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MicroRNA-based therapeutics for inflammatory disorders of the microbiota-gut-brain axis

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ABSTRACT

An emerging but less explored shared pathophysiology across microbiota-gut-brain axis disorders is aberrant miRNA expression, which may represent novel therapeutic targets. miRNAs are small, endogenous non-coding

Abbreviations: ABX464, Obefazimod; AAV, Adeno-associated viruses; Ad, Adenoviruses; AGO2, Agonaute2; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; APPs, Amyloid precursor proteins; APCs, Antigen-presenting cells; AMOs, Anti-sense miRNA oligonucleotides; ASOs, Anti-sense oligonucleotides; AGO, Argonaute; AGO2, Argonaute RISC Catalytic Component 2; BACE1, B-site APP cleavage enzyme; BBB, Blood-Brain-Barrier; BV2, Brain-derived microglia cells 2; BDNF, Brain-derived neurotrophic factor; CACNA1C, Calcium voltage-gated channel subunit alpha-1 C; CNR1, Cannabinoid receptor 1; CBC, Cap binding complex; CCR4, C-C Motif Chemokine Receptor 4; Cdc42, Cell division control protein 42 homolog; JNK, C-Jun N-terminal kinase; CDI, *Clostridioides difficile* infection; CD68, Cluster of differentiation 68; CRISPR Cas9, Clustered regularly interspaced short palindromic repeats -associated nuclease 9; CFH, Complement factor H; CD, Crohn's disease; CXCL12β, C-X-C motif chemokine ligand 12 beta; COX-2, Cyclooxygenase-2; DCP2, Decapping protein 2; DSS, Dextran Sodium Sulphate; DBH, Dopamine beta-hydroxylase; DA, Dopaminergic; dsRNA, Double-stranded RNA; EMT, Epithelial to mesenchymal transition; EEF2K, Eukaryotic elongation factor 2 kinase; elF4F, Eukaryotic translation initiation factor 4 F; XRN1, Exoribonuclease 1; FMT, Faecal microbiota transplantation; FOXO3a, Forkhead box protein O3a; GI, Gastrointestinal tract; GBM, Glioblastoma; GLUL, Glutamine synthetase gene; GW182, Glycine-tryptophan 182 kilodaltons; Gal-NP@siRNA, Glycosylated 'triple-interaction' stabilised polymeric siRNA; AuNPs, Gold nanoparticles; PBMCs, Human peripheral blood mononuclear cells; HPA, Hypothalamic-pituitary-adrenal; HIF, Hypoxia-inducible factor; iNOS, Inducible nitric oxide synthase; IBDs, Inflammatory bowel diseases; ip3k2, Inositol 1,4,5-triphosphate kinase 2; IFN-β, Interferon-beta; IFNs, Interferons; IL, Interleukin; IRAK1, Interleukin receptor-associated kinase 1; IEC, Intestinal epithelial cell; Fe3O4, Iron oxide; IBS, Irritable bowel syndrome; JAG-GED1, Jagged canonical notch ligand 1; Jarid2, Jumonji and AT-rich interaction domain-containing protein 2; LC01, Lactobacillus casei; LVs, Lentiviruses; LNPs, Lipid nanoparticles; LPs, Lipopolysaccharide; LNA, Locked-nucleic-acid; MMP-9, Matrix metalloproteinase-9; mRNA, Messenger RNA; MGBA, Microbiota- gut-brain axis; MCAO, Middle cerebral artery occlusion-induced; miRNA, MiRNA inhibitors, microRNAanti-miRs/antagomiRs; agomiRs, MiRNA mimics; MREs, MiRNA response elements; miRISC, MiRNA-induced silencing complex; MAPK, Mitogen-activated protein kinase; MCP-1, Monocyte chemoattractant protein-1; NGO, Nanographene oxide; NOT, Negative on TATA-less; NO, Nitric oxide; NOS2, Nitric oxide synthase 2; NLRP3, NOD- LRR- and pyrin domain-containing protein 3; NLRP3, NOD-like receptor protein 3; NKRF, Nuclear factor-κB–repressing factor; NR4A2, Nuclear receptor subfamily 4 group A member 2; NF-Kb, Nuclear transcription factor kappa B; NOD 2, Nucleotide-binding oligomerisation domain-containing protein 2; OAS, Oligoadenylate synthetase; OOACs, Organ-on-chip models; PD, Parkinson's Disease; PTEN, Phosphatase and Tensin Homolog; PI3K/AKT, Phosphatidylinositol 3-kinase/protein kinase B; PLL, Poly L-Lysine; PAN, Poly(A)-deadenylases complexes; PAMAM, Polyamidoamine; PEG, Polyethylene glycol; PEIs, Polyethyleneimine; NPs, Polymer-based nanoparticles; PKIB, Protein kinase inhibitor beta; PKR, Protein kinase receptor; PTK6, Protein tyrosine kinase 6; RhoB, Ras homolog gene family member B; rCDI, Recurrent CDI; RGS2, Regulator of G-protein signalling 2; RVs, Retroviral vectors; RNase H, Ribonuclease H-dependent; RNases, Ribonucleases; RISC, RNA-induced silencing complex; SAMP8, Senescence-accelerated mouse prone 8; SERT, Serotonin transporter; SOX9, Sex-determining region Y box 9; SCFAs, Short-chain fatty acids; STAT3, Signal Transducer and Activator of Transcription 3; siRNAs, Small interfering RNA; SOCS1, suppressor of cytokine signalling 1; SHIP-1, Src Homology 2-containing Inositol Phosphatase-1; SNpc, Substantia nigra pars compacta; TRAF6, TNF receptor-associated factor 6; TLRs, Toll-like receptors; TcdA, Toxin A; TcdB, Toxin B; TRBP1/2, Trans-activation response RNA binding protein 1/2; TGFβ, Transforming growth factor beta; TRPV1, Transient receptor potential vanilloid type 1; TFF, Trefoil factor; TNBS, Trinitrobenzenesulphonic acid; TNF-α, Tumour necrosis factor-alpha; UC, Ulcerative colitis; UTR, Untranslated region; VCAM-1, Vascular cell adhesion molecule-1; VLP, Virus-like particle; ZEB, Zinc finger E-box-binding homeobox; ZO-1, Zona Occludens 1.

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Gut-brain axis
Delivery mechanisms
AntagomiRs
AgomiRs

Chemical compounds studied in this article:
Obefazimod (PubChem CID: 49846599
Miravirsen (PubChem CID: 56843415)
Cobomarsen (PubChem CID: 126480232)
Alicaforsen (PubChem CID: 16197725)

RNAs that are important transcriptional repressors of gene expression. Most importantly, they regulate the integrity of the intestinal epithelial and blood-brain barriers and serve as an important communication channel between the gut microbiome and the host. A well-defined understanding of the mode of action, therapeutic strategies and delivery mechanisms of miRNAs is pivotal in translating the clinical applications of miRNA-based therapeutics. Accumulating evidence links disorders of the microbiota-gut-brain axis with a compromised gut-blood-brain-barrier, causing gut contents such as immune cells and microbiota to enter the bloodstream leading to low-grade systemic inflammation. This has the potential to affect all organs, including the brain, causing central inflammation and the development of neurodegenerative and neuropsychiatric diseases. In this review, we have examined in detail miRNA biogenesis, strategies for therapeutic application, delivery mechanisms, as well as their pathophysiology and clinical applications in inflammatory gut-brain disorders. The research data in this review was drawn from the following databases: PubMed, Google Scholar, and Clinicaltrials.gov. With increasing evidence of the pathophysiological importance for miRNAs in microbiota-gut-brain axis disorders, therapeutic targeting of cross-regulated miRNAs in these disorders displays potentially transformative and translational potential. Further preclinical research and human clinical trials are required to further advance this area of research.

1. Introduction

1.1. RNA-based therapeutics: types and modes of action

RNA therapeutics are fast becoming a key instrument in the treatment of previously 'undruggable' medical conditions, due to their functional and structural versatility [1]; thus allowing them to surpass the obstacles imposed by small-molecule-based drugs [2]. In theory, RNA biopharmaceuticals such as anti-sense oligonucleotides (ASOs), small interfering RNA (siRNAs), and microRNAs (miRNAs) can selectively act on any nucleotide sequence on the target transcript or gene via Watson-Crick base pairing. This offers the potential for both personalised treatment and adjustment to evolving pathogens [3]. In comparison, protein-targeted therapeutics can only target 0.05% of the human genome [4], whilst solely 1.5% of the human genome encodes proteins [5]. Additionally, only 10–14% of proteins have active binding sites for small-molecules, indicating the limitations of small-molecule therapy, which creates more incentive for further research on RNA therapeutics [6]. A primary concern of RNA therapeutics is their large size and anionic nature, which limits their cellular uptake and subjects them to cleavage and degradation via circulating ribonucleases (RNases) and hydrolases [7]. However, recent developments in RNA therapeutics, such as chemical modification and the use of viral and non-viral delivery systems have led to a proliferation of phase III trials and clinically approved RNA drugs [8].

Single-stranded antisense oligonucleotides (ASOs) are DNA/RNA-based molecules characterised by their ability to modify the expression of proteins via complimentary base-pairing with messenger RNA (mRNAs) and pre-mRNAs [9]. Consequently, gene expression is modulated through ribonuclease H-dependent (RNase H) or RNase H-independent mechanisms [10]. In RNase H-dependent mechanisms, the RNA-ASO heteroduplex acts as a substrate for either RNase H1 or ribozymes, leading to mRNA cleavage [11]. Alternatively, occupancy-only mechanisms indirectly alter target RNA and permit additional nucleotide alterations. For example, splice-switching ASOs can alter RNA splicing to either include or exclude exons, leading to translational enhancement or inhibition of target proteins [12]. Alternative mechanisms also include ASOs, which bind to endogenous miRNAs to perturb their function, as well as lead to nonsense-mediated mRNA decay [13]. A large and growing body of literature has investigated the therapeutic potential of ASOs in the last 5 years. These ASOs can be used as a novel concept for the treatment of inflammatory bowel diseases. Alicaforsen is an ASO, which targets ICAM1 mRNA [14]. Raised levels of ICAM1 in endothelial cells in IBD mediates the adhesion and movement of leucocytes to areas of high inflammation [15]. Phase II trials indicated that Alicaforsen did not show therapeutic efficacy in Crohn's disease when applied parenterally [16,17]. Nonetheless, therapeutic efficacy was shown when used as a topical enema in distal ulcerative colitis (UC) and refractory pouchitis [18,19]. Another novel double-stranded oligonucleotide is STNM01, which blocks the expression of CHST15 mRNAs. Consequently, this impedes excessive colonic production of glycosaminoglycans in fibroblasts [20]. When used as a treatment for Crohn's colitis, a phase I double-blind placebo-controlled trial showed both safety and efficacy [21]. Positive outcomes have originated from successful late-stage clinical trials addressing ASOs in the treatment of IBD. However, no ASO-based therapeutic has successfully reached clinical use as of yet [14].

Another class of double-stranded RNA (dsRNA) molecules are small interfering RNAs (siRNAs), which are usually 20–25 base pairs in length and serve as mRNA inhibitors [22]. They do so by silencing the expression of specific genes via the use of the RNAi pathway, as follows. Once the functional siRNA enters the cytoplasm, it is cleaved by Agonaute2 (AGO2) to form a sense (passenger) strand [23]. Subsequently, the resultant anti-sense (guide) strand associates with the RNA-induced silencing complex (RISC) and pairs up with the target mRNA sequence. This leads to the cleavage and degradation of the specific mRNA, therefore silencing the target gene [24]. A key aspect of siRNAs is their ability to silence multiple mRNA molecules, due to their ability to recycle the RISC and anti-sense strand [22]. This highly efficient functionality makes siRNAs attractive therapeutic agents and provokes an incentive for further research. For instance, one recent study investigated the use of nanoparticle-based NF-κB p65-specific siRNAs to treat UC in an in vivo murine model. These NF-κB proteins are critical in the disease progression of UC [25]. Results revealed that these siRNAs are effective in attenuating both clinical and histopathological features of UC via increased suppression of NF-κB proteins (p50, p52, p65, and p100) in mouse colon. Moreover, there was dampened secretion of pro-inflammatory mediators such as tumour necrosis factor-alpha (TNF-α), interferon-beta (IFN-β), monocyte chemoattractant protein-1 (MCP-1), and interleukins both locally and systemically. This promising data creates the potential for future studies and the use of this treatment in IBD [26]. siRNAs also show potential for use in inflammatory disorders of the brain, such as Alzheimer's disease (AD). Cleavage of amyloid precursor proteins (APPs) by B-site APP cleavage enzyme (BACE1) and y-secretase leads to the accumulation of amyloid-β in AD [27]. Thus, targeted silencing of BACE1 by siRNAs is considered a viable therapeutic strategy, as demonstrated by the glycosylated 'triple-interaction' stabilised polymeric siRNA (Gal-NP@siRNA) in a transgenic AD mouse model [28]. This therapeutic exhibits efficient blood-brain-barrier (BBB) penetration via Glut-1-mediated transport, prolonged blood circulation, and physiological stability, due to the additional Gu+ /PO34 − salt bridge. These features could make Gal-NP@siRNA suitable for 'gene therapy cocktail' applications and could also be used to deliver siRNA in other neurodegenerative conditions [29]. Likewise, miRNAs are another type of small, endogenous non-coding RNA that influence gene expression via either the inhibition or destruction of the mRNA transcript [30]. The function and applications of miRNAs in inflammatory disorders of the gut and brain will be

discussed in depth in later sections and is the main subject focus of this review.

In recent years, mRNA-based vaccines have emerged as a promising alternative to conventional non-RNA vaccines, as seen by the high translational success of the SARS-CoV-2 mRNA vaccines [31]. The mRNA vaccines essentially induce an immune response by delivering antigen-encoding mRNA into the cytoplasm of antigen-presenting cells (APCs) via lipid nanoparticles (LNPs). This subsequently leads to the translation and presentation of the targeted antigens on the surface of the APCs by the major histocompatibility complexes. As a result, this induces B cell/antibody-mediated humoral immunity, as well as CD4 + T/CD8 + cytotoxic T-cell mediated immunity; a key advantage over conventional non-RNA vaccines [32]. The formulation of mRNA vaccines does not directly involve infectious agents and results in the degradation of the RNA strand once the protein is produced. This therefore reduces the risk of interaction with genomic DNA. Unlike traditional vaccines, mRNA vaccines are more economical and have a faster production time since production is laboratory-based and cell-free [33]. This was demonstrated during the COVID-19 pandemic when processes were able to be standardised and scaled up rapidly, leading to the first approved mRNA vaccines: BNT162b2 and mRNA-1273 [34]. It is this rapid acceleration, flexibility, and scale of development that proves the potential of RNA therapeutics and the urgent requirement for such technologies to be applied to other (infectious) diseases.

1.2. Aims and objectives

A well-defined understanding of the mode of action and therapeutic targeting strategies of miRNAs is pivotal in their translational application. This review aims to thoroughly evaluate the literature related to miRNAs and their therapeutic potential for treating inflammatory disorders of the microbiota-gut-brain axis (MGBA). Specific attention will be given to evaluating and critically appraising articles where the role of specific miRNAs has been explored, including their biogenesis, strategies for therapeutic application, delivery mechanisms, as well as their pathophysiology and clinical applications in inflammatory gut-brain disorders. The review will also highlight gaps in the current literature and the future directions of miRNA-based therapeutics for treating disorders of the MGBA.

1.3. Search strategy and selection criteria

The data in this literature review is drawn from the following databases: PubMed, Google Scholar, and Clinicaltrials.gov. References from relevant articles were found using the search phrases 'micro(mi)RNA therapeutics,' 'mimics,' 'inhibitors,' and 'inflammatory disorders of the gut-brain axis.' Only articles published between 2005 and 2023 were included in this review, with particular attention given to more recently published papers. This inclusion strategy has been adopted due to the exponential rise in RNA therapeutic-based research over this time frame.

2. miRNAs: role and translational relevance

miRNAs are a class of endogenous, single-stranded, non-coding RNAs that are ~ 12–23 nucleotides in length [35]. They interfere post-transcriptionally with gene expression by either inhibiting translation or stimulating the destruction of mRNA [36]. Evidentially, miRNAs play a pivotal role in several biological processes including cell proliferation, metabolism, development, inflammation, and apoptosis [37]. For instance, miR-146a regulates the innate immune response to bacterial infections by targeting the TNF receptor-associated factor 6 (TRAF6) and Interleukin-1 receptor-associated kinase 1 (IRAK1) [38]. Furthermore, during developmentally regulated cell death, miR-14 can suppress autophagy by targeting inositol 1,4,5-triphosphate kinase 2 (ip3k2) [39]. miRNAs such as miR-30a/b/d, miR-125b, and miR-214 have been shown to act as direct negative regulators of p53 (a tumour-suppressor gene that facilitates apoptosis in the stress response) [40]. As a result, dysregulation of miRNAs can interfere with cell function and lead to pathological effects.

It is approximated that 60% of protein-coding genes can be targeted by miRNAs, hence indicating the therapeutic capacity of miRNAs [41]. miRNAs are made up of two distinct parts: the seed sequences and the seed-distal sequences. The seed sequence, which is common amongst members of miRNA families is 7–8 nucleotides in length and is a major determinant of miRNA targeting patterns. It is only the seed-distal sequence that differs between family members [42,43]. This, alongside non-homologous binding, permits multiple miRNAs within the same family to target the same mRNA with limited complementarity [44]. This multi-functionality makes them highly attractive therapeutic targets. Moreover, miRNAs are secreted under both physiological and pathological conditions and can be detected in plasma, saliva, urine, breast milk, and faeces. This gives them the potential to be used as biomarkers of disease [45].

miRNAs have been characterised as master regulators of gene expression by the fact that target sequences for a given miRNA exist in 10–1000 s of different mRNAs, and by virtue of the experimentally (by RNA-Seq and mass spectrometry) evaluated multiplicity of transcripts/proteins regulated by a single microRNA [46]. This presents therapeutic opportunities, with miRNA effects on integrated pathways deregulated in disease, instead of a single molecule, but also disadvantages due to potential on-target effects which may elicit toxicity and adverse events [46]. Therefore, prospective miRNA-based therapeutics should be evaluated in the context of global gene and pathway regulation in multiple cell types and organ systems.

