are distinct in lymphoid cells and act additively. FAS or FASL deficiency also perturbs the homeostasis or function of other mouse tissues, including (but not limited to) the liver [360], kidney [363], retina [364], pancreas [365] and intestinal epithelium [366], but these effects may all be a consequence of the deregulation of the lymphoid system in these mice, for example causing excess production of certain cytokines and chemokines.

Conditional deletion of *Fas* and *Fasl* in specific immune cell subsets as well as transgenic expression of FAS in lymphocytes confirms the crucial role of FASL-FAS signaling in the homeostasis of lymphocytes and dendritic cells (DCs) [367, 368, 369, 370, 371]. In this context, experiments in *lpr*/*lpr* mice deleted of BH3-

only protein BCL2 like 11 (*Bcl2l11*, the gene encoding BIM) demonstrate some degree of cooperation between FAS and BIM in preserving the functionality of the immune system [362]. However, abrogating FAS-FASL signaling ultimately has heterogeneous organismal consequences. The lymphoproliferative disorder caused by *Fas* or *Fasl* deletion confers protection from autoimmune diabetes [372]. This may be explained by the fact that the distortion of the T cell repertoire caused by the lymphadenopathy in the *lpr*/*lpr* and *gld*/*gld* mice prevents the development of diabetogenic T cells. Finally, FAS appears to exert tumor suppressive effects in lymphoid cells. Indeed, both *gld*/*gld* mice as well as *lpr*/*lpr* mice lacking the T cell compartment have increased incidence of B cell lymphoma [373, 374, 375]. Loss of FAS also predisposes humans to B lymphoma (see below).

As for the other DRs, mice lacking TNF receptor superfamily member 10b (TNFRSF10B, best known as TRAIL-R2 or mTRAIL-R) or its ligand TNF superfamily member 10 (*TNFSF10*, beast known as TRAIL) are viable, fertile, and do not spontaneously develop autoimmune diseases [376, 377, 378, 379]. Moreover, these mice exhibit normal immune system development and function [380, 381, 382, 383]. Along similar lines, the whole-body deletion of the DR ligand tumor necrosis factor (*Tnf*) does not affect mouse development and fertility [384, 385]. However, $Tnf^{-/-}$ mice often show early hearing loss and, despite presenting with an overtly functional immune system, these mice exhibit abnormally increased susceptibility to spontaneous bacterial infection, which has been ascribed to multiple defects including defective lymphoid organ architecture as well as deficient granuloma and germinal center formation [384, 385, 386, 387, 388]. Impaired responses to pathogens have been documented in $Tnf^{+/-}$ mice [384] as well as in mice lacking TNF receptor superfamily member 1A (TNFRSF1A, best known as TNF-R1) [386, 389, 390]. Conversely, mice overexpressing TNF in cardiomyocytes suffer from lethal dilated cardiomyopathy, demonstrating that balanced TNF signaling is essential for the homeostasis of the cardiac tissue [391, 392, 393]. Of note, while the lack of TRAIL enhances the severity of lymphoproliferative and autoimmune disorders in *gld*/*gld* mice [394], the lack of TNF attenuates the lymphoproliferative phenotype, extending

436 the survival of *gld*/*gld* mice [395]. The latter is probably due to the reduction in TNF-mediated inflammation
437 attenuating lymphadenopathy caused by the absence of FAS ligand. These findings confirm the
438 pleiotropy and redundancy of DR signaling, encompassing not only apoptotic and non-apoptotic
439 regulated cell death (RCD)-related effects, but also various pro-survival and pro-inflammatory modules.

440 Multiple clinical observations support the role of FAS ligand/FAS signaling in human hematopoiesis [396,
441 397]. Most human patients with autoimmune lymphoproliferative syndrome (ALPS) - a primary
442 immunodeficiency manifesting with lymphadenopathy, splenomegaly as well as abnorrmal numbers,
443 development and function of lymphocytes carry loss-of-function mutations in *FAS* or *FASLG* [398, 399, 400,
444 401, 402, 403, 404]. ALPS patients also display an increased incidence of non-Hodgkin and Hodgkin lymphoma
445 [405]. While no mutations in the genes encoding TRAIL, TRAIL-R1 and TRAIL-R2 have so far been linked
446 to human autoimmune diseases, autosomal dominant mutations in *TNFRSF1A* (leading to lack of TNF-
447 R1) have been identified in patients affected by TNF receptor-associated periodic syndrome (TRAPS),
448 characterized by severe abdominal pain, arthralgias, and myalgias [406, 407, 408].