2.1. Biogenesis and mechanisms of action

The biogenesis of mature miRNA involves multiple processes within the cytoplasm and nucleus. There are two miRNA biogenesis pathways: canonical and non-canonical (Fig. 1).

miRNAs can mediate both gene suppression and activation. miRNA-mediated gene suppression is carried out through the miRNA-induced silencing complex (miRISC) [47]. The miRISC is formed from the binding of a specific miRNA guide strand, 1 of 4 Argonaute (AGO) proteins, and accessory factors, such as the human trans-activation response RNA binding protein 1/2 (TRBP1/2) and *Dicer* [35]. This resultant miRISC then associates with complementary sequences on target mRNA, known as miRNA response elements (MREs). There are two subsequent consequences: Argonaute RISC Catalytic Component 2 (AGO2)-dependent cleavage of target mRNA or miRISC-controlled inhibition of translation. Both consequences are dependent on the degree of MRE fidelity [48]. Provided that there is complete complementarity, the AGO2 endonuclease activates mRNA cleavage. Degradation occurs due to the weakened link between AGO and the 3' untranslated region (UTR) of the mRNA. Alternative binding sites of miRNA include the 5'UTR and coding regions. In contrast, if there is incomplete complementarity, mRNA remains structurally intact, whilst translation is inhibited [49,50].

Under specific conditions, miRNAs can also activate gene expression. The upregulation of miRNAs can result in a lower expression of encoded proteins, whilst downregulation leads to a higher level of protein expression [51]. For example, whereas in normal cycling cells miRNAs such as miR-369–3 and let-7b elicit translational suppression, under serum starvation (cell cycle arrest) they induce translation by altering the composition of the AGO complex in the 3'UTR of target transcripts [52]. Under amino acid starvation, miR-10a reverses the suppression of its ribosomal protein mRNA by targeting their 5′UTR [53]. In hepatocytes, the well-studied miR-122 interacts with 5' end of the Hepatitis C virus genome positively modulating viral RNA replication [54].

The functional miRISC complex can induce translational inhibition by interference with the eukaryotic translation initiation factor 4 F (elF4F) complex [55]. Following this, the AGO-bound

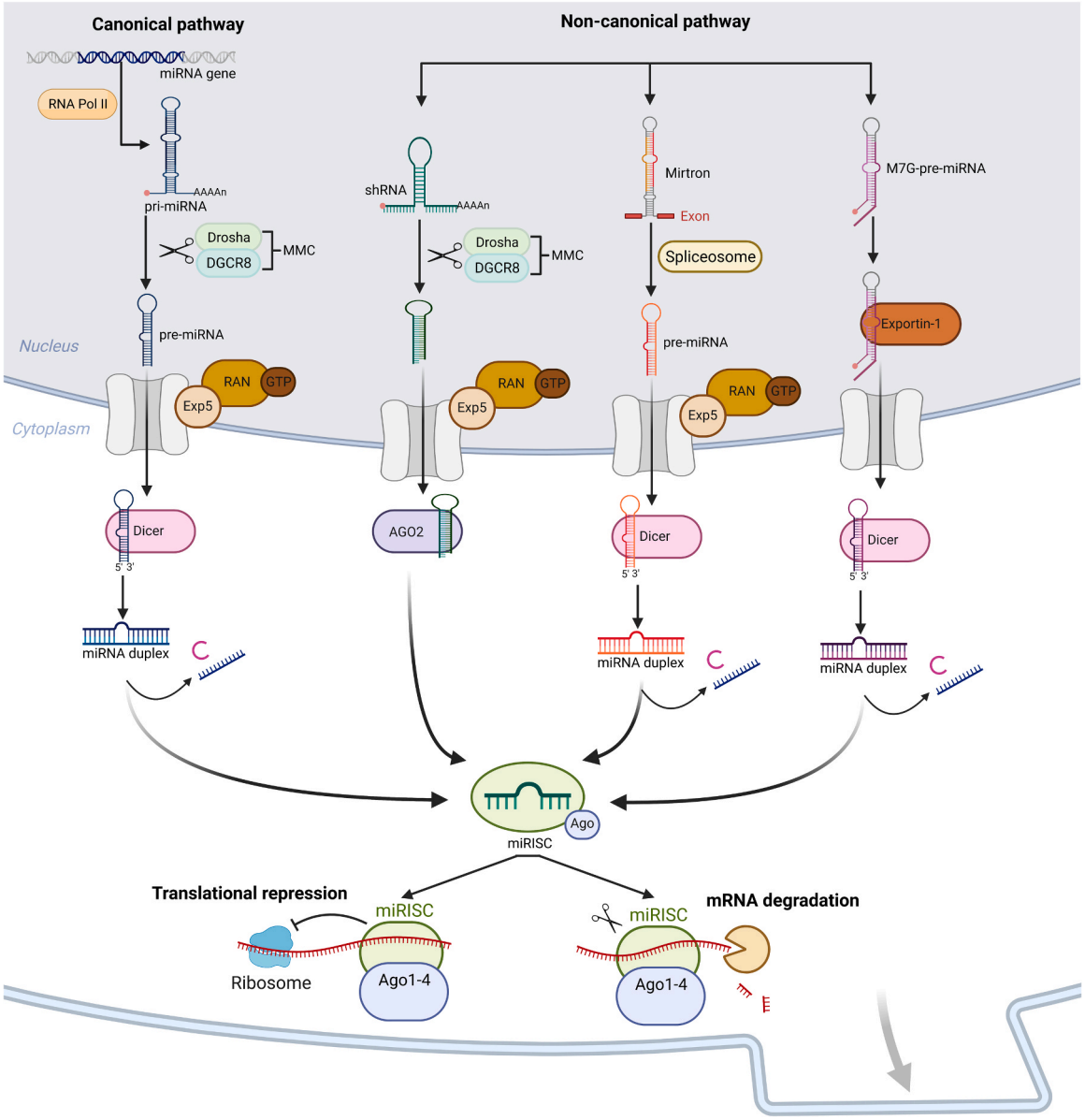

Fig. 1. Biogenesis of miRNAs. The first step of the canonical pathway takes place in the nucleus [364]. The miRNAs are encoded by genes, polycistronic clusters or intronic regions, which are transcribed by RNA Polymerase II to form the primary precursor (pri-miRNA) [365]. Pri-miRNAs have a distinctive hairpin loop structure with three spiral turns and single-stranded, unpaired flanking sequences. The pri-miRNAs interact with the Microprocessor Multiprotein Complex (MMC), formed from RNA binding protein DiGeorge Syndrome Critical Region 8 (DGCR8) and a ribonuclease II enzyme, *Drosha* [366]. This produces a 70-nucleotide precursor-miRNA (pre-miRNA). Exportin5/RanGTP-dependent export of pre-miRNA into the cytoplasm leads to its cleavage by the RNase III endonuclease - *Dicer* [367]. The removal of terminal loops in this step produces a mature, 22-nucleotide-long miRNA duplex. Consequently, either 5p or 3p strands of the mature miRNA duplex are generated. Both strands can be packed in varying proportions with AGO proteins in an ATP-dependent manner to form the miRISC [368]. Non-canonical pathways employ different combinations of the same protein complexes involved in the canonical pathway, such as *Drosha*, *Dicer*, exportin-5, and AGO2. For instance, *Dicer*-independent miRNAs are formed from the cleavage of short hairpin RNA (shRNA) transcripts by the MMC and subsequent transportation to the cytoplasm via Exportin5/RanGTP. The resultant pre-miRNA lacks the sufficient length to act as a *Dicer*-substrate. Instead, they require AGO2 and 3'– 5' trimming of the 5p strand to complete their maturation; thus promoting AGO2-dependent cleavage of the 3p strand [369]. Alternatively, in *Drosha*-independent pathways, pre-miRNAs mirror *Dicer*-substrates, as seen in mirtrons, which are a product of spliced mRNA introns [370,371]. 7-methylguanosine(m7G)-capped pre-miRNA is also dependent on *Dicer* to conclude its cytoplasmic maturation. These RNAs do not require *Drosha* cleavage and instead are directly exported to the cytoplasm via exportin 1 [372]. The resultant formation of a miRISC is like that of the canonical pathway. Figure is adapted from O'Brien et al. [369].

glycine-tryptophan 182 kilodaltons (GW182) family proteins provide the structural architecture required to bind other effector proteins. These proteins include poly(A)-deadenylases complexes (PAN)2/3 and C-C Motif Chemokine Receptor 4 (CCR4)- negative on TATA-less (NOT) [56]. Effective deadenylation occurs as a result of the PAN2/3 and CCR4-NOT complex, leading to the removal of the m7G cap from target mRNA, followed by decapping protein 2 (DCP2) [57,58]. Consequently, 5'– 3' exoribonuclease 1 (XRN1) can mediate 5'– 3' mRNA degradation [58,59].

3. miRNA-based therapeutic strategies

3.1. miRNA inhibition therapy

miRNA therapeutics can be split into two strategies, miRNA inhibitors (anti-miRs, antagomiRs) and miRNA mimics (agomiRs). There

are currently several miRNA therapeutics in clinical trials, as summarised in Table 1. One of these trials involving MRX34, a liposomal miR-34a mimic designed to treat patients with various types of advanced solid tumours, was prematurely terminated in 2016 due to lack of convincing efficacy and multiple immune-related severe adverse events [60,61]. The anti-miRs downregulate overexpressed endogenous miRNAs to enhance gene expression [62]. Chemically synthesised anti-sense miRNA oligonucleotides (AMOs) are widely used miRNA inhibitors. Possessing only one binding site to target miRNA, they are complementary to the mature miRNA strand [63]. The addition of a methyl or hydroxyl group to AMOs provides increased binding capacity and reduced nuclease cleavage [64]. Another class of anti-miRs are the plasmid construct miRNA sponges, which contain 4–10 multiple complementary target sites to a specific miRNA. Via competitive inhibition, the levels of endogenous miRNA decrease [65]. Locked-nucleic-acid (LNA) antisense oligonucleotides have the most enhanced binding affinity to miRNAs due to their increased stability and resistance to endogenous nucleases [66]. This is due to the methylene bridge connecting the 2'-O and 4'-C on the ribose ring [67].

3.2. miRNA mimics

In contrast to anti-miRs, miRNA mimics replace a lost miRNA, thus reducing the levels of that specific miRNA target. miRNA mimics are RNA duplexes that consist of a guide strand and a complementary passenger strand. The guide strand comprises of an identical sequence to that of the endogenous mature miRNA. As a result, it can restore their loss of function [68]. Single-stranded synthetic RNA molecules also have this ability, however, double-stranded miRNA mimics have 100–1000 more potency [69]. An alternative option is synthetic miRNA precursor mimics, which have additional nucleotides or full-length pri-miRNA conjoined [70].

3.3. CRISPR-based therapeutic strategies

The clustered regularly interspaced short palindromic repeats (CRISPR)-associated nuclease 9 (Cas9) system can be used to inhibit the biogenesis and expression of target miRNAs. This is a result of the introduction of mutations to the *Drosha/Dicer* processing site on oncogenic miRNA precursors [71]. The downregulation of miRNAs via this system has been shown to be highly stable for up to 30 days, as demonstrated in both in vitro and in vivo models [72]. This mechanism can be applied to inhibit cancer cell proliferation and promote apoptosis, as seen in CRISPR/Cas9 inhibition of oncogenic miR-17, miR-21, miR-141, and miR-3188 [73,74]. CRISPR/Cas9-mediated inhibition of oncogenic miR-10b has suppressive effects on glioblastoma (GBM) cells and GMB-initiating stem cells in culture [75]. Moreover, CRISPR/Cas9 can enhance the sensitivity of cancer cells to chemotherapeutics, such as cisplatin and paclitaxel [73,74]. Although promising, additional research is warranted to investigate the safety and distribution in humans subjects [76].

4. Challenges associated with miRNA therapeutics

4.1. Immunogenicity

By interacting with RNA-binding proteins, such as Toll-like receptors (TLRs), 2'– 5'-oligoadenylate synthetase (OAS), and protein kinase receptor (PKR), miRNA therapeutics may activate an immune response. This can lead to toxicities and unwanted side effects, as seen in the systemic administration of miRNA duplexes [77]. This activates the TLR-mediated release of type I interferons (IFNs) and inflammatory cytokines [78]. TLRs 3, 7, and 8 are stimulated when sensing dsRNAs in cellular endosomal and lysosomal compartments [79]. Activation of the immune response is also dependent on the chemical modification, length, secondary structure, immunostimulatory sequence, dose, delivery vehicle, and route of the miRNA [78]. Moreover, the nucleotide sequence of the miRNAs influences the activation of TLRs. On the other hand, TLR 3 and 7 are triggered by uridine and guanosine rich-dsRNAs, resulting in IFN-α, IFN-β and IL-6 secretion [80].

4.2. miRNA stability

It is integral that miRNA therapeutics remain stable in conditions where they are manufactured, delivered, and stored. Unmodified miRNAs are degraded instantaneously by circulating nucleases, such as

Table 1
Clinical trials of miRNA-based therapeutics. [318].

Therapeutic name	Target miRNA	Target Disease	Modes of Action	Stage of Development (Clinical Trial)	Clinical trial number (s)
Miravirsen (SPC3649)	miR-122	Hepatitis C	LNA-antagomiR	Phase II completed	EudraCT numbers 2015–001535–21, 2015–004702–42, 2016–002069–77
MRX34	miR-34a	Advanced Hepatocellular Carcinoma, Pancreatic Carcinoma, Cholangiocarcinoma	miRNA mimic	Phase I discontinued*	NCT01829971, NCT02862145
Cobomarsen (MRG-106)	miR-155	Cutaneous T-cell lymphoma (CTCL), Mycosis Fungoides	LNA-antagomiR	Phase II completed	NCT02580552, NCT03713320, NCT03837457
RG-101	miR-122	Hepatitis C	GalNac conjugated-antagomiR	Phase II completed	NCT02508090, NCT02452814, NCT01200420, NCT01872936, NCT01727934, NCT01646489
MRG-201 (Remlarsen)	miR-29	Fibrous scar, Keloids	Cholesterol-conjugated miRNA mimic	Phase II completed	NCT02603224, NCT03601052
RG-012 /SAR339375 (Lademirsen)	miR-21	Alport Syndrome	AntagomiR	Phase II ongoing	NCT03373786, NCT02855268
RG-125/AZD4076	miR-103/107	Non-alcoholic steatohepatitis (NASH) in patients with type 2 diabetes/prediabetes	GalNac conjugate-antagomiR	Phase I completed	NCT02612662, NCT02826525
MRG-110	miR-92a	Wounds	LNA-antagomiR	Phase I completed	NCT03603431
MesomiR 1	miR-16	Malignant pleural mesothelioma, non–small cell lung cancer	miRNA mimic	Phase I completed	NCT02369198
CDR132L	miR-132	Heart failure	LNA-antagomiR	Phase I completed	NCT04045405
ABX464 (Obefazimod)	miR-124	Ulcerative Colitis	MiRNA mimic	Phase III ongoing	NCT03368118

* Trial was terminated due to serious immune mediated adverse events in patients receiving MRX34, which did not appear in preclinical toxicology animal models [60,61].

serum RNase A. This is a result of miRNAs' polyanionic nature and high water solubility, leading to a short half-life and poor tissue bioavailability [81]. Chemical modifications to the phosphodiester backbone or the ribose ring of oligoribonucleotides can help resist nuclease degradation and boost its circulation time [82]. Advantageous modifications include phosphodiester linkages, ribose backbone, 2'-O-(2-methoxyethyl), 2'-O-methyl, and 2'- locked nucleic acids (LNAs). Such modifications have enhanced miRNA potency by improving target binding affinity [83]. However, this can result in miRNAs losing their structural dynamics, biological activity, and safety profiles. Other challenges that need to be overcome include increased cytotoxicity and complement cascade activation from chemical modifications, as well as thermal instability [78,84–86].

4.3. miRNA pharmacokinetics and pharmacodynamics

Upon intracellular delivery, RNA sequestration by endosomes can limit the therapeutic response of miRNAs [87]. It has been estimated that only 1–2% of RNA molecules that enter the endosome can escape to the cytosol so that they can degrade or block target mRNA [88]. Despite cationic lipids, nanoparticles, or cell-type-specific delivery mechanisms, which can enhance cellular uptake by a range of endocytosis processes, in most cases the endosomal contents are delivered to lysosomes for degradation. The highly acidic endosomal environment triggers certain specific nucleases to catalyse the degradation of miRNA mimics. Therefore, there is a need to enhance endo-lysosomal escape to maintain sufficient miRNA levels in the cytoplasm [83]. Strategies to promote endosomal escape include the use of pH-sensitive lipoplexes, pH-sensitive polyplexes, photosensitive molecular rearrangements, and nanoparticles with polycationic components designed to buffer across the endolysosomal pH ranges [89–92].

4.4. miRNA off-target effects

Upon delivery to the cytoplasm, there can still be off-target effects as well as unwanted on-target effects. Due to the gene-silencing function of miRNAs, off-target effects may result in cytotoxicity and undesirable alterations of gene expression, resulting in undesired phenotypes [77]. Cross-hybridisation between the short 'seed sequence' of miRNAs with non-target mRNA transcripts can often lead to side effects. Hyperactivation of cellular RNAi pathways can also occur, either by competitive inhibition via exogenous miRNA agents or through binding of endogenous miRNA into RISC [78]. The lack of capacity for normal incorporation of endogenous miRNA into RISC leads to its processing. Thus, a build-up of toxic aggregates such as pri-miRNAs, pre-miRNAs, and shRNAs causes excessive loading of the nuclear export pathway by exportin-5 [84,93,94]. A novel approach evaluated to date in vitro is the combination of miRNAs whose effects on pathways or cell functions are complimentary [95–100]. In the same line, we have shown that although miR-23a and miR-150 alone have minimal effects, their combination significantly improves the resistance of intestinal epithelial cells (IECs) to *C. difficile* toxins [101]. We propose that such approaches could permit the reduction of the therapeutic miRNA dosage, limiting off-target effects and reducing the harmful on-target effects. In fact, we recently showed that miR-23a and miR-150 combination at low concentrations protects the intestinal epithelial barrier from different colitogenic toxins as well as brain-derived cell lines from LPS [102].