449

## Box 7. Impact of extrinsic apoptosis complexes and caspases on health.

Several signal transducers in the death receptor (DRs) pathway are essential for embryonic development in mice. Thus, deletion of Fas (TNFRSF6)-associated via death domain (*Fadd*), caspase 8 (*Casp8*) or CASP8 and FADD-like apoptosis regulator (*Cflar*) is embryonic lethal at mid-gestation as a consequence of severe vascular as well as cardiac defects associated with spontaneous intra-abdominal hemorrhage [409, 410, 411, 412, 413, 414]. Of note, CASP8-deficient mice also exhibit neural tube defects [413]. A similar embryonic lethality has also been documented in mice expressing a mutant form of FADD deficient in its death domain [410]. The absence of other components of DR-associated signaling complexes, such as TNFRSF1A associated via death domain (TRADD) and receptor-interacting serine/threonine kinase 1 (RIPK1), causes different abnormalities. Thus, while *Tradd*$^{-/-}$ mice develop normally and do not display major hematopoietic defects [415, 416, 417], *Ripk1*$^{-/-}$ mice die early after birth due to severe multiorgan inflammation [418, 419]. These findings are attributed to the pleiotropic contribution of RIPK1 and TRADD to a variety of processes beyond apoptosis, most notably necroptotic regulated cell death (RCD) and inflammation. This is exemplified by the observation that the embryonic lethality caused by the absence of CASP8 or FADD can be rescued by the concomitant loss of MLKL or RIPK3 (see text). Mice lacking baculoviral IAP repeat-containing 3 (BIRC3; best known as IAP1) and X-linked inhibitor of apoptosis (XIAP) or IAP1 and BIRC2 (best known as IAP2) but not mice lacking IAP2 and XIAP display embryonic lethality [420]. These findings indicate specific functional redundancies among the inhibitor of apoptosis protein family. IAP1/IAP2-deficient mice display mid-gestation lethality, which was rescued to birth by the deletion of TNF receptor superfamily member 1A (*Tnfrsf1a*, encoding TNF-R1) but not that of TNF receptor superfamily member 1B (*Tnfrsf1b*, best known as TNF-R2) [420]. Loss of one allele of *Ripk1* or loss of *Ripk3* prolonged embryonic survival of these mice [420]. It is noteworthy, that, as discussed above, genetic background effects might contribute to the phenotype, as mice with concomitant

knockout of the genes encoding IAP1 and IAP2 using mutant alleles generated in C57BL/6 embryonic stem cells die in midgestation [420], whereas *Iap1*$^{-/-}$ and *Xiap*$^{-/-}$ double mutants generated using 129Sv embryonic stem cells are viable [421].

It was demonstrated that embryonic lethality in *Casp8*$^{-/-}$ and *Fadd*$^{-/-}$ mice is due to excessive necroptosis, reflecting the ability of CASP8 to limit necroptosis downstream of DR activation [349, 350, 422, 423]. Accordingly, deletion of genes encoding key components of the necroptotic machinery such as RIPK3 or MLKL prevents all developmental defects and embryonic lethality in FADD- or CASP8-deficient embryos [349, 350, 351, 352, 354, 423, 424]. Of note, *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ and *Casp8*$^{-/-}$*Mlkl*$^{-/-}$ mice develop progressive lymphoproliferative disorders that resemble those caused by the absence of FAS or FASL [350, 351, 423]. Moreover, embryonic lethality around E10.5 in mice lacking c-FLIP and the perinatal lethality of *Ripk1*$^{-/-}$ mice depend on aberrant activation of both DR-induced apoptosis and DR-induced necroptosis. Indeed, the lethality of these animals can be rescued by concomitant deletion of *Fadd* and *Ripk3*, *Casp8* and *Ripk3*, or *Fadd* and *Mlkl* [349, 350, 351, 352, 353, 354]. Of note, mice with loss of *Ripk1* that prevents its CASP8-mediated cleavage die around E10.5 of embryonic development and this can be prevented by the combined absence of RIPK3 and CASP8 [340, 425, 426]. In a heterozygous state these mutations in the gene encoding RIPK1 cause severe auto-inflammation. As an additional layer of complexity, although the deletion of *Tradd* rescues *Ripk1*$^{-/-}$*Ripk3*$^{-/-}$ embryos from perinatal lethality, triple knockout mice die postnatally [427, 428]. Moreover, TRADD deficiency does not prevent the embryonic lethality caused by the loss of FADD [428]. Additional studies confirm the importance of the inter-connectivity between multiple regulated cell death (RCD) pathways. Mice with a mutation that prevents auto-proteolytic activation of CASP8 develop normally [429], but akin to complete loss of *CASP8*, mutations in the CASP8 catalytic site result in embryonic lethality around E10.5 due to aberrant necroptosis [425, 430], while the genetic ablation of *Mlkl* or *Mlkl* plus *Fadd* prevent E10.5 embryonic lethality in these mice, the compound mutant mice

die soon after birth, likely due to aberrant inflammation and pyroptosis [431, 432]. These observations point to the central role for CASP8 in the regulation of multiple RCD variants and inflammatory processes [433].

The tissue-specific deletion of *Fadd* or *Casp8* in mouse endothelial cells results in an embryonic lethal phenotype that resembles that of germline *Fadd* or *Casp8* deletion [434, 435]. Conversely, the absence of FADD in cardiomyocytes or cardiac progenitor cells appears to have no impact on embryonic development [434]. Again, abrogation of necroptosis rescued the lethal phenotype of endothelial cell specific *Fadd* or *Casp8* deletion [434], lending additional support to inhibitory role of FADD and CASP8 in necroptotic RCD. FADD, CASP and CFLAR (best known as c-FLIP) have also been implicated in hematopoietic system homeostasis. However, the absence of FADD in specific immune cell subsets in mice via distinct experimental approaches, such as conditional gene deletion, injection of *Fadd*$^{-/-}$ embryonic stem cells into *Rag1*$^{-/-}$ blastocysts or transgenic expression of a dominant-negative variant of FADD does not drive lymphoproliferative disorders. Instead, FADD appears to be critical for the proliferation and/or development of T lymphocytes [436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446] and B cells [447], most likely by preventing necroptosis through activation of CASP8 which then prevents RIPK1/RIPK3 mediated activation of MLKL. Similar conclusions were derived from the analysis of mice with lymphocyte-specific ablation of *Casp8* or *Cflar* [448, 449, 450, 451, 452, 453]. A role for CASP8 in T cell proliferation has also emerged from the realization of the anti-proliferative effects of caspase inhibitors [454]. The T cell-specific deletion of *Casp8* attenuates autoimmunity and improved the survival of mice lacking the BH3-only protein BCL2 like 11 (BCL2L11, best known as BIM) by limiting T cell proliferation and survival [455]. Apparently at odds with these findings, the conditional deletion of *Casp8* in T cells has also been associated with an age-dependent, lymphoproliferative immune disorder resembling the condition of patients with *CASP8* mutations [456]. Whether mouse genetic background or other contextual variables (*e.g.*, the mouse microbiota) underlie such apparent discrepancies remains to be elucidated.

The conditional loss of the functions of FADD or CASP8 also revealed a role for these proteins in early hematopoiesis, which may relate to their ability to promote the proliferation and differentiation of hematopoietic stem and progenitor cells by preventing necroptosis [435, 457, 458]. Conditional deletion of *Fadd* in myeloid cells resulted in increased myeloid and B cell populations coupled to activation of inflammatory responses [459]. Along similar lines, the macrophage-restricted deletion of *Casp8* induced a mild systemic inflammatory disease potentially linked to altered macrophage polarization [460, 461], while the DC-specific deletion of the genes encoding c-FLIP or CASP8 elicited splenomegaly, inflammatory responses and autoimmune disorders [462, 463, 464]. These effects all seem to be unrelated to the pro-apoptotic functions of FADD and CASP8 but reflect their ability to prevent necroptosis [350, 423, 443, 459, 460, 465, 466, 467]. Corroborating these findings, loss-of-function mutations in *FADD* [468, 469, 470, 471], *CASP8* or *CASP10* [472, 473, 474] and *TRADD* [475] have been associated with ALPS-like syndromes and certain hematological diseases in humans. Of note, patients with ALPS bearing mutations in *FADD* or *CASP8* but not ALPS patients with mutations in *FAS* or *FASLG* also exhibit immunodeficiency coupled with lymphocytic infiltrations in multiple organs, granulomas and/or inflammatory bowel disease [468, 472, 476, 477, 478].

Tissue-specific deletion of *Fadd*, *Casp8* and *Cflar* has also revealed a role for these proteins in the homeostasis of the liver, skin and intestine, although severity of the phenotype varies quite considerably, ranging from mild inflammatory response to embryonic or early postnatal lethality, again likely due to unleashed necroptosis. Conditional deletion of *Cflar* (resulting in lack of c-FLIP) in intestinal epithelial cells, hepatocytes or keratinocytes resulted in embryonic or perinatal lethality due to aberrant activation of cell death [479, 480, 481, 482]. The inducible deletion of *Cflar* from the intestinal epithelium of adult mice caused severe inflammation that was often fatal [482]. These findings are in line with the crucial role of c-FLIP as an inhibitor of necroptosis [349, 483]. Along similar lines, *Fadd* deletion in epidermal keratinocytes or intestinal epithelial cells causes severe chronic inflammation due to the induction of aberrant necroptosis [484, 485, 486, 487, 488, 489, 490]. Accordingly, the removal of FADD (or CASP8) in intestinal