5. Delivery mechanisms of miRNAs

5.1. Viral-based delivery mechanisms

Considering the challenges associated with miRNA agents, safe and

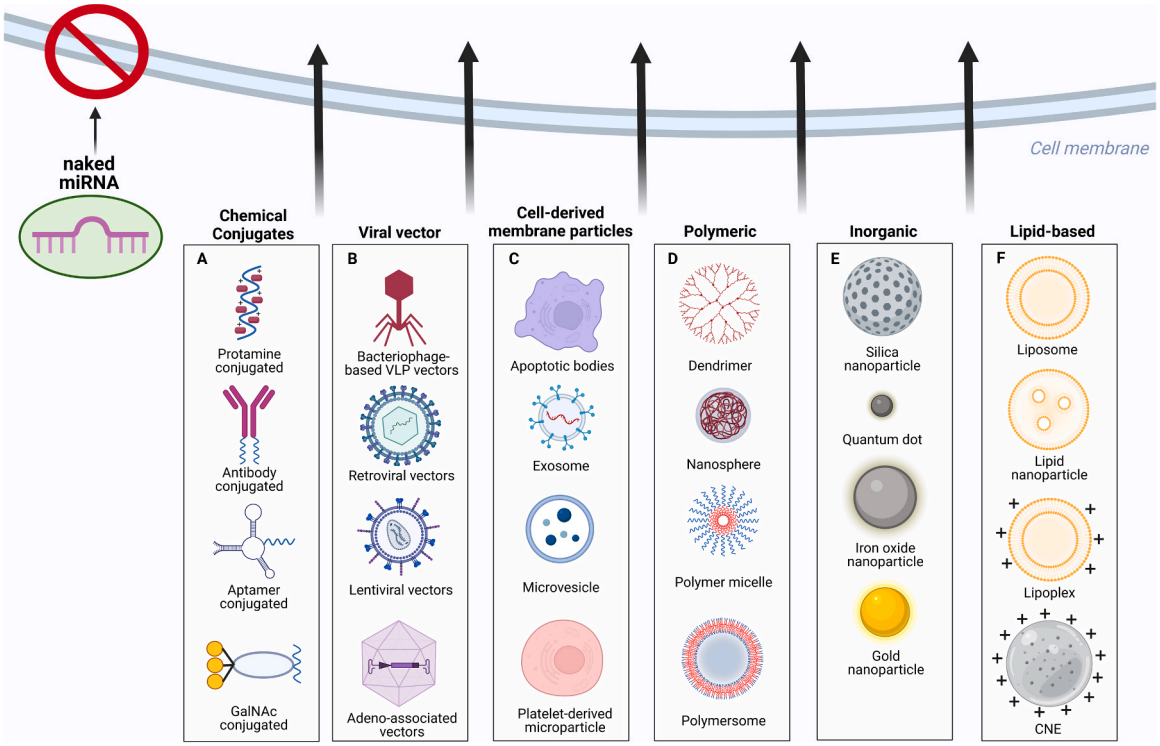

Fig. 2. Strategies for cellular delivery of miRNA therapeutics. Challenges associated with the delivery of miRNA therapeutics can be minimised by chemical modifications to miRNAs and adaptive use of delivery vehicles. (A) miRNAs can be chemically conjugated to antibodies, aptamers, GalNAc and cholesterol to aid delivery. (B) Viral-based vectors have been modified to provide increased transfection and long-term gene expression. Stable transgene transmission and reduced toxicity are achieved via the elimination of pathogenic elements from these viruses. (C) Cell-derived membrane particles can also be utilised. (D) Use of polymers is another efficient delivery strategy. (E) Inorganic nanoparticles are a novel delivery system. (F) Lipid-based delivery systems are popular due to their high gene transfection efficiency. Naked miRNA delivery can result in immunogenetic effects, degradation, sequestration, and instability. Figure adapted from Pandey et al. and O'Brien et al. [2, 369].

versatile delivery mechanisms are essential for therapeutic success (Fig. 2). Retroviral vectors (RVs) are lipid-enveloped RNA viruses employed to stably deliver miRNAs into somatic and germline cells [103]. Since genomic DNA deposition occurs during the mitotic phase of the cell cycle, the use of RVs is limited to dividing cells only. Upon entry to the cytoplasm, viral RNA is reverse transcribed into double-stranded DNA, which incorporates with the host's chromosome[104]. RVs have a multi-faceted nature. On one hand, they can continuously increase transgenic expression. However, they can also inactivate key genes, resulting in cell dysregulation[105]. Similar to RVs, lentiviruses (LVs) can transfer gene sequences into host cells but can additionally infect postmitotic and terminally differentiated cells, facilitating application in the treatment of neurological conditions.[106].

Adenoviruses (Ad) and adeno-associated viruses (AAV) are non-enveloped viruses that contain double-stranded and single-stranded DNA genomes, respectively. Their non-pathogenic profile, widespread targeting abilities and stability make them an efficient delivery system of choice. Like LVs, Ads and AAVs infect resting or dividing cells but do not incorporate exogenous sequences into the host's genome [107,108]. The small size of miRNA genes makes AAV vectors ideal candidates, as they can hold up to 4.8KB of exogenous genetic material [109]. In addition, Ad-based hemagglutinin-specific artificial miRNAs could alleviate disease manifestations and protect against specific influenza virus strains [110]. However, in preclinical and human studies, AAV vectors have been shown to activate an immune response [111]. One exception is the Oxford Chimpanzee Adenovirus approach applied to COVID-19 vaccines, which overcame the challenges associated with human immunity [112]. The use of tissue-specific promotors and enhancers can help increase transgene expression, thus attenuating the immune response [113]. Despite the successful attributes of virus-based miRNA delivery strategies, their potential is limited by high cytotoxicity, immunogenicity and carcinogenicity [114]. Nevertheless, manipulation of the encapsidation system has led to the development of bacteriophages, which could override these effects [115]. Disadvantages of bacteriophage-based virus-like particle (VLP) vectors include their low loading capacity and the requirement for further analysis of their immunogenetic profile [115]. Despite the high delivery potency of viral vectors, the use of nonviral vectors, which is described in the next section, can help overcome the potential for immunogenicity and reduction in efficacy during chronic or repeated dosing.

5.2. Non-viral-based delivery mechanisms

Non-viral-based strategies can help overcome cellular nuclease degradation via chemical and physical approaches to achieve therapeutic success. Physical aids to transfection, such as gene gun, electroporation, hydrodynamic and laser-based energy have been used widely in cell culture studies to increase cell membrane permeability for gene delivery [116]. Such physical approaches are challenging to adopt for clinical miRNA delivery, as they can impact cell integrity and lead to a high apoptotic rate, thus increasing the risk of nuclease cleavage [117]. Lipid-, polymer-, and inorganic carrier-based methods have been more popular in academic studies and offer many advantages for practical delivery of nucleic acids [118]. Lipid-based vectors are the most commonly used, and many commercially available examples exist which are non-toxic, non-immunogenic, and easy to manufacture [116]. These factors have led to their use in delivery of siRNA in the Onpattro formulation, and in the Comirnaty and Spikevax Covid-19 vaccines [119]. However, the compositions of these lipid systems are critical to function, and while they rely on cationic or ionisable lipids to condense the nucleic acids in the formulation, interactions of cationic lipids with anionic serum proteins can result in opsonization and a short half-life, and the stability of the formulations can also be problematic [120]. This problem is usually overcome via the use of lipids which are conjugated to polyethylene glycol (PEG). This hydrophilic and flexible polymer can help to avoid phagocytosis and increases the half-life by up to 72 h [116]. For example, the delivery of miR29b via cationic lipoplexes into non-small cell lung carcinoma cells generated increased miR-29b levels and reduced tumour growth rate by approximately 60% [121]. Furthermore, targeting ligands, such as transferrin and folic acid, which can bind to overexpressed receptors on the surfaces of certain cancer cells can be attached to the exterior components of liposomes to boost cell-specific delivery of miRNAs [122].

An alternative strategy is the use of polymeric delivery systems, of which the most widely explored have benthos based polyethyleneimine (PEIs). PEI is a polycation with a wide pKa range, which forms polyelectrolyte complexes with the negatively charged phosphate groups on RNA, thus protecting the nucleic acid from degradation by RNases. In addition, excess cationic charges can enhance the uptake of the complexes leading to high transfection efficiencies in cell culture [123]. However, the transfection rate in vivo is generally less than that for viral vectors and the cellular toxicity of PEIs has limited its clinical use for high-molecular-weight branched PEIs [78]. As a substitute, the combination of PEGs and poly L-Lysine (PLL) with PEIs can improve biocompatibility without too severe detriment to cellular uptake if formulated carefully [124]. Efficient transfection of miR-150 in human leukaemia cells was demonstrated with the use of a PEG-PEI-conjugate delivery vector [125]. Other positively charged, biodegradable polymers, such as polyamidoamine (PAMAM) dendrimers also have shown high transfection efficiencies and lower cytotoxic effects. This is shown in the successful PEG-nanographene oxide (NGO) and PAMAM-mediated delivery of anti-miR-21 for limiting the proliferation of tumour tissue [126]. Nanoparticles formulated from natural materials, such as CPPs and chitosan have fewer cytotoxic effects than some of the above-mentioned synthetic materials and have accordingly been used as miRNA vectors [127]. Combination therapies utilising small molecule cytotoxic agents alongside miRNAs have also been developed, for which polymeric micelles and mixed polymer-lipid systems have been used as the delivery agents [105]. The co-delivery of doxorubicin and tumour-suppressor miR-34a has been successfully carried out in tumour tissue by mixed polymer-lipid micellar-like nanoparticles [128].

In addition to lipid and organic polymer systems, inorganic material-based vectors, such as gold nanoparticles (AuNPs), iron oxide (Fe_3O_4), and silica-based nanoparticles can aid the effective delivery of miRNAs [129–131]. Important advantages of inorganic-based vectors include their range of degradation rates in vivo and low immunogenicity. Nevertheless, the extent of association between nucleic acids and particulate inorganic carriers can be limited, owing to the relatively lower area of particle surfaces compared to polyelectrolyte complexes. In addition, the stability of some inorganic particles can be poor in biological fluids, owing to adsorption of plasma and other proteins. These problems can be overcome via combining inorganic components with organic matrices [116]. For example, high transfection efficiency and low cellular toxicity was associated with the administration of PEG-conjugated AuNPs to transport miR-1 to cancer cells [132].

6. Microbiota-gut-brain-axis in health and disease

The microbiota-GBA (MGBA) is an increasingly important and evolving topic of research, which is thought to be involved in many aspects of homeostasis in addition to the pathogenesis of several diseases. The MGBA is described as a bidirectional communication between the gut microbiota and brain, involving the central, enteric, and autonomic nervous systems and the hypothalamic-pituitary-adrenal (HPA) axis [133,134]. The MGBA comprises microorganisms, such as bacteria, viruses, fungi, and archaea, in addition to microbial metabolic by-products, which are major contributors in this bidirectional communication [134–136]. These complex and interconnected communication pathways are associated with direct and indirect signalling, as well as alteration of the permeability of the BBB and gut epithelial barrier [135,137–139]. Gut dysbiosis has been implicated in the pathophysiology of gastrointestinal and neurodegenerative diseases,

such as ulcerative colitis (UC), Crohn's disease (CD), irritable bowel syndrome (IBS), Parkinson's Disease (PD), Alzheimer's Disease (AD) and ischaemic stroke, as well as acute intestinal infections, such as *Clostridioides difficile* infection [140–146].

The dysregulation of miRNA expression has been implicated in the pathogenesis of several gut and brain disorders, underscoring the importance of miRNAs in maintaining a healthy GBA [147]. As part of the MGBA, the gut microbiota modulates systemic inflammation, neurotransmitter synthesis, and immune responses that can influence CNS function [147]. Gut dysbiosis develops from both intrinsic and extrinsic factors including antibiotic use, diet, environmental factors, genetics, and infections [148]. This manifests as a decrease in the relative abundance of bacterial taxa, disruption to microbial diversity, and an overall shift in the microbial community structure [149]. This imbalance between beneficial and harmful microbial populations compromises gut barrier function and increases intestinal permeability [149]. A weakened intestinal epithelial barrier allows the translocation of microbial products, such as lipopolysaccharides (LPS), into the circulation [147]. Systemic endotoxemia resulting from increased LPS levels can consequently induce pro-inflammatory reactions and elicit a central and peripheral cytokine storm [150]. Furthermore, the translocation of microbial metabolites, such as short-chain fatty acids (SCFAs), neurotransmitters, and neuroactive substances through the BBB can directly affect neuronal function, neurotransmission, and can in some instances induce neuroinflammation [147]. Gastrointestinal tract (GI) derived toxins such as *Bacteroides fragilis* derived LPS have strong potential to trigger the NF-kB (p50-p65)-miRNA-146a-miRNA-155 signalling system to convey GI-tract microbiome-derived pathogenic signals into the brain [151], leading to downregulation of miRNA-146a-miRNA-155 regulated mRNA targets encoding complement factor H (CFH), a soluble complement control glycoprotein and key repressor of the innate immune response [151]. Gut dysbiosis can additionally trigger the formation of inflammasome complexes, the activation of caspase 1 and subsequent release of interleukin-1β and interleukin-18 cytokines, and pyroptosis [152].

miRNAs have been shown to regulate the expression of key genes involved in gut barrier integrity [153]. For instance, miR-93 has been shown to reduce protein tyrosine kinase 6 (PTK6) expression, with associated improvement in claudin-3 expression and thus epithelial barrier integrity [154]. miR-31, a key miRNA in GI/CNS diseases is associated with the Hippo signalling pathway, an evolutionarily conserved pathway that exerts profound effects on the regulation of organ size, tumorigenesis, embryonic development, stem cell homeostasis, and epithelial to mesenchymal transition [155]. miR-31 targets the transforming growth factor beta (TGFβ) pathway, regulates the Wnt pathway and promotes epithelium regeneration [156]. Additionally, miR-122a has been shown to regulate the TNFα-dependent expression of zonula occludens-1 (ZO-1), a key protein involved in maintaining the integrity of tight junctions [157]. It also plays a role in increasing zonulin protein levels by targeting the EGFR pathway [157]. The dysregulation of these miRNAs may contribute to impaired gut barrier function, leading to gut inflammation and increased susceptibility to gut-derived pathologies.

miRNAs can modulate gut homeostasis by regulating the interaction between gut microbiota and the host immune system [158]. For example, proinflammatory miR-155 is expressed in intestinal immune cells and regulates gut immune homeostasis by regulating SOCS1 (suppressor of cytokine signalling 1), thus maintaining IFN-γ expression in natural killer cells [159]. Similarly, miR-223 has been shown to suppress NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) expression, which translates to reduced NLRP3 inflammasome activity, and can inhibit IL-18 mediated neutrophil extracellular trap formation [160, 161]. Moreover, the downregulation of miR-144 by *Lactobacillus Casei* (LC01) causes the upregulation of occludin and zonula occludens 1 in intestinal epithelial cells, promoting intestinal homeostasis[162]. Dysregulation of these miRNAs can disrupt gut homeostasis, leading to chronic gut inflammation and compromised gut functionality. miRNAs are secreted from intestinal epithelial cells in the lumen and accumulate in faeces. Faecal miRNA profiles can be differentially and specifically impacted by the gut microbiota composition, where miRNAs could serve as markers of the colitogenic potential of the microbiota [163]. Host faecal miRNAs can also regulate microbial fitness and host gene expression [164]. Specifically, faecal miRNAs can enter *F. nucleatum* and *E. coli* and specifically regulate bacterial gene transcripts and affect bacterial growth. Faecal miRNA transplantation can also restore the gut microbiota in intestinal epithelial cell (IEC) miRNA deficient mice and rescued Dextran Sodium Sulphate (DSS) colitis in Dicer1 $^{\Delta IEC}$ mice [164]. Furthermore, faecal miR-142a-3p from DSS-challenge recovered mice prevents colitis by promoting the growth of *Lactobacillus reuteri*, and this protective effect also extends to its associated metabolite, reuterin, which is a broad-spectrum antimicrobial and anti-inflammatory compound [165]. These observations suggest that the faeces of subjects who have recovered from disease may be enriched with miRNAs with preventative effects against those diseases [166].

In the CNS, the gut microbiota has been demonstrated to control miRNA expression through various mechanisms, such as the production of metabolites, immune signalling, and direct interaction with IECs. For instance, miR-132 has been shown to regulate synaptic plasticity and memory formation, while miR-124 has been implicated in neurogenesis [167,168]. miRNAs have also emerged as critical regulators of BBB integrity by directly targeting endothelial tight junctions or by regulating endothelial cell survival, inflammatory pathways, and apoptosis [169]. Upon neuronal release of miR-132-containing exosomes to brain endothelial cells, miR-132 directly targets eukaryotic elongation factor 2 kinase (EEF2K) to regulate VE-cadherin, enhancing BBB integrity [170]. Furthermore, targeting of vascular cell adhesion molecule-1 (VCAM-1) by miR-126 reduces intracerebral haemorrhage-induced leukocyte adhesion and BBB disruption [171].

Previous reviews have comprehensively addressed MGBA dysregulation, particularly in relation to CNS disorders [172]. Here we highlight specific miRNAs implicated in the pathophysiology of common gastrointestinal and neurodegenerative disorders associated with MGBA dysregulation. These are summarised in Fig. 3. We envisage future novel miRNA-based therapeutics which could increase the resilience of the intestinal epithelial barrier and secondarily delay or even prevent the onset of neuroinflammatory diseases.