544 epithelial cells resulted in chronic inflammatory colitis and ileitis, which was prevented by concomitant
545 deletion of *Ripk3* or *Mklk* [430, 432, 485, 487, 490, 491]. In one of these studies, acute deletion of *Casp8* in the gut
546 of adult mice resulted in enterocyte death, leading to disruption of tissue homeostasis, sepsis and death
547 [490]. In this context, CASP8-deficient enterocytes displayed decreased *in vivo* survival and migration
548 potential [492]. Specific deletion of *Casp8* in endothelial cells results in small intestinal hemorrhage and
549 bowel inflammation, suggesting a key role of CASP8 in vascular homeostasis in the small intestine [493].
550 Expression of a catalytically inactive variant of CASP8 resulted in embryonic lethality similar to *Casp8*$^{-}$
551 $^{/-}$ mice, which was rescued by concomitant deletion of *Mlkl* [430]. However, unexpectedly, catalytically
552 inactive CASP8 mutant mice also deficient for MLKL died perinatally. Loss of CASP8 catalytic activity
553 specifically in intestinal epithelial cells induced intestinal inflammation similar to absence of CASP8 in
554 the intestinal epithelium. This intestinal phenotype was aggravated by *Mlkl* deletion, resulting in
555 premature death dependent on the induction of inflammatory responses and pyroptosis [430]. As an added
556 layer of complexity, deletion of tumor necrosis factor (*Tnf*) or *Tnfrsf1a* (encoding TNF-R1) attenuated
557 colitis, but not ileitis, in mice with an intestinal epithelial cell-specific deletion of *Fadd* or *Casp8* [482, 485].
558 A recent study indicated that this effect may also involve the aberrant activation of pyroptosis. Indeed,
559 the CASP8-dependent activation of gasdermin D (GSDMD) appears to promote ileitis in mice with
560 FADD-deficient intestinal epithelial cells [494]. These results are in line with the crucial involvement of
561 CASP8 and FADD in the activation of inflammation [495, 496] and indicate that the FADD-CASP8 axis
562 regulates tissue homeostasis by balancing apoptosis, necroptosis, pyroptosis and inflammation.

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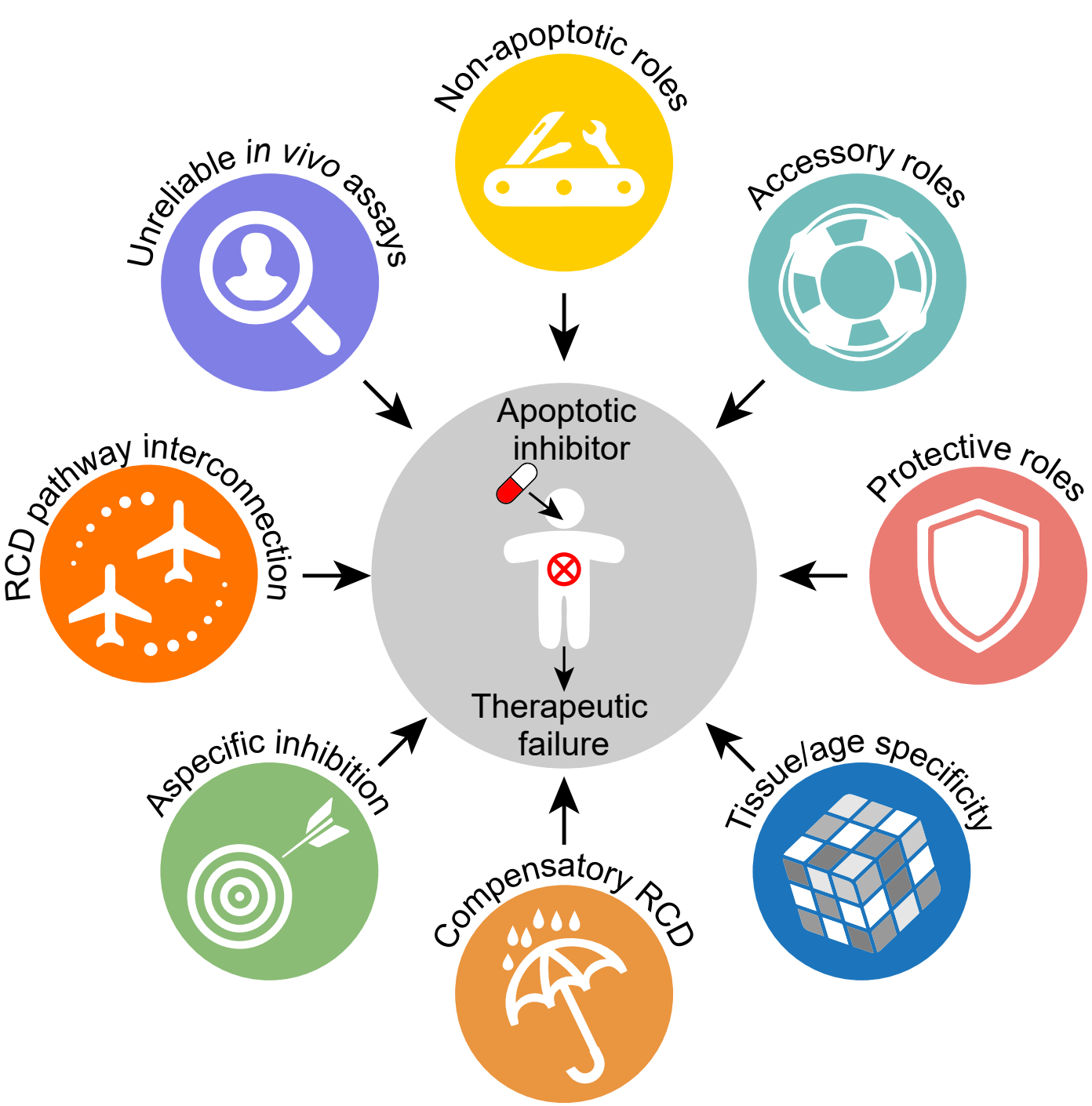
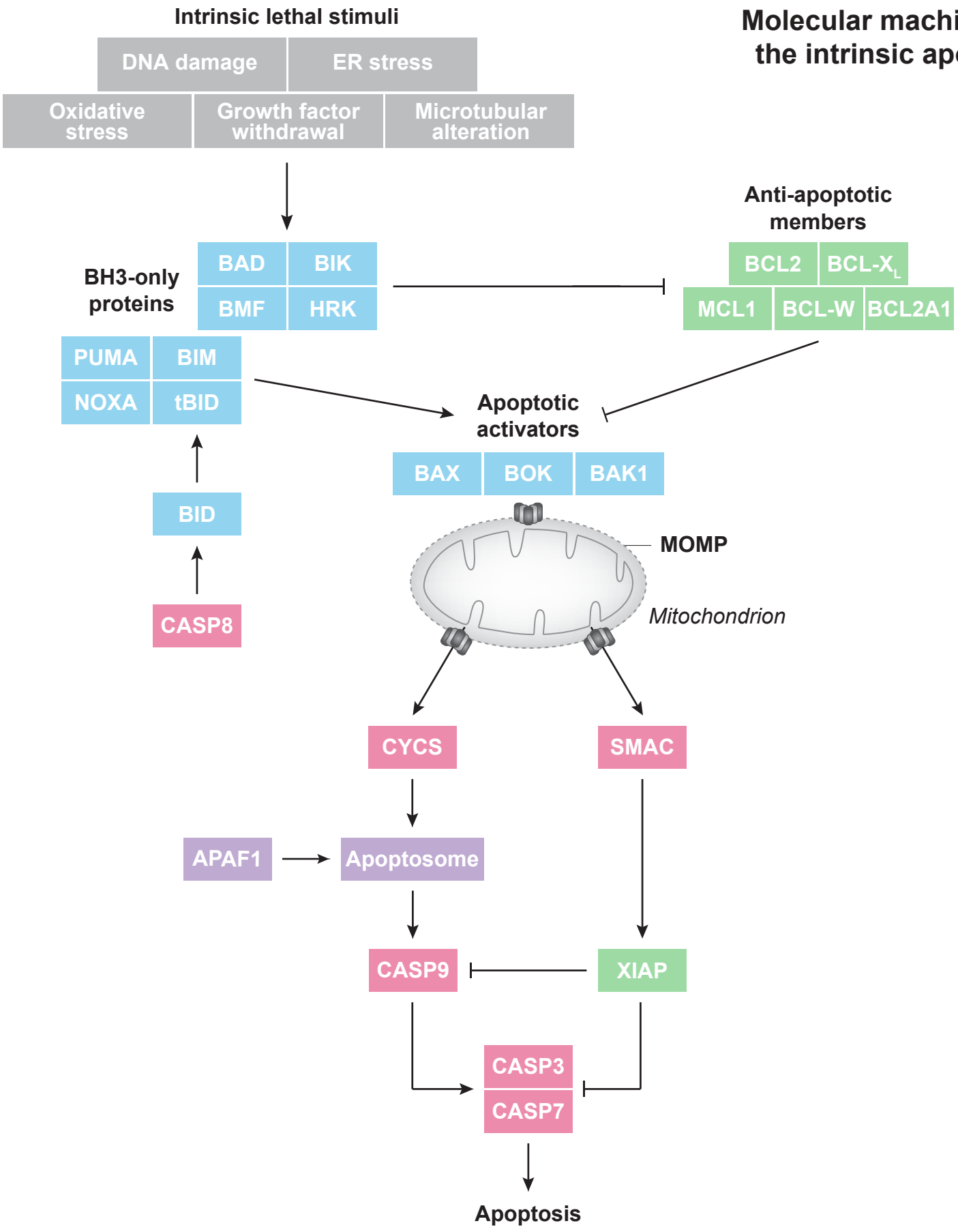