6.1. Ulcerative colitis

It is estimated that approximately 2.5–3 million individuals in Europe are living with inflammatory bowel diseases (IBDs), directly costing the healthcare system ~ 4.6–5.6 billion Euros each year [173]. Studies have demonstrated a 94% incline in the incidence of IBD in adolescents [174]. The prevalence of IBD also influences the risk of developing additional diseases, such as colorectal cancer [175]. These statistics highlight the necessity for further understanding of the contribution of miRNAs to the pathogenesis of UC and CD and their role as both diagnostic markers and therapeutic targets [176]. Currently, there are several anti-miRNAs being investigated in animal models of colitis for their potential therapeutic effects in the context of intestinal inflammation and infection.

miR-21, miR-155 and miR-31 are repeatedly observed in studies as key players in the pathogenesis of IBD [177–179]. In IBD, pro-inflammatory pathways, specifically the nuclear transcription factor kappa B (NF-κB) pathway, IL23/IL23R pathway, and IL-6/ Signal Transducer and Activator of Transcription 3 (STAT3) pathway are regulated by miRNAs [180–183]. miR-21 plays an active role in inflammation of UC via the activation of macrophages. When associated with nitric oxide synthase 2 (NOS2) and cluster of differentiation 68 (CD68), miR-21 impacts nitric oxide (NO) levels, thus leading to the deterioration of adjacent epithelial cells [184]. As seen in cultured colon cancer cells, miR-21 can also trigger the degradation of Ras homolog

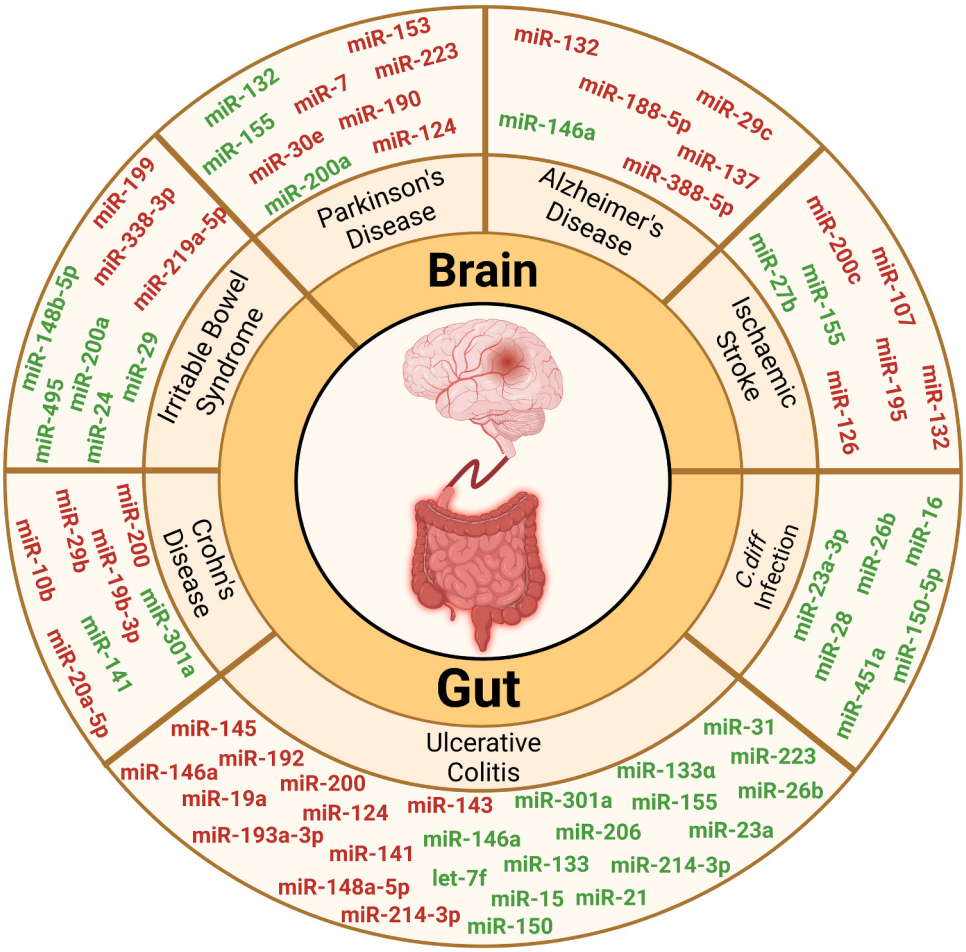

Fig. 3. miRNA expression patterns in gut and brain diseases. Downregulated miRNAs are shown in red, whilst those upregulated are shown in green.

gene family member B (RhoB) mRNA and RhoB proteins, disrupting tight junctions in intestinal epithelial cells [185].

Highly expressed in colonic tissue, miR-31 has been shown to suppress inflammatory signalling in the DSS-induced colitis mouse model. This is achieved via downregulation of the inflammatory cytokine receptors, IL7R and IL17RA, as well as the signalling protein, GP130 [156]. In BALB/C mice with 2,4,6-Trinitrobenzenesulphonic acid (TNBS)-induced colitis, anti-miR-31 was shown to normalise colonic IL-25 expression and downregulate Th1/Th17 cell responses, thus demonstrating improved clinical outcome [186].

An additional DSS model-based study revealed the role of miR-155 in the pathogenesis of UC, in which it directly binds to Src Homology 2-containing Inositol Phosphatase-1 (SHIP-1) mRNA. The levels of SHIP-1, which usually influence cell membrane trafficking decreases significantly [187,188]. Upregulation of miR-31 and miR-155 have been shown to positively correlate with IL-13 levels [189]. High IL-13 levels are associated with dysregulation of the epithelial wall, due to modified claudin-2 expression in tight junctions [190]. Use of a miR-155 inhibitor may be of value in UC, due to its association with suppressor of cytokine signalling 1 (SOCS1) and its contribution to intestinal wall destruction via hypoxia-inducible factor (HIF)− 1α/trefoil factor (TFF)− 3 axis [191]. miR-155 antagomirs have been demonstrated to protect against DSS-induced colitis in mouse models by reducing intestinal barrier damage and inflammation [192]. This was achieved via restoration of the SHIP-1 pathway and regulation of Th17 cells and Jumonji and AT-rich interaction domain-containing protein 2 (Jarid2) Wnt/β-catenin [192]. Use of anti-miR-223 in a TNBS-induced colitis model also exhibited enhanced regulation of Claudin 8 levels and increased colonic barrier function [193]. Further examples of miRNAs implicated in UC pathogenesis are summarised in (Table 2). Despite these promising results, only one miRNA agent has successfully reached clinical trials.

ABX464 (recently renamed Obefazimod) is a newly emerging miRNA-based therapeutic agent, which could potentially act as the next transformative drug for IBD, specifically UC [194]. Following success in the phase IIb clinical trial, evaluating the long-term follow-up of ABX464 in moderate-to-severe UC, it has recently entered phase III clinical trials (NCT05507216) [195]. As an anti-inflammatory agent, it aims to upregulate miR-124 and has achieved statistically significant increased levels in peripheral blood cells and rectal tissue, in the phase IIa trial [196]. By month 24, 68.8% of patients demonstrated endoscopic improvement, of which 43.8% showed endoscopic remission, thus indicating its long-term efficacy [195]. miR-124 exhibits vast potential due to its anti-inflammatory role in the downregulation of pro-inflammatory cytokines and chemokines, such as TNF- α, IL-6, MCP-1 and IL-17, as well as Th17 + cells [197]. ABX464 promotes specific splicing of a single long non-coding RNA by binding to a cap binding complex (CBC) [198]. This generates miR-124, leading to its upregulation. One successful factor of ABX464 is its specificity; miR-124 is the only miRNA that is targeted and upregulated by this agent [199]. Another striking feature is its alternative ability to enhance splicing of a HIV-required segment of viral RNA, which is necessary for replication in infected human peripheral blood mononuclear cells (PBMCs) [200]. The resultant spliced viral RNA species could potentially trigger the immune system to detect HIV-infected cells. ABX464 could therefore be used not only as an anti-inflammatory agent but to additionally treat HIV [201, 202].

Table 2
Dysregulated miRNAs associated with the pathogenesis of UC.

miRNA	Target	Sample Type	Function	Degree of expression in UC	References
miR-26b	DIP1, MDM2, CREBBP, BRCA1	Fresh frozen colon biopsies, sera	Facilitates inflammation and colitis-associated cancer via the DIP1/DAPK axis	↑	[319]
miR-223	NLRP3	Colonic tissue	Promotes intestinal innate immunity	↑	[160,320,
	CLDN8	Colonic tissue	Modulates IL23/Th17 pathway	↑	321]
	C/EBPβ	Colonic tissue	Inhibits intestinal macrophages and dendritic cells and increases pro-inflammatory mediators	↑	[322,323] [324,325]
miR-23a	LB1	Colonic tissue	Initiates genome instability via DBS accumulation and reduces colon healing	↑	[326]
miR-155	RAD51	Colonic tissue	Initiates genome instability via DBS accumulation and reduces	↑	[326,327]
	JARID2	Colonic tissue	colon healing	↑	[328–330]
	IL 13RA1	Colonic tissue	Regulates cytokine gene expression in Th17 cells Maintains the functionality of epithelial cells	↑	[189,331]
miR-301a	BTG1	Colonic tissue	Contributes to intestinal wall damage and increases	↑	[332]
	SNIP1	Colonic tissue, peripheral blood mononuclear cells	permeability of intestinal epithelial cells Regulates pro-inflammatory cytokine gene expression in Th17 cells	↑	[333]
miR-200family	Snail, slug	Colonic tissue	Inhibits epithelial-mesenchymal transition of colonic mucosa	↓	[334–336]
miR-214–3p	STAT6	Colonic tissue	Supresses levels of IFN- γ and intestinal inflammation	↓	[337]
	PDLIM2, PTEN	Colonic tissue	Activates pro-inflammatory NF-κB pathway	↑	[338,339]
miR-206	A3AR	Colonic tissue	Activates pro-inflammatory NF-κB pathway	↑	[340]
miR-21	PDCD4	Colonic tissue	Induces NF-κB, STAT3 and BCL-2 pathway	↑	[341–344]
miR-148a-3p	GP130, IKKα, IKKβ, TNFR2	Colonic tissue	Supresses NF-κB and STAT3 pathway, thus inhibiting tumorigenesis	↓	[345,346]
miR-148a-5p	IL1R1	Colonic tissue	Supresses NF-κB and STAT3 pathway, thus inhibiting tumorigenesis	↓	[345]
let-7 f	HMGA2, FZD3	Colonic tissue	Supresses Th17 differentiation via targeting of STAT3	↑	[347–349]
miR-146a	MyD88, TLR4, NF-κB	Intestinal tissue	Mediates the TLR4, MyD88, NF-κB signalling pathway	↑	[350]
	CCL8	Colonic tissue	Supresses levels of NF-κB, CRP, IL-1β, IL-6 and TNF-α	↓	[351]
miR-133α	AFTPH	Tissue	Induces intestinal inflammation	↑	[352,353]
miR-193a-3p	IL17RD	Colonic tissue	Downregulates IL17RD, thus hinders carcinogenesis	↓	[354,355]
miR-31	IL13RA1	Colonic tissue	Maintains the functionality of epithelial cells	↑	[189]
miR-19a	TNF-α, IL-8, GM-CSF	Colonic tissue	directly regulates TNF-α expression	↓	[356]
miR-124	VEGF, BCL2, BCLXL, MMP9	Colonic tissue	Regulates STAT3-mediated expression of Th17 differentiation	↓	[357,358]
miR-141	CXCL5	Colonic tissue	Downregulates levels of CXCL5 in HT29 cells	↓	[359]
miR-192	MIP-2a	Colonic tissue	Targets MIP-2a, a chemokine expressed by epithelial cells	↓	[349]
miR-15	A2aAR	Colonic tissue	Upregulates the expression of IL-8 and IFN-γ in colonic epithelial cells and targets A2aAR in HT-29 cells	↑	[360]
miR-143	IRS-1, K-RAS, API5	Colonic tissue	Role in tumour suppression	↓	[361]
miR-145	K-RAS, API5, MEK-2	Colonic tissue	Role in tumour suppression	↓	[361]
miR-150	c-Myb	Colonic tissue	Modulates cell apoptosis,	↑	[362]

↓ denotes reduced levels of the expressed miRNA in the sample type, in UC. ↑ denotes increased levels of the expressed miRNA. UC, ulcerative colitis; DAPK, death-associated protein kinase; DIP1, DAPK-interacting protein-1; MDM2, murine double minute-2; CREBBP, cyclic AMP response element-binding protein (CREB)-binding protein; BRCA1, breast cancer genes one; CAC, colitis-associated cancer; NLRP3, NOD-like receptor (NLR) family pyrin domain containing-3; CLDN8, claudin eight; Th17, T helper 17 cell; C/EBPβ,/enhancer binding protein beta; DCs, dendritic cells; LB1, lamin B1; DSB, double-strand break; JARID2, jumonji and AT-rich interaction domain containing two; SOCS1, suppressor of cytokine signalling one; IL13RA1, interleukin 13 receptor subunit alpha one; BTG1, B-cell translocation gene-1; IECs, intestinal epithelial cells; SNIP1, Smad nuclear interacting protein one; EMT, epithelial-mesenchymal transition; STAT6, signal transducer and activator of transcription six; IFN-γ, interferon gamma; PDLIM2, PDZ and LIM domain protein two; PTEN, phosphatase and tensin homolog; NF-κB, nuclear factor kappa B; A3AR, adenosine A3 receptor, alternatively known as ADORA3; PDCD4, programmed cell death protein four; STAT3, signal transducer and activator of transcription three; BCL-2, B-cell lymphoma-2; GP130, glycoprotein 130; IKKα, IκB kinase α; IKKβ, IkB kinase β; TNFR2, tumour necrosis factor receptor two; IL1R1, interleukin one receptor type 1; HMGA2, high-mobility group AT-hook two; FZD3, frizzled class receptor three; MyD88, myeloid differentiation primary response 88; TLR4, toll-like receptor four; CCL8, chemokine (C-C motif) ligand eight; AFTPH, aftiphilin; IL17RD, interleukin seventeen receptor D; IL13RA1, interleukin thirteen receptor, alpha one; TNF-α, tumour necrosis factor α; IL-8, interleukin 8; GM-CSF, granulocyte-macrophage colony-stimulating factor; VEGF, vascular endothelial growth factor; BCL2; b-cell lymphoma two; BCLXL, b-cell lymphoma-extra-large; MMP9, matrix metallopeptidase nine; CXCL5, C-X-X motif chemokine ligand five; MIP-2a, macrophage inflammatory protein two a; A2Aar, A2A adenosine receptor; IRS-1, insulin receptor substrate 1; K-RAS, Kirsten rat sarcoma virus; API5, apoptosis inhibitor five; MEK-2, mitogen-activated protein kinase two. Table 2 is adapted from Zhou et al. [363]

6.2. Crohn's disease

The incidence of CD in the UK is 6.6 per 100,000 people and varies geographically with highest incidence rates in Europe, Oceania and North America [203,204]. Differentiating between UC and CD can be difficult due to the overlapping features. The up or downregulation of miRNAs can play a key role in the pathogenesis of CD, as summarised in several reviews [188,205,206]. Altered regulation of nucleotide-binding oligomerisation domain-containing protein 2 (NOD2), a key activator of the NF-κB pathway, can lead to the downregulation of miR-29b in CD. As a result, there is increased TGF-β signalling and collagen III protein production, which stimulates increased fibrotic activity and stricture formation [207]. This TGF-β1-induced collagen overexpression can be regulated by administration of miR-29b mimics [208]. TGF-β1 can also significantly downregulate miR-200b levels [209]. Additional disruption to epithelial to mesenchymal transition (EMT) due to loss of E-cadherin has also been associated with reduced miR-200 levels and contribution to intestinal fibrosis [210,211]. Intestinal fibrosis in CD can be alleviated by administration of miR-200b mimics, which act to directly decrease the levels of zinc finger E-box-binding homeobox one

(ZEB1) and (ZEB2) in colorectal adenocarcinoma cells (DLD-1 cells) [209]. These genes play a role in the transcriptional repression on interleukin-2 and TGFβ signalling pathways, respectively.

miR-19a-3p has been indicated to downregulate suppressor of cytokine signalling 3 (SOCS3) and accelerate the STAT3-mediated IFN-α and IL-6 inflammatory signalling pathways [212]. As a result of miR-19b downregulation in CD, treatment with pre-miR-19b in a TNBS-induced colitis model can possibly dampen intestinal inflammation. This is thought to be due to inhibition of SOCS3 and resultant chemokine production, as corroborated in histological scores. The upregulation of miR-19b led to reduced oedema, epithelial damage, and limited changes in colon length [213]. Dysregulated levels of miR-20a-5p promotes the development of CD through STAT3/IL-17 signalling pathways in CD patients. Delivery of miR-20a-5p mimics *to IL-10-/-* mice with colitis significantly dampened the colitis, mucosal inflammation and enhanced epithelial barrier function, via targeting of STAT3 and improvement to Th17 differentiation [214]. Significant upregulation of miR-301a has been observed in PBMCs and inflamed mucosa of IBD patients, further enhancing Th17 cell differentiation. Colonic administration of miR-301a inhibitors in TNBS-induced mouse colitis models significantly reduced inflammatory mediators, such as interleukin (IL)− 17A+ cells, IL-17A and TNF-α [215]. Furthermore, miR-141 targets C-X-C motif chemokine ligand 12 beta (CXCL12β) mRNA, thus affecting leukocyte trafficking and accelerating CD inflammation. Treatment via upregulation of miR-141 in the TNBS-induced colitis colon in mouse models ameliorated inflammation in CD, indicating a potential approach to CD treatment [216]. Downregulated levels of miR-10b are linked to dysregulated expression of Zona Occludens 1 (ZO-1) and occludin, resulting in attenuated intestinal barrier function. As a result, in vivo and in vitro treatment with miR-10b antagomiR suppresses inflammatory responses by enhancing intestinal barrier gene expression in Caco-2 cells [217]. In addition, treatment with ABX464 is a viable option for CD, with the size of the target market increasing by approximately 20% and full-scale launch set for 2028. It is currently in phase IIa trial testing to evaluate its safety in patients with moderate to severe CD [218].

6.3. Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic gastrointestinal (GI) condition that approximately affects 1 in 10 individuals worldwide [219]. IBS is defined by persistent defecation-related abdominal pain and altered bowel movement, such as diarrhoea, constipation, or a combination of both. Such symptoms are associated with dysregulation of the MGBA and intestinal barrier [220]. Furthermore, there is a correlation between the onset of IBS and psychological conditions, such as anxiety disorders, depression, and chronic fatigue [219,221]. Dysregulation of intestinal miRNAs can alter gut permeability, induce visceral hyperalgesia, and aggravate inflammation, thereby increasing the risk of IBS [222]. Several reviews have been published identifying dysregulated miRNAs implicated in the pathogenesis of IBS in more detail [223–226].

One study suggested that upregulated levels of miR-29 increase intestinal membrane permeability. This occurs via the regulation of glutamine synthetase gene (GLUL), which subsequently downregulates Claudin-1 and nuclear factor-κB–repressing factor (NKRF) in blood microvesicles and intestinal tissue [227,228]. In addition, miR-219a-5p and miR-338–3p, which are both downregulated in IBS, have been identified to influence permeability and visceral hypersensitivity. This is a result of mitogen-activated protein kinase (MAPK) release of pro-inflammatory cytokines and regulation of cell proliferation and motility [229]. In human colonic epithelial cells, IBS patient-derived serum exosomes raised expression levels of miR-148b-5p. This elevation effect increases membrane permeability via interaction between miR-148b-5p and the inflammatory mediator, regulator of G-protein signalling 2 (RGS2), potentially contributing to the pathogenesis of IBS [230]. Downregulation of miR-199, which mediates transient receptor potential vanilloid type 1 (TRPV1)-associated hyperalgesia pathways has been linked to visceral pain in IBS-diarrhoea patients and increased visceral hypersensitivity in murine colonic tissue [231]. Consequently, miR-199 may be a biomarker of visceral pain and a prospective therapeutic target. An additional exacerbator of visceral hyperalgesia and hypersensitivity is suppression of cannabinoid receptor 1 (CNR1) and serotonin transporter (SERT) by miR-200a [232]. Interestingly, low serotonin levels have been implicated in IBS pathogenesis [233]. Both miR-24 and miR-200a regulate SERT, thus inhibiting serotonin reuptake [234]. Treatment with miR-24 inhibitors has demonstrated a reduction in abdominal pain and dampened inflammation in IBS-treated mice [234]. In addition, upregulation of miR-495 alleviates visceral hypersensitivity in IBS-diarrhoea mice. This is a result of the modulation of protein kinase inhibitor beta (PKIB) and subsequent suppression of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signalling pathway. Hence, miR-495 mimics or inducers could also be a therapeutic option in the treatment of IBS [235].