Non-apoptotic roles
Unreliable in vivo assays
Accessory roles
Apoptotic inhibitor
RCD pathway interconnection
Protective roles
Therapeutic failure
Aspecific inhibition
Tissue/age specificity
Compensatory RCD

**Figure 1**


Molecular machinery of the intrinsic apoptosis
Intrinsic lethal stimuli
DNA damage
ER stress
Oxidative stress
Growth factor withdrawal
Microtubular alteration
BH3-only proteins
BAD
BIK
BMF
HRK
PUMA
BIM
NOXA
tBID
BID
CASP8
Anti-apoptotic members
BCL2
BCL-XL
MCL1
BCL-W
BCL2A1
Apoptotic activators
BAX
BOK
BAK1
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CASP9
XIAP
CASP3
CASP7
Apoptosis

Figure 2

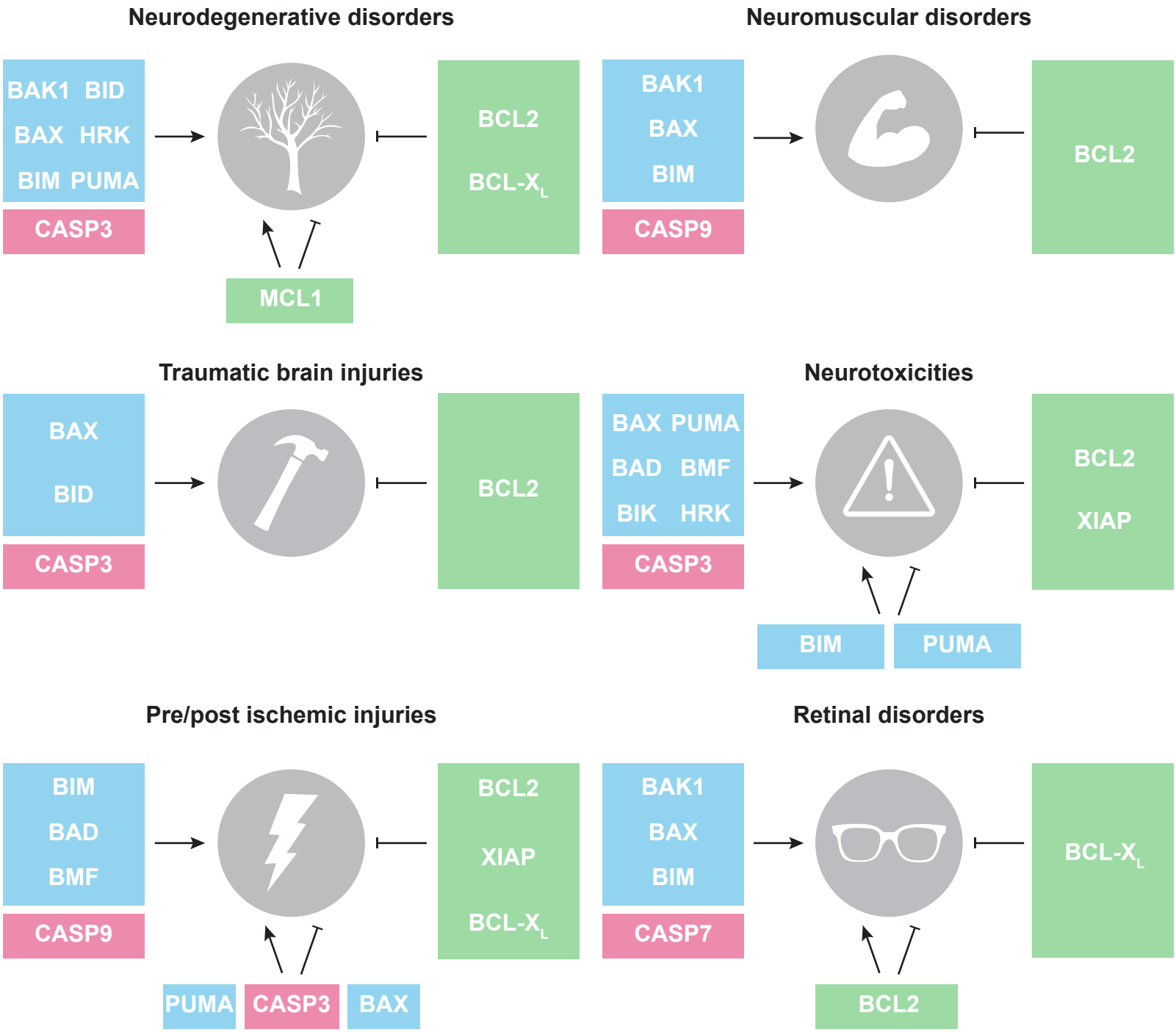
Neurodegenerative disorders
BAK1 BID
BAX HRK
BIM PUMA
CASP3
BCL2
BCL-X$_L$
MCL1
Neuromuscular disorders
BAK1
BAX
BIM
CASP9
BCL2
Traumatic brain injuries
BAX
BID
CASP3
BCL2
Neurotoxicities
BAX PUMA
BAD BMF
BIK HRK
CASP3
BCL2
XIAP
BIM
PUMA
Pre/post ischemic injuries
BIM
BAD
BMF
CASP9
BCL2
XIAP
BCL-X$_L$
PUMA
CASP3
BAX
Retinal disorders
BAK1
BAX
BIM
CASP7
BCL-X$_L$
BCL2