6.4. Clostridioides difficile infection

Clostridioides difficile infection (CDI) is a leading cause of healthcare-associated infections and has been associated with substantial morbidity and mortality worldwide [236]. With the global yearly incidence ranging from 1.12 to 631.80 per 100,000, CDI accounted for 2992 cases in the UK in the first 3 months of 2021 [236,237]. Alarmingly, the prevalence of community-onset associated CDI continues to rise, with highest rates observed in healthcare-acquired CDI and in patients greater than the age of sixty-five. This is due to immunological attenuation, long-term antibiotic and proton-pump inhibitor use and multiple co-morbidities in these patient groups [238]. Infection with the anaerobic, spore-forming, Gram-positive *C.difficile* bacterium occurs via the transmission of spores orofaecally, triggering the onset of diarrhoeal symptoms, which can rapidly lead to pseudomembranous colitis, hypoalbuminemia and resultant circulatory shock [239]. Damage to the cytoskeleton of IECs is induced by cytotoxic virulence factors, toxin A (TcdA) and toxin B (TcdB). These toxins trigger the necrosis of the intestinal mucosal surface via the release of the pro-inflammatory chemokines and cytokines [239]. Microbial dysbiosis, which is an alteration in the balance of protective gut commensals in the GI tract results in a leaky gut and germination of *C. difficile* spores into toxin-producing vegetative cells [240]. These gut commensals can affect miRNA expression, of which the levels and release of extracellular faecal miRNA-containing exosome-like vesicles can in-turn affect the gut microbiome [164]. In fact, loss of miRNAs in the intestinal contents has been identified as a contributor to gut microbiota dysbiosis [164].

Following faecal microbiota transplantation (FMT) in patients with recurrent CDI (rCDI), one study detected the upregulation of 64 miRNAs in circulation, in two independent randomised controlled trials [241]. Additional investigations confirmed that the most highly upregulated miRNAs, specifically miR-23a, miR-150, miR-26b, and miR-28 targeted the inflammatory genes *IL-12B, IL-18, FGF-21,* and *TNFRSF9*, respectively. These findings were further demonstrated in both rCDI-FMT and toxin-treated murine intestinal mucosa and *ex vivo* human intestinal colonoids [241]. In a follow-on multi-factorial observational study, the same authors identified miR-16 and miR-451a as potential biomarkers of treatment outcome to FMT in patients with refractory CDI [242]. Furthermore, the downregulation of miRNAs in CDI is influenced by TcdB, as a result of *Drosha* inhibition- an enzyme heavily involved in miRNA biogenesis [241,243]. Overexpression of both miR-23a and miR-150 in IECs displayed cytoprotective effects against TcdB cytotoxicity in CDI [241,244]. The upregulation of these miRNAs displays therapeutic potential for the treatment and/or prevention of toxin-induced gut barrier damage in CDI [244]. However, additional studies are required in animal models to further demonstrate this effect [244]. As further proof of concept, a recent report demonstrated the cytoprotective properties of polymer-based nanoparticles (NPs) loaded with miR-23a and miR-150–5p in IECs against colitogenic toxins

(TcdA+TcdB) and LPS [245]. The miRNA-NPs were able to increase intracellular levels of miR-23a-3p and miR-150–5p in all IECs without inducing cytotoxicity effects [245]. In addition, the NPs also protected brain-derived cell lines (SH-SY5Y, LUHMES, A-172 glioma/glial cells) from LPS, suggesting that both miRNAs in combination may elicit protective effects on the gut and brain [245].

Interestingly, from a gut-brain axis perspective, significant alterations in dopamine metabolism have been reported in major dopaminergic brain regions of antibiotic-induced *C. difficile*-infected mice [246]. The most notable observation in the latter study was significantly increased dopamine in the striatum in the *C. difficile* group compared to the control mice. Infected animals also showed increased caecal and serum p-cresol levels and reduced serum dopamine beta-hydroxylase (DBH) activity [246]. Of note, *C. difficile* produces 10–1000 times more p-cresol than other known p-cresol producing bacteria in the gut, and this same metabolite can induce behavioural alterations in mice by dysregulating the dopaminergic axis [247–250]. These findings may have direct implications in the precipitation and aggravation of neurodevelopmental disorders and merit further study. Furthermore, TcdB has also been shown to induce a senescence phenotype in enteric glial cells. This effect which is dependent on p27 expression and activation of AKT and JNK, may confer increased risk of diseases such as IBS, IBD, and tumorigenesis due to persistent inflammation, transfer of senescence status and stimulation of pre-neoplastic cells [251]. Finally, lending further support for the potential importance of the MGBA, FMT may also directly contribute to mental health alleviation via GBA modifications [252]. To this effect, one recent study reported significant improvements in clinical symptoms and cognitive functions compared to a control group in patients receiving FMT for severe *C. difficile* with dementia, suggesting the importance of the brain-gut-microbiome axis in regulating cognitive decline [253].

7. Role of miRNAs in neurodegenerative disorders

7.1. Parkinson's disease

As the second most common age-related neurodegenerative disease, Parkinson's disease (PD) is predicted to be prevalent in a minimum of eight million individuals globally by 2030 [254]. As a result of loss of striatal dopamine in the nigrostriatal pathway and degeneration of the basal ganglia, PD can lead to rigidity, postural instability, resting tremor, and bradykinesia [255]. With an aging-population, efficient treatment of PD is an urgent, unmet need. Despite therapeutic strategies to alleviate motor and nonmotor PD symptoms, there are currently no therapeutic agents that can halt the continuous neurodegeneration which leads to serious motor disruption and cognitive decline. Several detailed reviews have been published identifying dysregulated miRNAs that are associated with the pathogenesis of PD [256–260]. Yet, there has been no substantial human clinical trial data on the use of miRNA therapeutics in PD. Therefore, for the purpose of this review, we will focus mainly on describing the most promising emerging preclinical data derived from PD murine models.

Various miRNAs have been implicated in α-synuclein-mediated neurotoxicity, either via direct control or chaperone-mediated autophagy, resulting in impaired vesicle trafficking and increased neuroinflammation. Both miR-153 and miR-223 are associated with reduced levels of α-synuclein in PD murine models [261]. The inflammasome NOD-like receptor protein 3 (NLRP3) facilitates the degradation and apoptosis of dopaminergic (DA) neurons in PD via the excessive release of pro-inflammatory mediators (IL-1β and IL-18) [262]. Interestingly, NLRP3 has been shown to be a downstream target of miR-190, in a luciferase reporter assay. Therefore, use of miR-190 mimics could therapeutically target and downregulate NLRP3 expression to hinder neuronal apoptosis and neuroinflammation, as demonstrated in LPS-induced brain-derived microglia cells 2 (BV2) cells and 1-methyl-4--phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD murine model [263,264]. Furthermore, overexpression of miR-190 inhibited pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS), IL-6, TNF-α, and TGF-β1 but simultaneously upregulated the anti-inflammatory mediator IL-10 LPS-induced BV2 cells [263]. In MPTP-induced PD mice, raised levels of miR-190 dampened the activation of microglial cells and downregulated the pro-inflammatory cytokines IL-6 and TNF-α in the substantia nigra pars compacta (SNpc) [263].

miR-7 can also directly bind and inhibit nigrostriatal α-synuclein and NLRP3-mediatated inflammasome expression, thereby inducing neuroinflammation in PD [265]. This effect can be resolved by injection of miR-7 mimics in mouse striatum, resulting in diminished activation of NLRP3 and reduced DA neuron loss [266]. miR-132 is another key molecule that specifically targets nuclear receptor subfamily 4 group A member 2 (NR4A2) expression to regulate embryonic stem cell differentiation for midbrain DA neurons [267]. Upregulation of miR-132 in PD mouse and rat models leads to loss of DA neuron differentiation, resulting in temporospatial and memory deficits in the brain [268,269]. Use of the miRNA sponge mmu-circRNA-0003292 inhibits miR-132 activity and limits the progression of PD [270,271]. The use of mmu_-circRNA_0001320 has been demonstrated to upregulate miR-124 levels, which are commonly downregulated in the pathogenesis of PD [272]. However, further studies are warranted to validate this observation [270]. In fact, use of miR-124 mimics in a focal ischaemic mouse model can enhance the movement of DA neurons into the striatum and reduce dopamine transmitter levels, thus reducing the motor symptoms of PD [273]. miR-124 mimics also inhibited the non-neuronal genes, sex-determining region Y box 9 (SOX9) and jagged canonical notch ligand 1 (JAGGED1), which are both implicated in the regulation of stem cell differentiation [274].

miR-30e plays a neuroprotective role by downregulating inflammatory cytokines TNF-α, cyclooxygenase-2 (COX-2) and iNOS and inhibiting the NLlrp3 inflammasome in PD. Therefore, administration of miR-30e agomirs in the MPTP-induced PD murine model was shown to dampen α-synuclein expression and re-establish brain-derived neurotrophic factor (BDNF) secretion. This resulted in the improvement of motor control and behavioural performances in the mice [275]. Furthermore, treatment with a miR-200a inhibitor in a 6-hydroxydopamine rat model demonstrated striatal downregulation of the cAMP/PKA signalling pathway and increased cell survival rates in PD [276]. Use of antagomir-155 might also be a potential therapeutic agent for the treatment of PD. miR-155 acts by regulating the microglia-based inflammatory pathway to α-synuclein aggregation in PD [277]. Although not investigated in PD animals or humans, administration of anatgomir-155 into two in vivo lymphoma murine models demonstrated a decrease in tumour growth [278]. As a result, a phase II study has been launched to investigate the safety and tolerability of synthetic LNA-antagomir-155 on patients with mycosis fungoides-type cutaneous T-cell lymphoma has been launched (NCT03713320).

7.2. Alzheimer's disease

Alzheimer's disease (AD) is the leading age-related neurodegenerative disease, defined by a cognitive decline in executive function, spatial awareness, and episodic memory. The rising prevalence of AD is a growing concern due to associated high socioeconomic costs and lack of diagnostic biomarkers and therapeutic agents to limit the progression of AD [279]. AD is estimated to affect 1% of the global population by 2050 [280]. The presence of extracellular beta-amyloid plaques, intracellular neurofibrillary tau protein aggregates, neuroinflammation, and oxidative stress are defining factors of AD. Reversal of dysregulated levels of miRNAs in AD could lead to better treatment options for AD. As with PD, the role of miRNAs in AD and the biological matrices in which they were profiled has been extensively studied and summarised in several excellent review papers [280–283].

One specific miRNA that is downregulated in AD is miR-132, which

is normally negatively correlated with intracellular hyperphosphorylated TAU protein accumulation and extracellular beta-amyloid aggregate deposition in the pre-frontal cortex. It bimodally regulates both these processes by targeting ITPKB, as demonstrated in late-stage human AD hippocampal samples [284]. Direct regulation of Phosphatase and Tensin Homolog (PTEN), forkhead box protein O3a (FOXO3a) and E1A binding protein P300 by miR-132 also prompts the inhibition of neuronal apoptosis. Restored miR-132 levels by direct administration of miR-132 mimics into the brain of AD murine models has been demonstrated to reduce Aβ40–42 levels, TAU hyperphosphorylation, and limit the decline of adult hippocampal neurogenesis [284–286]. Furthermore, peripheral blood samples from AD patients revealed downregulated levels of miR-29c and raised levels of beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1), which plays a role in the processing of the amyloid-beta peptides and their subsequent aggregation in neurons [287]. The in vivo study investigated the effect of miR-29c mimic injections into the hippocampus of AD senescence-accelerated mouse prone 8 (SAMP8) [287]. Results indicated that miR-29c upregulation correlated with reduced BACE-1 expression and amyloid-beta proteins [287]. Observed in APP/PSEN1 transgenic mice, miR-137 regulates the calcium voltage-gated channel subunit alpha-1 C *(CACNA1C)* gene, which codes for the calcium-channel CAV1.2 [288]. In AD, downregulation of miR-137 results in increased hippocampal *CACNA1AC* expression and beta-amyloid aggregation [288]. An increase in $Ca2+$ influx contributes to the pathogenesis of AD. Use of miR-137 mimics might possibly reduce neuronal dysregulation in AD [288]. Hippocampal and temporal cortex upregulation of miR-146a contributes to the pathogenesis of AD by targeting interleukin (IL)− 1 receptor-associated kinase 1 (IRAK1), and tumour necrosis factor (TNF) receptor-associated factor 6 (TRAF6), which are regulators of innate immunity pathways [289,290]. The identification of the functional SNP in the promotor region of miR-146a has been linked to the deterioration of cognitive behaviour in AD patients [290]. The intranasal, non-invasive delivery of miR-146 agomirs (M136AG) dampened neuroinflammation and repaired cognitive impairment in APP/PS1 transgenic mice [290]. Downregulation of miR-188–5p has been linked to cognitive decline in AD pathology in AD patients and 7-month-old five familial AD (5XFAD) transgenic mice [291]. Long-term potentiation is regulated by miR-188–5p and plays a role in the consolidation of long-term memory [291]. Therefore, induction of miR-188–5 P mimics in five familial Alzheimer's disease mutations (5XFAD) mice ameliorates synaptic and cognitive decline by enhancing synaptic strength and spine density via negative regulation of NRP-2 [291]. Downregulated levels of hippocampal miR-388–5p also contributes to AD pathology by targeting BACE1 to enhance beta-amyloid aggregation and neuroinflammation in AD patients and 5XFAD transgenic mice. Stereotactic administration of miR-338–5p into the dentate gyrus in the 5XFAD murine model reduces neuroinflammation and improve spatial memory decline [292].

7.3. Ischaemic stroke

Stroke, which can be divided into haemorrhagic or ischaemic stroke is a leading global cause of death and adult disability [293–297]. With ischaemic stroke contributing to most of all cases, it is critical to accurately diagnose stroke at the earliest stage to prevent further deterioration [298]. Both environmental and genetic factors influence the onset of stroke [293]. miRNAs play a key role in the onset of excitotoxicity, oxidative stress, and BBB damage in ischaemic stroke. It has been reported that ischaemia-induced neurogenesis plays a significant role in post-stroke repair [299]. Most studies investigating the prognostic, diagnostic and therapeutic role of miRNAs in ischaemic stroke have been conducted in animal models. However, the therapeutic capabilities of miRNAs in these preclinical studies might not be reflective of their effects in humans and warrants further investigation.

For example, miR-126 contributes to angiogenesis and neurogenesis but is significantly downregulated following ischaemic stroke. As a result, intracerebral delivery of miR-126 agomirs to middle cerebral artery occlusion-induced (MCAO) mice can substantially enhance vascular remodelling, promote neurogenesis and limit neurobehavioral decline [300]. In addition, miR-195 has an anti-inflammatory role by directly inhibiting the NF-kB, Semaphorin 3 A, cell division control protein 42 homolog (Cdc42) and c-Jun N-terminal kinase (JNK) signalling pathways, reducing endothelial dysfunction, and promoting neural regeneration and stem cell proliferation. Following ischaemic stroke, it is significantly downregulated. Intravenous injection of miR-195 agomirs six hours post ischaemic injury dampens neuroinflammation and decreases infarct size in ischaemic stroke-induced rats [301]. Upregulation of AMP-activated protein kinase (AMPK) has been shown to aggravate neuronal apoptosis following ischaemic stroke. Use of miR-27b antagomirs in MCAO mice promotes post-stroke recovery by reducing neuronal degradation, inducing hippocampal AMPK-mediated neurogenesis, and enhancement of spatial awareness and cognitive behaviour [302]. In a distal MCAO murine model, intravenous delivery of miR-155 antagomirs dampens the effect of neuronal damage in the peri-infarct area. This results in increased blood flow, preservation of microvascular integrity and impediment of the expression of neuroinflammatory cytokines and chemokines [303].

In post-ischaemic stroke, intraventricular administration of miR-132 agomirs in MCAO mice leads to the inhibition of matrix metalloproteinase-9 (MMP-9) and regulation of the tight-junction regulators, VE-cadherin and the adhesion molecule, beta-catenin, as well as infarct shrinkage and oedema depletion [304]. In post-ischaemic stroke, miR-107 promotes angiogenesis by targeting *Dicer-1*. However, induction of miR-107 antagomirs to MCAO rats results in the suppression of VEGF mRNA and enhanced Dicer-1-mediated angiogenesis. As a result, this leads to a reduced infarct size and increased capillary numbers within the ischaemic borders [305]. Therefore, miR-107 antagomirs could be used as a unique therapeutic tool in stroke therapy. Another example of a protective miRNA therapeutic is the intraventricular use of the miR-200c antagomir in the MCAO murine model. The downregulation of miR-200c causes a decrease in infarct size by targeting Reelin, a key regulator of neuronal movement and synaptogenesis [306]. Clearly, miRNAs may hold therapeutic potential for ischaemic stroke. However, there are still important therapeutic details that are yet to be established, such as understanding the optimal route and timing of delivery.

8. Discussion: towards shared therapeutics for inflammatory disorders of the GBA

A growing body of evidence links NDDs with gut inflammation or a leaky gut [307] through shared pathophysiology's including aberrant miRNA expression. Patients with IBD have a much higher risk of all cause dementia and AD dementia than the general population [308–310]. Thus, one can postulate that future miRNA therapeutics could potentially delay or even prevent the onset of NDDs by maintaining the integrity of the intestinal epithelial barrier and through consequently dampening systemic and neuroinflammation. miRNA therapeutics which target these overlapping dual pathologies could be an attractive therapeutic prospect.

For example, miR-124 represents an interesting therapeutic target for both IBD and NDD. In PD, downregulation of miR-124 in human plasma and subsequent restoration in PD mice can reduce dopamine transmitter levels, thus reducing the motor symptoms of PD via suppression of Axin1 and triggering of Wnt/β-catenin signalling pathways [311]. Similarly, use of ABX464 (Obefazimod), which selectively upregulates levels of miR-124 in IBD and has demonstrated significant anti-inflammatory effects in UC patients, may find therapeutic utility in PD. Although treatment of brain-derived cells with Obefazimod in neuronal cells resulted in the downregulation of miR-124, it had cell-type specific protective effects on cells exposed to

lipopolysaccharide [245]. Nonetheless, further in vitro and in vivo research is required to determine the CNS protective effects of Obefazimod.