**Figure 3**

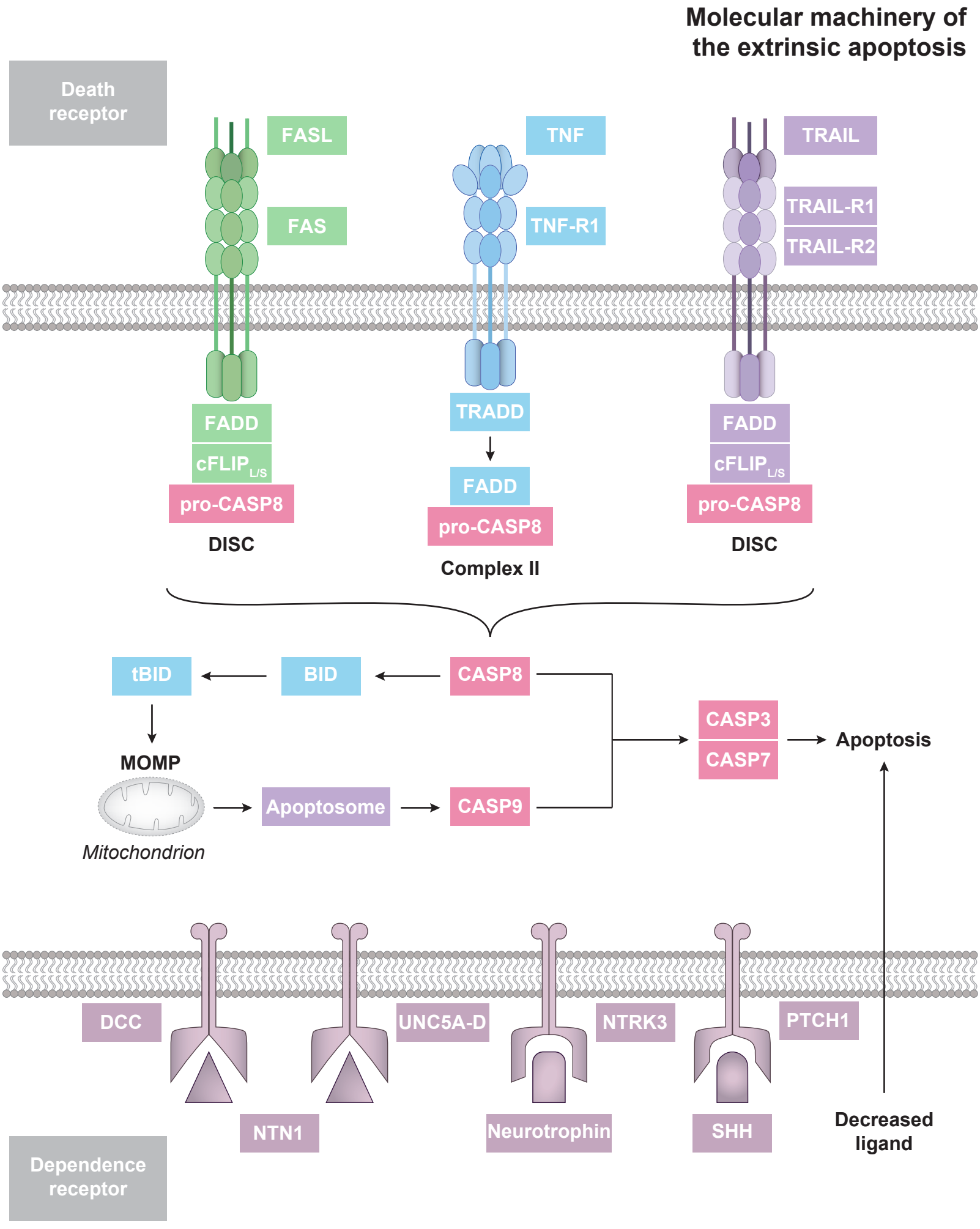
Molecular machinery of the extrinsic apoptosis
Death receptor
FASL
FAS
TNF
TNF-R1
TRAIL
TRAIL-R1
TRAIL-R2
FADD
cFLIP L/S
pro-CASP8
DISC
TRADD
FADD
pro-CASP8
Complex II
FADD
cFLIP L/S
pro-CASP8
DISC
tBID
BID
CASP8
CASP3
CASP7
Apoptosis
MOMP
Apoptosome
CASP9
Mitochondrion
DCC
UNC5A-D
NTRK3
PTCH1
NTN1
Neurotrophin
SHH
Decreased ligand
Dependence receptor

Figure 4

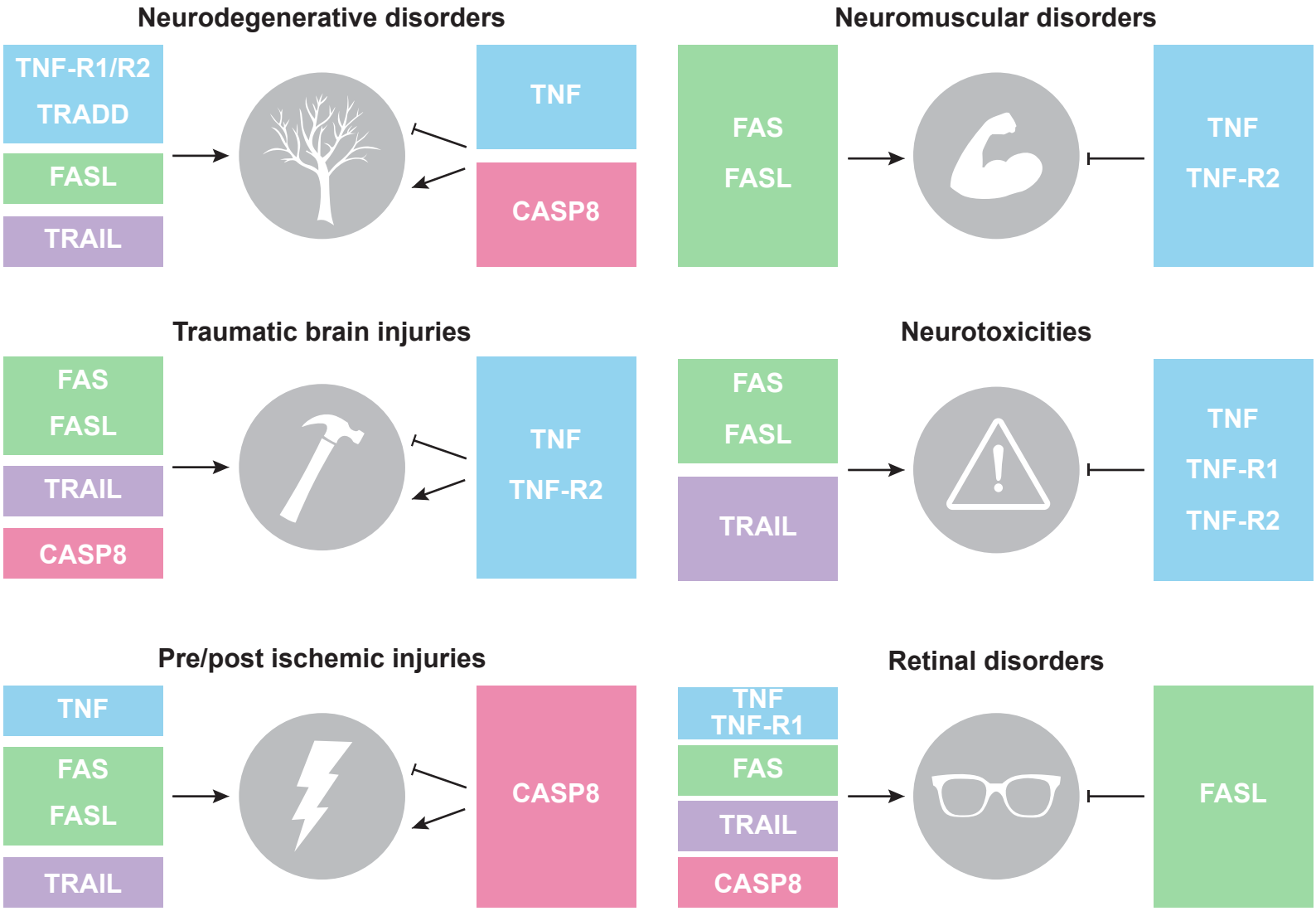
Neurodegenerative disorders
TNF-R1/R2
TRADD
FASL
TRAIL
TNF
CASP8
Neuromuscular disorders
FAS
FASL
TNF
TNF-R2
Traumatic brain injuries
FAS
FASL
TRAIL
CASP8
TNF
TNF-R2
Neurotoxicities
FAS
FASL
TRAIL
TNF
TNF-R1
TNF-R2
Pre/post ischemic injuries
TNF
FAS
FASL
TRAIL
CASP8
Retinal disorders
TNF
TNF-R1
FAS
TRAIL
CASP8
FASL

**Figure 5**