Dysregulated levels of miR-155 is also common in both PD and UC. miR-155 antagomirs can protect against DSS-induced colitis in mice by reducing intestinal barrier damage and inflammation, via restoration of the SHIP-1 pathway and regulation of Th17 cells and Jarid2Wnt/β-catenin signalling pathways [192]. Similarly, the antagomir-155 regulates α-synuclein aggregation in PD and might also be a potential therapeutic agent [312]. The development of a miRNA therapeutic which can tackle these two related inflammatory conditions could be an interesting direction for future research.

Another fascinating observation is the pathophysiological overlapping of miRNAs implicated in both IBD and *C. difficile* infection (CDI). Following successful FMT in CDI patients, upregulated levels of both miR-23a and miR-150 displayed cytoprotective effects against TcdB cytotoxicity by targeting the inflammatory genes, *1 L-12B* and *1 L-18*, respectively in human IECs [101]. Given this observation, it would be interesting in future work to investigate the effects of combining the gut barrier protective properties of both miR-23a and miR-150 with anti-inflammatory ABX464. Alternatively, miR-23a and miR-150 could be combined with a pre-existing antimicrobial agent. Use of gut-protecting miRNA nanotherapeutics, alone or in conjunction with antimicrobials, could help reduce the risk of gut dysbiosis and emergence of antimicrobial resistance.

In addition, miR-150 also plays a role in the regulation of the BBB and neuroinflammation by targeting the gene AKT3 in microglial cells, in which significant downregulation in the plasma of PD patients has been observed [313]. Likewise, reduced levels of miR-23a in serum and CSF samples from AD patients has been noted compared to controls [314]. The recent observations that polymer-based NPs loaded with miR-23a-3p and miR-150–5 p show protective effects in brain-derived and IECs against LPS suggests that miR-150 and miR-23a may treat and prevent downstream neurodegenerative complications that could arise from gut barrier dysregulation [245]. Thus, it may be advantageous to identify additional miRNAs which are implicated across multiple MGBA disorders which may facilitate the development of novel multipurpose therapeutics.

Despite research into the delivery mechanisms for miRNA therapeutics, several major challenges need to be overcome for clinical adoption. Limited correlations between in vitro performance and in vivo efficacy require the development of better models for preclinical evaluation of RNA delivery. Increasingly, there are opportunities to test the properties of miRNA nanotherapeutics in organ-on-chip models (OOACs). These platforms are now being used to emulate the gut physiological environment to model disease states and evaluate drug efficacy [315]. Alternatively, the use of high dimensional platforms such as digital spatial transcriptomics might be applied to interrogate the precise targeting abilities of miRNAs [316]. Use of combination polymer-lipid miRNA-vectors offers further ways for modulating immune responses or overcoming detrimental immunological side effects. In addition, advances in BBB-penetrating agents, for example, the anti-transferrin receptor antibody 272 might enhance delivery of miRNAs to the brain via absorptive transcytosis into the CNS [317].

Ultimately, large human clinical trials which study patient cohorts with epidemiologically and pathophysiologically linked MGBA disorders are required to further propel this area of research. These should be coupled with advanced and improved animal models that help to understand and validate molecular mechanisms of action of these miRNA therapeutics. Inspired by the recent and ongoing success of ABX464 in IBD, miRNA therapeutics offer potentially transformative and translational potential in treating inflammatory disorders of the MGBA.

CRediT authorship contribution statement

Tanya Monaghan: Conceptualization, supervision, writing – review & editing, Project administration. **Neha Datta**: data curation, investigation, visualization, writing - original draft. **Charlotte Johnson**: software, visualization. **Dina Kao**: Writing – review & editing. **Pratik Gurnani**: Writing – review & editing. **Cameron Alexander**: Writing – review & editing, Funding acquisition. **Christos Polytarchou**: Writing – review & editing, Supervision.

Declaration of Competing Interest

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References

[1] C.M. Connelly, M.H. Moon, J.S. Schneekloth Jr., The emerging role of RNA as a therapeutic target for small molecules, Cell Chem. Biol. 23 (2016) 1077–1090, https://doi.org/10.1016/j.chembiol.2016.05.021.
[2] M. Pandey, D. Ojha, S. Bansal, A.B. Rode, G. Chawla, From bench side to clinic: Potential and challenges of RNA vaccines and therapeutics in infectious diseases, Mol. Asp. Med 81 (2021), 101003, https://doi.org/10.1016/j.mam.2021.101003.
[3] S.T.W.J. Crooke, C.F. Bennett, B.F. Baker, RNA-targeted therapeutics, Cell Metab. 27 (2018) 714–739, https://doi.org/10.1016/j.cmet.2018.03.004.
[4] J.D.A. Falese, A. Hargrove, Targeting RNA with small molecules: from fundamental principles towards the clinic, Chem. Soc. Rev. 50 (2021) 2224–2243, https://doi.org/10.1039/d0cs01261k.
[5] I. Ezkurdia, D. Juan, J.M. Rodriguez, A. Frankish, M. Diekhans, J. Harrow, J. Vazquez, A. Valencia, M.L. Tress, Multiple evidence strands suggest that there may be as few as 19,000 human protein-coding genes, Hum. Mol. Genet 23 (2014) 5866–5878, https://doi.org/10.1093/hmg/ddu309.
[6] K. Paunovska, D. Loughrey, J.E. Dahlman, Drug delivery systems for RNA therapeutics, Nat. Rev. Genet 23 (2022) 265–280, https://doi.org/10.1038/s41576-021-00439-4.
[7] T.C. Roberts, R. Langer, M.J.A. Wood, Advances in oligonucleotide drug delivery, Nat. Rev. Drug Discov. 19 (2020) 673–694, https://doi.org/10.1038/s41573-020-0075-7.
[8] Y. Zhu, L. Zhu, X. Wang, H. Jin, RNA-based therapeutics: an overview and prospectus, Cell Death Dis. 13 (2022) 644, https://doi.org/10.1038/s41419-022-05075-2.
[9] S. Bajan, G. Hutvagner, RNA-based therapeutics: from antisense oligonucleotides to miRNAs, Cells 9 (2020) 137, https://doi.org/10.3390/cells9010137.
[10] T.R. Damase, R. Sukhovershin, C. Boada, F. Taraballi, R.I. Pettigrew, J.P. Cooke, The limitless future of RNA therapeutics, Front Bioeng. Biotechnol. 9 (2021), 628137, https://doi.org/10.3389/fbioe.2021.628137.
[11] C. Rinaldi, M.J.A. Wood, Antisense oligonucleotides: The next frontier for treatment of neurological disorders, Nat. Rev. Neurol. 14 (2018) 9–22, https://doi.org/10.1038/nrneurol.2017.148.
[12] J. Desterro, P. Bak-Gordon, M. Carmo-Fonseca, Targeting mRNA processing as an anticancer strategy, Nat. Rev. Drug Discov. 19 (2020) 112–129, https://doi.org/10.1038/s41573-019-0042-3.
[13] L.Y. Zhou, Z. Qin, Y.H. Zhu, Z.Y. He, T. Xu, Current RNA-based therapeutics in clinical trials, Curr. Gene Ther. 19 (2019) 172–196, https://doi.org/10.2174/1566523219666190719100526.
[14] P. Scarozza, H. Schmitt, G. Monteleone, M.F. Neurath, R. Atreya, Oligonucleotides-a novel promising therapeutic option for IBD, Front Pharm. 10 (2019) 314, https://doi.org/10.3389/fphar.2019.00314.
[15] B.E. Sands, Leukocyte anti-trafficking strategies: current status and future directions, Dig. Dis. 35 (2017) 13–20, https://doi.org/10.1159/000449077.
[16] B. Yacyshyn, W.Y. Chey, M.K. Wedel, R.Z. Yu, D. Paul, E. Chuang, A randomized, double-masked, placebo-controlled study of alicaforsen, an antisense inhibitor of

intercellular adhesion molecule 1, for the treatment of subjects with active Crohn's disease, Clin. Gastroenterol. Hepatol. 5 (2007) 215–220, https://doi.org/10.1016/j.cgh.2006.11.001.
[17] T. Lobatón, S. Vermeire, G. Van Assche, P. Rutgeerts, Review article: anti-adhesion therapies for inflammatory bowel disease, Aliment Pharm. Ther. 39 (2014) 579–594, https://doi.org/10.1111/apt.12639.
[18] S. Vegter, K. Tolley, T. Wilson Waterworth, H. Jones, S. Jones, D. Jewell, Meta-analysis using individual patient data: efficacy and durability of topical alicaforsen for the treatment of active ulcerative colitis, Aliment. Pharmacol. Ther. 38 (2013) 284–293, https://doi.org/10.1111/apt.12369.
[19] E.L. McConnell, F. Liu, A.W. Basit, Colonic treatments and targets: issues and opportunities, J. Drug Target. 17 (2009) 335–363, https://doi.org/10.1080/10611860902839502.
[20] K. Suzuki, S. Arumugam, J. Yokoyama, Y. Kawauchi, Y. Honda, H. Sato, Y. Aoyagi, S. Terai, K. Okazaki, Y. Suzuki, S. Mizumoto, K. Sugahara, R. Atreya, M.F. Neurath, K. Watanabe, T. Hashiguchi, H. Yoneyama, H. Asakura, Pivotal role of carbohydrate sulfotransferase 15 in fibrosis and mucosal healing in mouse colitis, PLoS ONE 11 (2016), e0158967, https://doi.org/10.1371/journal.pone.0158967.
[21] K. Suzuki, J. Yokoyama, Y. Kawauchi, Y. Honda, H. Sato, Y. Aoyagi, S. Terai, K. Okazaki, Y. Suzuki, Y. Sameshima, T. Fukushima, K. Sugahara, R. Atreya, M. F. Neurath, K. Watanabe, H. Yoneyama, H. Asakura, Phase 1 clinical study of siRNA targeting carbohydrate sulphotransferase 15 in Crohn's disease patients with active mucosal lesions, J. Crohn'S. Colitis 11 (2017) 221–228, https://doi.org/10.1093/ecco-jcc/jjw143.
[22] N. Dammes, D. Peer, Paving the road for RNA therapeutics, Trends Pharm. Sci. 41 (2020) 755–775, https://doi.org/10.1016/j.tips.2020.08.004.
[23] H. Dana, G.M. Chalbatani, H. Mahmoodzadeh, R. Karimloo, O. Rezaiean, A. Moradzadeh, N. Mehmandoost, F. Moazzen, A. Mazraeh, V. Marmari, M. Ebrahimi, M.M. Rashno, S.J. Abadi, E. Gharagouzlo, Molecular mechanisms and biological functions of siRNA, Int J. Biomed. Sci. 13 (2017) 48–57.
[24] P.E. Saw, E.W. Song, siRNA therapeutics: a clinical reality, Sci. China Life Sci. 63 (2020) 485–500, https://doi.org/10.1007/s11427-018-9438-y.
[25] S. Sargazi, R. Arshad, R. Ghamari, A. Rahdar, A. Bakhshi, S.F. Karkan, N. Ajalli, M. Bilal, A.M. Díez-Pascual, siRNA-based nanotherapeutics as emerging modalities for immune-mediated diseases: A preliminary review, Cell Biol. Int. 46 (2022) 1320–1344, https://doi.org/10.1002/cbin.11841.
[26] E.K. Müller, N. Białas, M. Epple, I. Hilger, Nanoparticles carrying NF-κB p65-specific siRNA alleviate colitis in mice by attenuating NF-κB-related protein expression and pro-inflammatory cellular mediator Secretion, Pharmaceutics (2022) **14**, https://doi.org/10.3390/pharmaceutics14020419.
[27] N.M. Moussa-Pacha, S.M. Abdin, H.A. Omar, H. Alniss, T.H. Al-Tel, BACE1 inhibitors: Current status and future directions in treating Alzheimer's disease, Med Res Rev. 40 (2020) 339–384, https://doi.org/10.1002/med.21622.
[28] M. Zheng, Y. Liu, Y. Wang, D. Zhang, Y. Zou, W. Ruan, J. Yin, W. Tao, J.B. Park, B. Shi, ROS-responsive polymeric siRNA nanomedicine stabilized by triple interactions for the robust glioblastoma combinational RNAi therapy, Adv. Mater. 31 (2019), e1903277, https://doi.org/10.1002/adma.201903277.
[29] Y. Zhou, F. Zhu, Y. Liu, M. Zheng, Y. Wang, D. Zhang, Y. Anraku, Y. Zou, J. Li, H. Wu, X. Pang, W. Tao, O. Shimoni, A.I. Bush, X. Xue, B. Shi, Blood-brain barrier-penetrating siRNA nanomedicine for Alzheimer's disease therapy, Sci. Adv. (2020) **6**, https://doi.org/10.1126/sciadv.abc7031.
[30] L.A. Macfarlane, P.R. Murphy, MicroRNA: biogenesis, function and role in cancer, Curr. Genom. 11 (2010) 537–561, https://doi.org/10.2174/138920210793175895.
[31] J.W. Park, P.N.P. Lagniton, Y. Liu, R.H. Xu, mRNA vaccines for COVID-19: what, why and how, Int J. Biol. Sci. 17 (2021) 1446–1460, https://doi.org/10.7150/ijbs.59233.
[32] N. Chaudhary, D. Weissman, K.A. Whitehead, mRNA vaccines for infectious diseases: principles, delivery and clinical translation, Nat. Rev. Drug Discov. 20 (2021) 817–838, https://doi.org/10.1038/s41573-021-00283-5.
[33] F. Kowalzik, D. Schreiner, C. Jensen, D. Teschner, S. Gehring, F. Zepp, mRNA-based vaccines, Vaccines (2021) **9**, https://doi.org/10.3390/vaccines9040390.
[34] E.J. Wherry, E.M. Jaffee, N. Warren, G. D'Souza, A. Ribas, COVID-19 obotA and Force CT, How did we get a COVID-19 vaccine in less than 1 year? Clin. Cancer Res. 27 (2021) 2136–2138, https://doi.org/10.1158/1078-0432.Ccr-21-0079.
[35] J. Winter, S. Jung, S. Keller, R.I. Gregory, S. Diederichs, Many roads to maturity: microRNA biogenesis pathways and their regulation, Nat. Cell Biol. 11 (2009) 228–234, https://doi.org/10.1038/ncb0309-228.
[36] M. Ha, V.N. Kim, Regulation of microRNA biogenesis, Nat. Rev. Mol. Cell Biol. 15 (2014) 509–524, https://doi.org/10.1038/nrm3838.
[37] N. Lawless, A.B. Foroushani, M.S. McCabe, C. O'Farrelly, D.J. Lynn, Next generation sequencing reveals the expression of a unique miRNA profile in response to a gram-positive bacterial infection, PLoS One 8 (2013), e57543, https://doi.org/10.1371/journal.pone.0057543.
[38] A.E. Williams, M.M. Perry, S.A. Moschos, H.M. Larner-Svensson, M.A. Lindsay, Role of miRNA-146a in the regulation of the innate immune response and cancer, Biochem Soc. Trans. 36 (2008) 1211–1215, https://doi.org/10.1042/bst0361211.
[39] C. Nelson, V. Ambros, E.H. Baehrecke, miR-14 regulates autophagy during developmental cell death by targeting ip3-kinase 2, Mol. Cell 56 (2014) 376–388, https://doi.org/10.1016/j.molcel.2014.09.011.
[40] Z. Su, Z. Yang, Y. Xu, Y. Chen, Q. Yu, MicroRNAs in apoptosis, autophagy and necroptosis, Oncotarget 6 (2015) 8474–8490, https://doi.org/10.18632/oncotarget.3523.
[41] R.C. Friedman, K.K.-H. Farh, C.B. Burge, D.P. Bartel, Most mammalian mRNAs are conserved targets of microRNAs, Genome Res. 19 (2009) 92–105, https://doi.org/10.1101/gr.082701.108.
[42] L.F. Gulyaeva, N.E. Kushlinskiy, Regulatory mechanisms of microRNA expression, J. Transl. Med 14 (2016) 143, https://doi.org/10.1186/s12967-016-0893-x.
[43] X. Wang, Composition of seed sequence is a major determinant of microRNA targeting patterns, Bioinformatics 30 (2014) 1377–1383, https://doi.org/10.1093/bioinformatics/btu045.
[44] M.E. Peter, Targeting of mRNAs by multiple miRNAs: the next step, Oncogene 29 (2010) 2161–2164, https://doi.org/10.1038/onc.2010.59.
[45] J.R. Chevillet, I. Lee, H.A. Briggs, Y. He, K. Wang, Issues and prospects of microRNA-based biomarkers in blood and other body fluids, Molecules 19 (2014) 6080–6105, https://doi.org/10.3390/molecules19056080.
[46] W. Filipowicz, S.N. Bhattacharyya, N. Sonenberg, Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight, Nat. Rev. Genet 9 (2008) 102–114, https://doi.org/10.1038/nrg2290.
[47] T. Kawamata, Y. Tomari, Making RISC, Trends Biochem. Sci. 35 (2010) 368–376, https://doi.org/10.1016/j.tibs.2010.03.009.
[48] H. Jo Myung, S. Shin, S.-R. Jung, E. Kim, J.-J. Song, S. Hohng, Human argonaute 2 has diverse reaction pathways on target RNAs, Mol. Cell 59 (2015) 117–124, https://doi.org/10.1016/j.molcel.2015.04.027.
[49] Y. Iwakawa H-o and Tomari, The Functions of MicroRNAs: mRNA decay and translational repression, Trends Cell Biol. 25 (2015) 651–665, https://doi.org/10.1016/j.tcb.2015.07.011.
[50] J. Antunes, O. Lee, A.H. Alizadeh, J. LaMarre, T.G. Koch, Why the hype - What are microRNAs and why do they provide unique investigative, diagnostic, and therapeutic opportunities in veterinary medicine? Can. Vet. J. 61 (2020) 845–852.
[51] R.E. Drury, D. O'Connor, A.J. Pollard, The clinical application of MicroRNAs in infectious disease, Front. Immunol. 8 (2017), https://doi.org/10.3389/fimmu.2017.01182.
[52] S. Vasudevan, Y. Tong, J.A. Steitz, Switching from repression to activation: microRNAs can up-regulate translation, Science 318 (2007) 1931–1934, https://doi.org/10.1126/science.1149460.
[53] U.A. Ørom, F.C. Nielsen, A.H. Lund, MicroRNA-10a binds the 5'UTR of ribosomal protein mRNAs and enhances their translation, Mol. Cell 30 (2008) 460–471, https://doi.org/10.1016/j.molcel.2008.05.001.
[54] C.L. Jopling, K.L. Norman, P. Sarnow, Positive and negative modulation of viral and cellular mRNAs by liver-specific microRNA miR-122, Cold Spring Harb. Symp. Quant. Biol. 71 (2006) 369–376, https://doi.org/10.1101/sqb.2006.71.022.
[55] G. Mathonnet, M.R. Fabian, Y.V. Svitkin, A. Parsyan, L. Huck, T. Murata, S. Biffo, W.C. Merrick, E. Darzynkiewicz, R.S. Pillai, W. Filipowicz, T.F. Duchaine, N. Sonenberg, MicroRNA inhibition of translation initiation in vitro by targeting the cap-binding complex eIF4F, Science 317 (2007) 1764–1767, https://doi.org/10.1126/science.1146067.
[56] S. Jonas, E. Izaurralde, Towards a molecular understanding of microRNA-mediated gene silencing, Nat. Rev. Genet. 16 (2015) 421–433, https://doi.org/10.1038/nrg3965.
[57] I. Behm-Ansmant, J. Rehwinkel, T. Doerks, A. Stark, P. Bork, E. Izaurralde, mRNA degradation by miRNAs and GW182 requires both CCR4: NOT deadenylase and DCP1: DCP2 decapping complexes, Genes Dev. 20 (2006) 1885–1898, https://doi.org/10.1101/gad.1424106.
[58] M. Christie, A. Boland, E. Huntzinger, O. Weichenrieder, E. Izaurralde, Structure of the PAN3 pseudokinase reveals the basis for interactions with the PAN2 deadenylase and the GW182 proteins, Mol. Cell 51 (2013) 360–373, https://doi.org/10.1016/j.molcel.2013.07.011.
[59] J.E. Braun, V. Truffault, A. Boland, E. Huntzinger, C.-T. Chang, G. Haas, O. Weichenrieder, M. Coles, E. Izaurralde, A direct interaction between DCP1 and XRN1 couples mRNA decapping to 5′ exonucleolytic degradation, Nat. Struct. Mol. Biol. 19 (2012) 1324–1331, https://doi.org/10.1038/nsmb.2413.
[60] D.S. Hong, Y.K. Kang, M. Borad, J. Sachdev, S. Ejadi, H.Y. Lim, A.J. Brenner, K. Park, J.L. Lee, T.Y. Kim, S. Shin, C.R. Becerra, G. Falchook, J. Stoudemire, D. Martin, K. Kelnar, H. Peltier, V. Bonato, A.G. Bader, S. Smith, S. Kim, V. O'Neill, M.S. Beg, Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours, Br. J. Cancer 122 (2020) 1630–1637, https://doi.org/10.1038/s41416-020-0802-1.
[61] L. Liang, X. He, A narrative review of microRNA therapeutics: understanding the future of microRNA research, Precis. Cancer Med. (2021) **4**, https://doi.org/10.21037/pcm-21-28.
[62] R. Rupaimoole, F.J. Slack, MicroRNA therapeutics: towards a new era for the management of cancer and other diseases, Nat. Rev. Drug Discov. 16 (2017) 203–222, https://doi.org/10.1038/nrd.2016.246.
[63] K. Schramedei, N. Mörbt, G. Pfeifer, J. Läuter, M. Rosolowski, J.M. Tomm, M. von Bergen, F. Horn, K. Brocke-Heidrich, MicroRNA-21 targets tumor suppressor genes ANP32A and SMARCA4, Oncogene 30 (2011) 2975–2985, https://doi.org/10.1038/onc.2011.15.
[64] C.C. Esau, Inhibition of microRNA with antisense oligonucleotides, Methods 44 (2008) 55–60, https://doi.org/10.1016/j.ymeth.2007.11.001.
[65] M. Ishida, F.M. Selaru, miRNA-based therapeutic strategies, Curr. Anesth. Rep. 1 (2013) 63–70, https://doi.org/10.1007/s40139-012-0004-5.
[66] U.A. Ørom, S. Kauppinen, A.H. Lund, LNA-modified oligonucleotides mediate specific inhibition of microRNA function, Gene 372 (2006) 137–141, https://doi.org/10.1016/j.gene.2005.12.031.

[67] H. Ling, M. Fabbri, G.A. Calin, MicroRNAs and other non-coding RNAs as targets for anticancer drug development, Nat. Rev. Drug Discov. 12 (2013) 847–865, https://doi.org/10.1038/nrd4140.

[68] N. Tyagi, S. Arora, S.K. Deshmukh, S. Singh, S. Marimuthu, A.P. Singh, Exploiting nanotechnology for the development of microRNA-based cancer therapeutics, J. Biomed. Nanotechnol. 12 (2016) 28–42, https://doi.org/10.1166/jbn.2016.2172.

[69] A.G. Bader, D. Brown, J. Stoudemire, P. Lammers, Developing therapeutic microRNAs for cancer, Gene Ther. 18 (2011) 1121–1126, https://doi.org/10.1038/gt.2011.79.

[70] K. Terasawa, K. Shimizu, G. Tsujimoto, Synthetic pre-miRNA-based shRNA as potent RNAi triggers, J. Nucleic Acids 2011 (2011), 131579, https://doi.org/10.4061/2011/131579.

[71] J. Yang, X. Meng, J. Pan, N. Jiang, C. Zhou, Z. Wu, Z. Gong, CRISPR/Cas9-mediated noncoding RNA editing in human cancers, RNA Biol. 15 (2018) 35–43, https://doi.org/10.1080/15476286.2017.1391443.

[72] H. Chang, B. Yi, R. Ma, X. Zhang, H. Zhao, Y. Xi, CRISPR/cas9, a novel genomic tool to knock down microRNA in vitro and in vivo, Sci. Rep. 6 (2016) 22312, https://doi.org/10.1038/srep22312.

[73] G. Aquino-Jarquin, Emerging role of CRISPR/Cas9 technology for microRNAs editing in cancer research, Cancer Res 77 (2017) 6812–6817, https://doi.org/10.1158/0008-5472.CAN-17-2142.

[74] W. Huo, G. Zhao, J. Yin, X. Ouyang, Y. Wang, C. Yang, B. Wang, P. Dong, Z. Wang, H. Watari, E. Chaum, L.M. Pfeffer, J. Yue, Lentiviral CRISPR/Cas9 vector mediated miR-21 gene editing inhibits the epithelial to mesenchymal transition in ovarian cancer cells, J. Cancer 8 (2017) 57–64, https://doi.org/10.7150/jca.16723.

[75] R. El Fatimy, S. Subramanian, E.J. Uhlmann, A.M. Krichevsky, Genome editing reveals glioblastoma addiction to microRNA-10b, Mol. Ther. 25 (2017) 368–378, https://doi.org/10.1016/j.ymthe.2016.11.004.

[76] A.N. Saiyed, A.R. Vasavada, S.R.K. Johar, Recent trends in miRNA therapeutics and the application of plant miRNA for prevention and treatment of human diseases, Futur J. Pharm. Sci. 8 (2022) 24, https://doi.org/10.1186/s43094-022-00413-9.

[77] Y. Deng, C.C. Wang, K.W. Choy, Q. Du, J. Chen, Q. Wang, L. Li, T.K. Chung, T. Tang, Therapeutic potentials of gene silencing by RNA interference: principles, challenges, and new strategies, Gene 538 (2014) 217–227, https://doi.org/10.1016/j.gene.2013.12.019.

[78] P. Pereira, J.A. Queiroz, A. Figueiras, F. Sousa, Current progress on microRNAs-based therapeutics in neurodegenerative diseases, Wiley Inter. Rev. RNA (2017) **8**, https://doi.org/10.1002/wrna.1409.

[79] H.-R. Yu, L.-H. Huang, S.-C. Li, Roles of microRNA in the immature immune system of neonates, Cancer Lett. 433 (2018) 99–106, https://doi.org/10.1016/j.canlet.2018.06.014.

[80] A.I. Villanueva, R.R. Kulkarni, S. Sharif, Synthetic double-stranded RNA oligonucleotides are immunostimulatory for chicken spleen cells, Dev. Comp. Immunol. 35 (2011) 28–34, https://doi.org/10.1016/j.dci.2010.08.001.

[81] M. Segal, A. Biscans, M.-E. Gilles, E. Anastasiadou, R. De Luca, J. Lim, A. Khvorova, F.J. Slack, Hydrophobically modified let-7b miRNA enhances biodistribution to NSCLC and downregulates HMGA2 in vivo, Mol. Ther. Nucleic Acids 19 (2020) 267–277, https://doi.org/10.1016/j.omtn.2019.11.008.

[82] K. Lennox, M. Behlke, Chemical modification and design of anti-miRNA oligonucleotides, Gene Ther. 18 (2011) 1111–1120, https://doi.org/10.1038/gt.2011.100.

[83] M. Segal, F.J. Slack, Challenges identifying efficacious miRNA therapeutics for cancer, Expert Opin. Drug Discov. 15 (2020) 987–992, https://doi.org/10.1080/17460441.2020.1765770.

[84] Z. Li, T.M. Rana, Therapeutic targeting of microRNAs: current status and future challenges, Nat. Rev. Drug Discov. 13 (2014) 622–638, https://doi.org/10.1038/nrd4359.

[85] E. van Rooij, S. Kauppinen, Development of microRNA therapeutics is coming of age, EMBO Mol. Med 6 (2014) 851–864, https://doi.org/10.15252/emmm.201100899.

[86] K.S. Park, X. Sun, M.E. Aikins, J.J. Moon, Non-viral COVID-19 vaccine delivery systems, Adv. Drug Deliv. Rev. 169 (2021) 137–151, https://doi.org/10.1016/j.addr.2020.12.008.

[87] C.V. Pecot, G.A. Calin, R.L. Coleman, G. Lopez-Berestein, A.K. Sood, RNA interference in the clinic: challenges and future directions, Nat. Rev. Cancer 11 (2011) 59–67, https://doi.org/10.1038/nrc2966.

[88] T. Kim, H.N. Hyun, R. Heo, K. Nam, K. Yang, Y.M. Kim, Y.S. Lee, J.Y. An, J. H. Park, K.Y. Choi, Y.H. Roh, Dual-targeting RNA nanoparticles for efficient delivery of polymeric siRNA to cancer cells, Chem. Commun. 56 (2020) 6624–6627, https://doi.org/10.1039/D0CC01848A.

[89] S.R. Paliwal, R. Paliwal, S.P. Vyas, A review of mechanistic insight and application of pH-sensitive liposomes in drug delivery, Drug Deliv. 22 (2015) 231–242, https://doi.org/10.3109/10717544.2014.882469.

[90] R.J. Christie, N. Nishiyama, K. Kataoka, Minireview: delivering the code: polyplex carriers for deoxyribonucleic acid and ribonucleic acid interference therapies, Endocrinology 151 (2010) 466–473, https://doi.org/10.1210/en.2009-1045.

[91] C.S. Linsley, B.M. Wu, Recent advances in light-responsive on-demand drug-delivery systems, Ther. Deliv. 8 (2017) 89–107, https://doi.org/10.4155/tde-2016-0060.

[92] E. Bilensoy, Cationic nanoparticles for cancer therapy, Expert Opin. Drug Deliv. 7 (2010) 795–809, https://doi.org/10.1517/17425247.2010.485983.

[93] S. Singh, A.S. Narang, R.I. Mahato, Subcellular fate and off-target effects of siRNA, shRNA, and miRNA, Pharm. Res 28 (2011) 2996–3015, https://doi.org/10.1007/s11095-011-0608-1.

[94] Z. Wang, D.D. Rao, N. Senzer, J. Nemunaitis, RNA interference and cancer therapy, Pharm. Res 28 (2011) 2983–2995, https://doi.org/10.1007/s11095-011-0604-5.

[95] W. Xue, J.E. Dahlman, T. Tammela, O.F. Khan, S. Sood, A. Dave, W. Cai, L. M. Chirino, G.R. Yang, R. Bronson, D.G. Crowley, G. Sahay, A. Schroeder, R. Langer, D.G. Anderson, T. Jacks, Small RNA combination therapy for lung cancer, Proc. Natl. Acad. Sci. USA 111 (2014) E3553–E3561, https://doi.org/10.1073/pnas.1412686111.

[96] A.L. Kasinski, K. Kelnar, C. Stahlhut, E. Orellana, J. Zhao, E. Shimer, S. Dysart, X. Chen, A.G. Bader, F.J. Slack, A combinatorial microRNA therapeutics approach to suppressing non-small cell lung cancer, Oncogene 34 (2015) 3547–3555, https://doi.org/10.1038/onc.2014.282.

[97] E.A. Orellana, C. Li, A. Lisevick, A.L. Kasinski, Identification and validation of microRNAs that synergize with miR-34a - a basis for combinatorial microRNA therapeutics, Cell Cycle 18 (2019) 1798–1811, https://doi.org/10.1080/15384101.2019.1634956.

[98] M. Abu-Laban, P. Hamal, J.H. Arrizabalaga, A. Forghani, A.S. Dikkumbura, R. R. Kumal, L.H. Haber, D.J. Hayes, Combinatorial delivery of miRNA-nanoparticle conjugates in human adipose stem cells for amplified osteogenesis, Small 15 (2019), e1902864, https://doi.org/10.1002/smll.201902864.

[99] R. Harati, A. Mabondzo, A. Tlili, G. Khoder, M. Mahfood, R. Hamoudi, Combinatorial targeting of microRNA-26b and microRNA-101 exerts a synergistic inhibition on cyclooxygenase-2 in brain metastatic triple-negative breast cancer cells, Breast Cancer Res Treat. 187 (2021) 695–713, https://doi.org/10.1007/s10549-021-06255-y.

[100] A.E. Pottash, D. Levy, A. Jeyaram, L. Kuo, S.M. Kronstadt, W. Chao, S.M. Jay, Combinatorial microRNA loading into extracellular vesicles for increased anti-inflammatory efficacy, Noncoding RNA (2022) **8**, https://doi.org/10.3390/ncrna8050071.

[101] T.M. Monaghan, A.M. Seekatz, N.O. Markham, T.O. Yau, M. Hatziapostolou, T. Jilani, N. Christodoulou, B. Roach, E. Birli, O. Pomenya, T. Louie, D.B. Lacy, P. Kim, C. Lee, D. Kao, C. Polytarchou, Fecal microbiota transplantation for recurrent clostridioides difficile infection associates with functional alterations in circulating microRNAs, e254, Gastroenterology 161 (2021) 255–270, https://doi.org/10.1053/j.gastro.2021.03.050.

[102] T.M. Monaghan, A. Ugun-Klusek, M. Finelli, P. Gurnani, L. Chakrabarti, D. Kao, C. Alexander, C. Polytarchou, Connecting inflammatory bowel and neurodegenerative diseases: microRNAs as a shared therapeutic intervention, Gut (2023), https://doi.org/10.1136/gutjnl-2022-327301.

[103] N. Yang, An overview of viral and nonviral delivery systems for microRNA, Int. J. Pharm. Investig. 5 (2015) 179, https://doi.org/10.4103/2230-973X.167646.

[104] Y.P. Liu, B. Berkhout, miRNA cassettes in viral vectors: problems and solutions, Biochim. Biophys. Acta BBA Gene Regul. Mech. 1809 (2011) 732–745, https://doi.org/10.1016/j.bbagrm.2011.05.014.

[105] I. Dasgupta, A. Chatterjee, Recent advances in miRNA delivery systems, Methods Protoc. 4 (2021), https://doi.org/10.3390/mps4010010.

[106] D. Escors, K. Breckpot, Lentiviral vectors in gene therapy: their current status and future potential, Arch. Immunol. Ther. Exp. 58 (2010) 107–119, https://doi.org/10.1007/s00005-010-0063-4.

[107] S. Daya, K.I. Berns, Gene therapy using adeno-associated virus vectors, Clin. Microbiol. Rev. 21 (2008) 583–593, https://doi.org/10.1128/CMR.00008-08.

[108] Y. Fu, J. Chen, Z. Huang, Recent progress in microRNA-based delivery systems for the treatment of human disease, ExRNA 1 (2019) 24, https://doi.org/10.1186/s41544-019-0024-y.

[109] B.R. Schultz, J.S. Chamberlain, Recombinant adeno-associated virus transduction and integration, Mol. Ther. 16 (2008) 1189–1199, https://doi.org/10.1038/mt.2008.103.

[110] X. Tang, H. Zhang, Y. Song, D. Zhou, J. Wang, Hemagglutinin-targeting artificial microRNAs expressed by adenovirus protect mice from different clades of H5N1 infection, Mol. Ther. -Nucleic Acids 5 (2016), e311, https://doi.org/10.1038/mtna.2016.25.

[111] H.C.J. Ertl, Immunogenicity and toxicity of AAV gene therapy, Front Immunol. 13 (2022), 975803, https://doi.org/10.3389/fimmu.2022.975803.

[112] L.H. Vandenberghe, J.M. Wilson, AAV as an immunogen, Curr. gene Ther. 7 (2007) 325–333, https://doi.org/10.2174/156652307782151416.

[113] B. Wang, J. Li, F. Fu, C. Chen, X. Zhu, L. Zhou, X. Jiang, X. Xiao, Construction and analysis of compact muscle-specific promoters for AAV vectors, Gene Ther. 15 (2008) 1489–1499, https://doi.org/10.1038/gt.2008.104.

[114] R.A. Tripp, S. Mark Tompkins, Antiviral effects of inhibiting host gene expression, Influenza Pathog. Control-Vol. II (2014) 459–477, https://doi.org/10.1007/82_2014_409.

[115] L. Vannucci, M. Lai, F. Chiuppesi, L. Ceccherini-Nelli, M. Pistello, Viral vectors: a look back and ahead on gene transfer technology, N. Microbiol 36 (2013) 1–22.

[116] N. Yang, An overview of viral and nonviral delivery systems for microRNA, Int J. Pharm. Invest. 5 (2015) 179–181, https://doi.org/10.4103/2230-973x.167646.

[117] N. Nayerossadat, T. Maedeh, P.A. Ali, Viral and nonviral delivery systems for gene delivery, Adv. Biomed. Res. 1 (2012) 27, https://doi.org/10.4103/2277-9175.98152.

[118] H. Wang, Y. Jiang, H. Peng, Y. Chen, P. Zhu, Y. Huang, Recent progress in microRNA delivery for cancer therapy by non-viral synthetic vectors, Adv. Drug Deliv. Rev. 81 (2015) 142–160, https://doi.org/10.1016/j.addr.2014.10.031.

[119] A. Akinc, M.A. Maier, M. Manoharan, K. Fitzgerald, M. Jayaraman, S. Barros, S. Ansell, X. Du, M.J. Hope, T.D. Madden, B.L. Mui, S.C. Semple, Y.K. Tam,

M. Ciufolini, D. Witzigmann, J.A. Kulkarni, R. van der Meel, P.R. Cullis, The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs, Nat. Nanotechnol. 14 (2019) 1084–1087, https://doi.org/10.1038/s41565-019-0591-y.
[120] E. Oude Blenke, E. Örnskov, C. Schöneich, G.A. Nilsson, D.B. Volkin, E. Mastrobattista, Ö. Almarsson, D.J.A. Crommelin, The storage and in-use stability of mRNA vaccines and therapeutics: not a cold case, J. Pharm. Sci. 112 (2023) 386–403, https://doi.org/10.1016/j.xphs.2022.11.001.
[121] Y. Wu, M. Crawford, Y. Mao, R.J. Lee, I.C. Davis, T.S. Elton, L.J. Lee, S.P. Nana-Sinkam, Therapeutic delivery of microRNA-29b by cationic lipoplexes for lung cancer, Mol. Ther. Nucleic Acids 2 (2013), e84, https://doi.org/10.1038/mtna.2013.14.
[122] C. Zylberberg, S. Matosevic, Pharmaceutical liposomal drug delivery: a review of new delivery systems and a look at the regulatory landscape, Drug Deliv. 23 (2016) 3319–3329, https://doi.org/10.1080/10717544.2016.1177136.
[123] S. Hobel, A. Aigner, Polyethylenimines for siRNA and miRNA delivery in vivo, Wires, Nanomed., Nanobiotech (2013), https://doi.org/10.1002/wnan.1228.
[124] S. Gao, H. Tian, Y. Guo, Y. Li, Z. Guo, X. Zhu, X. Chen, miRNA oligonucleotide and sponge for miRNA-21 inhibition mediated by PEI-PLL in breast cancer therapy, Acta Biomater. 25 (2015) 184–193, https://doi.org/10.1016/j.actbio.2015.07.020.
[125] Ç. Biray Avcı, İ. Özcan, T. Balcı, Ö. Özer, C. Gündüz, Design of polyethylene glycol–polyethylenimine nanocomplexes as non-viral carriers: mir-150 delivery to chronic myeloid leukemia cells, Cell Biol. Int. 37 (2013) 1205–1214, https://doi.org/10.1002/cbin.10157.
[126] F. Wang, B. Zhang, L. Zhou, Y. Shi, Z. Li, Y. Xia, J. Tian, Imaging dendrimer-grafted graphene oxide mediated anti-miR-21 delivery with an activatable luciferase reporter, ACS Appl. Mater. Interfaces 8 (2016) 9014–9021, https://doi.org/10.1021/acsami.6b02662.
[127] S. Gaur, Y. Wen, J.H. Song, N.U. Parikh, L.S. Mangala, A.M. Blessing, C. Ivan, S. Y. Wu, A. Varkaris, Y. Shi, G. Lopez-Berestein, D.E. Frigo, A.K. Sood, G.E. Gallick, Chitosan nanoparticle-mediated delivery of miRNA-34a decreases prostate tumor growth in the bone and its expression induces non-canonical autophagy, Oncotarget 6 (2015) 29161–29177, https://doi.org/10.18632/oncotarget.4971.
[128] G. Salzano, D.F. Costa, C. Sarisozen, E. Luther, G. Mattheolabakis, P. P. Dhargalkar, V.P. Torchilin, Mixed nanosized polymeric micelles as promoter of doxorubicin and miRNA-34a co-delivery triggered by dual stimuli in tumor tissue, Small 12 (2016) 4837–4848, https://doi.org/10.1002/smll.201600925.
[129] Y. Chen, Y. Xianyu, X. Jiang, Surface modification of gold nanoparticles with small molecules for biochemical analysis, Acc. Chem. Res 50 (2017) 310–319, https://doi.org/10.1021/acs.accounts.6b00506.
[130] A. Schade, E. Delyagina, D. Scharfenberg, A. Skorska, C. Lux, R. David, G. Steinhoff, Innovative strategy for microRNA delivery in human mesenchymal stem cells via magnetic nanoparticles, Int. J. Mol. Sci. 14 (2013) 10710–10726, https://doi.org/10.3390/ijms140610710.
[131] A. Bitar, N.M. Ahmad, H. Fessi, A. Elaissari, Silica-based nanoparticles for biomedical applications, Drug Discov. Today 17 (2012) 1147–1154, https://doi.org/10.1016/j.drudis.2012.06.014.
[132] R. Ghosh, L.C. Singh, J.M. Shohet, P.H. Gunaratne, A gold nanoparticle platform for the delivery of functional microRNAs into cancer cells, Biomaterials 34 (2013) 807–816, https://doi.org/10.1016/j.biomaterials.2012.10.023.
[133] K.G. Margolis, J.F. Cryan, E.A. Mayer, The microbiota-gut-brain axis: from motility to mood, Gastroenterology 160 (2021) 1486–1501, https://doi.org/10.1053/j.gastro.2020.10.066.
[134] A. Chakrabarti, L. Geurts, L. Hoyles, P. Iozzo, A.D. Kraneveld, G. La Fata, M. Miani, E. Patterson, B. Pot, C. Shortt, D. Vauzour, The microbiota-gut-brain axis: pathways to better brain health. Perspectives on what we know, what we need to investigate and how to put knowledge into practice, Cell Mol. Life Sci. 79 (2022) 80, https://doi.org/10.1007/s00018-021-04060-w.
[135] L.H. Morais, H.L. Schreiber, S.K. Mazmanian, The gut microbiota–brain axis in behaviour and brain disorders, Nat. Rev. Microbiol. 19 (2021) 241–255, https://doi.org/10.1038/s41579-020-00460-0.
[136] C.R. Martin, V. Osadchiy, A. Kalani, E.A. Mayer, The brain-gut-microbiome axis, Cell Mol. Gastroenterol. Hepatol. 6 (2018) 133–148, https://doi.org/10.1016/j.jcmgh.2018.04.003.
[137] T. Doifode, V.V. Giridharan, J.S. Generoso, G. Bhatti, A. Collodel, P.E. Schulz, O. V. Forlenza, T. Barichello, The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology, Pharmacol. Res. 164 (2021), 105314, https://doi.org/10.1016/j.phrs.2020.105314.
[138] K. Socała, U. Doboszewska, A. Szopa, A. Serefko, M. Włodarczyk, A. Zielińska, E. Poleszak, J. Fichna, P. Wlaź, The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders, Pharmacol. Res. 172 (2021), 105840, https://doi.org/10.1016/j.phrs.2021.105840.
[139] C. Long-Smith, K.J. O'Riordan, G. Clarke, C. Stanton, T.G. Dinan, J.F. Cryan, Microbiota-gut-brain axis: new therapeutic opportunities, Annu Rev. Pharm. Toxicol. 60 (2020) 477–502, https://doi.org/10.1146/annurev-pharmtox-010919-023628.
[140] X.Y. Guo, X.J. Liu, J.Y. Hao, Gut microbiota in ulcerative colitis: insights on pathogenesis and treatment, J. Dig. Dis. 21 (2020) 147–159, https://doi.org/10.1111/1751-2980.12849.
[141] R. Rashed, R. Valcheva, L.A. Dieleman, Manipulation of gut microbiota as a key target for crohn's disease, Front. Med. 9 (2022) 1332, https://doi.org/10.3389/fmed.2022.887044.
[142] G. Moser, C. Fournier, J. Peter, Intestinal microbiome-gut-brain axis and irritable bowel syndrome, Wien. Med Woche 168 (2018) 62–66, https://doi.org/10.1007/s10354-017-0592-0.
[143] I.-M. Vasilescu, M.-C. Chifiriuc, G.G. Pircalabioru, R. Filip, A. Bolocan, V. Lazăr, L.-M. Diţu, C. Bleotu, Gut Dysbiosis and Clostridioides difficile infection in neonates and adults, Front. Microbiol. 12 (2022) 4207, https://doi.org/10.3389/fmicb.2021.651081.
[144] Q. Wang, Y. Luo, K. Ray Chaudhuri, R. Reynolds, E.-K. Tan, S. Pettersson, The role of gut dysbiosis in Parkinson's disease: Mechanistic insights and therapeutic options, Brain 144 (2021) 2571–2593, https://doi.org/10.1093/brain/awab156.
[145] S. Liu, J. Gao, M. Zhu, K. Liu, H.-L. Zhang, Gut microbiota and dysbiosis in Alzheimer's disease: implications for pathogenesis and treatment, Mol. Neurobiol. 57 (2020) 5026–5043, https://doi.org/10.1007/s12035-020-02073-3.
[146] R. Pluta, S. Januszewski, S.J. Czuczwar, The role of gut microbiota in an ischemic stroke, Int. J. Mol. Sci. 22 (2021) 915, https://doi.org/10.3390/ijms22020915.
[147] A. Rutsch, J.B. Kantsjö, F. Ronchi, The gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology, Front. Immunol. (2020) **11**, https://doi.org/10.3389/fimmu.2020.604179.
[148] S. Carding, K. Verbeke, D.T. Vipond, B.M. Corfe, L.J. Owen, Dysbiosis of the gut microbiota in disease, Micro Ecol. Health Dis. 26 (2015) 26191, https://doi.org/10.3402/mehd.v26.26191.
[149] S. Schippa, M.P. Conte, Dysbiotic events in gut microbiota: impact on human health, Nutrients 6 (2014) 5786–5805, https://doi.org/10.3390/nu6125786.
[150] M. Kalyan, A.H. Tousif, S. Sonali, C. Vichitra, T. Sunanda, S.S. Praveenraj, B. Ray, V.R. Gorantla, W. Rungratanawanich, A.M. Mahalakshmi, M.W. Qoronfleh, T. M. Monaghan, B.-J. Song, M.M. Essa, S.B. Chidambaram, Role of endogenous lipopolysaccharides in neurological disorders, Cells 11 (2022) 4038, https://doi.org/10.3390/cells11244038.
[151] P. Alexandrov, Y. Zhai, W. Li, W. Lukiw, Lipopolysaccharide-stimulated, NF-kB-, miRNA-146a- and miRNA-155-mediated molecular-genetic communication between the human gastrointestinal tract microbiome and the brain, Folia Neuropathol. 57 (2019) 211–219, https://doi.org/10.5114/fn.2019.88449.
[152] Q. Ma, C. Xing, W. Long, H. Wang, Q. Liu, R. Wang, Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis, J. Neuroinfiamm. 16 (1) (2019) 53, https://doi.org/10.1186/s12974-019-1434-3.
[153] N.L. Morris, M.A. Choudhry, Maintenance of gut barrier integrity after injury: Trust your gut microRNAs, J. Leukoc. Biol. 110 (2021) 979–986, https://doi.org/10.1002/JLB.3RU0120-090RR.
[154] R.J. Haines, R.S. Beard Jr., R.A. Eitner, L. Chen, M.H. Wu, TNFα/IFNγ mediated intestinal epithelial barrier dysfunction is attenuated by microRNA-93 downregulation of PTK6 in mouse colonic epithelial cells, PLoS One 11 (2016), e0154351, https://doi.org/10.1371/journal.pone.0154351.
[155] Y. Gao, J. Yi, K. Zhang, F. Bai, B. Feng, R. Wang, X. Chu, L. Chen, H. Song, Downregulation of MiR-31 stimulates expression of LATS2 via the hippo pathway and promotes epithelial-mesenchymal transition in esophageal squamous cell carcinoma, J. Exp. Clin. Cancer Res 36 (2017) 161, https://doi.org/10.1186/s13046-017-0622-1.
[156] Y. Tian, J. Xu, Y. Li, R. Zhao, S. Du, C. Lv, W. Wu, R. Liu, X. Sheng, Y. Song, MicroRNA-31 reduces inflammatory signaling and promotes regeneration in colon epithelium, and delivery of mimics in microspheres reduces colitis in mice, Gastroenterology 156 (2281–2296) (2019), e2286, https://doi.org/10.1053/j.gastro.2019.02.023.
[157] B. Zhang, Y. Tian, P. Jiang, Y. Jiang, C. Li, T. Liu, R. Zhou, N. Yang, X. Zhou, Z. Liu, MicroRNA-122a regulates zonulin by targeting EGFR in intestinal epithelial dysfunction, Cell. Physiol. Biochem. 42 (2017) 848–858, https://doi.org/10.1159/000478629.
[158] S. Dhuppar, G. Murugaiyan, miRNA effects on gut homeostasis: therapeutic implications for inflammatory bowel disease, Trends Immunol. 43 (2022) 917–931, https://doi.org/10.1016/j.it.2022.09.003.
[159] J. Ge, Z. Huang, H. Liu, J. Chen, Z. Xie, Z. Chen, J. Peng, J. Sun, J. Hou, X. Zhang, Lower expression of microRNA-155 contributes to dysfunction of natural killer cells in patients with chronic hepatitis B, Front. Immunol. 8 (2017) 1173, https://doi.org/10.3389/fimmu.2017.01173.
[160] V. Neudecker, M. Haneklaus, O. Jensen, L. Khailova, J.C. Masterson, H. Tye, K. Biette, P. Jedlicka, K.S. Brodsky, M.E. Gerich, Myeloid-derived miR-223 regulates intestinal inflammation via repression of the NLRP3 inflammasome, J. Exp. Med. 214 (2017) 1737–1752, https://doi.org/10.1084/jem.20160462.
[161] T.-L. Liao, Y.-M. Chen, K.-T. Tang, P.-K. Chen, H.-J. Liu, D.-Y. Chen, MicroRNA-223 inhibits neutrophil extracellular traps formation through regulating calcium influx and small extracellular vesicles transmission, Sci. Rep. 11 (2021) 1–17, https://doi.org/10.1038/s41598-021-95028-0.
[162] Q. Hou, Y. Huang, Y. Wang, L. Liao, Z. Zhu, W. Zhang, Y. Liu, P. Li, X. Chen, F. Liu, Lactobacillus casei LC01 regulates intestinal epithelial permeability through miR-144 targeting of OCLN and ZO1, J. Microbiol Biotechnol. 30 (2020) 1480–1487, https://doi.org/10.4014/jmb.2002.02059.
[163] E. Viennois, B. Chassaing, A. Tahsin, A. Pujada, L. Wang, A.T. Gewirtz, D. Merlin, Host-derived fecal microRNAs can indicate gut microbiota healthiness and ability to induce inflammation, Theranostics 9 (2019) 4542–4557, https://doi.org/10.7150/thno.35282.
[164] S. Liu, A.P. da Cunha, R.M. Rezende, R. Cialic, Z. Wei, L. Bry, L.E. Comstock, R. Gandhi, H.L. Weiner, The host shapes the gut microbiota via fecal microRNA, Cell Host Microbe 19 (2016) 32–43, https://doi.org/10.1016/j.chom.2015.12.005.
[165] L. He, X. Zhou, Y. Liu, L. Zhou, F. Li, Fecal miR-142a-3p from dextran sulfate sodium-challenge recovered mice prevents colitis by promoting the growth of Lactobacillus reuteri, Mol. Ther. 30 (2022) 388–399, https://doi.org/10.1016/j.ymthe.2021.08.025.

[166] L. Prisciandaro, M. Geier, R. Butler, A. Cummins, G. Howarth, Probiotics and their derivatives as treatments for inflammatory bowel disease, Inflamm. Bowel Dis. 15 (2009) 1906–1914, https://doi.org/10.1002/ibd.20938.

[167] N. Xu, A.D. Li, L.L. Ji, Y. Ye, Z.Y. Wang, L. Tong, miR-132 regulates the expression of synaptic proteins in APP/PS1 transgenic mice through C1q, Eur. J. Histochem (2019) **63**, https://doi.org/10.4081/ejh.2019.3008.

[168] J. Xu, Y. Zheng, L. Wang, Y. Liu, X. Wang, Y. Li, G. Chi, miR-124: a promising therapeutic target for central nervous system injuries and diseases, Cell. Mol. Neurobiol. 42 (2022) 2031–2053, https://doi.org/10.1007/s10571-021-01091-6.

[169] J. Wang, F. Xu, X. Zhu, X. Li, Y. Li, J. Li, Targeting microRNAs to regulate the integrity of the blood–brain barrier, Front. Bioeng. Biotechnol. (2021) **9**, https://doi.org/10.3389/fbioe.2021.673415.

[170] B. Xu, Y. Zhang, X.-F. Du, J. Li, H.-X. Zi, J.-W. Bu, Y. Yan, H. Han, J.-L. Du, Neurons secrete miR-132-containing exosomes to regulate brain vascular integrity, Cell Res. 27 (2017) 882–897, https://doi.org/10.1038/cr.2017.62.

[171] X. Fu, T. Niu, X. Li, MicroRNA-126-3p attenuates intracerebral hemorrhage-induced blood-brain barrier disruption by regulating VCAM-1 expression, Front. Neurosci. 13 (2019) 866, https://doi.org/10.3389/fnins.2019.00866.

[172] L. Liu, J.R. Huh, K. Shah, Microbiota and the gut-brain-axis: Implications for new therapeutic design in the CNS, eBioMedicine (2022) **77**, https://doi.org/10.1016/j.ebiom.2022.103908.

[173] J. Burisch, T. Jess, M. Martinato, P.L. Lakatos, E. EpiCom, The burden of inflammatory bowel disease in Europe, J. Crohns Colitis 7 (2013) 322–337, https://doi.org/10.1016/j.crohns.2013.01.010.

[174] T.J. Pasvol, L. Horsfall, S. Bloom, A.W. Segal, C. Sabin, N. Field, G. Rait, Incidence and prevalence of inflammatory bowel disease in UK primary care: a population-based cohort study, BMJ Open 10 (2020), e036584, https://doi.org/10.1136/bmjopen-2019-036584.

[175] L. Van Der Kraak, P. Gros, N. Beauchemin, Colitis-associated colon cancer: Is it in your genes, World J. Gastroenterol. 21 (2015) 11688, https://doi.org/10.3748/wjg.v21.i41.11688.

[176] Y. Feng, Y. Zhang, D. Zhou, G. Chen, N. Li, MicroRNAs, intestinal inflammatory and tumor, Bioorg. Med. Chem. Lett. 29 (2019) 2051–2058, https://doi.org/10.1016/j.bmcl.2019.06.013.

[177] A. Zarjou, S. Yang, E. Abraham, A. Agarwal, G. Liu, Identification of a microRNA signature in renal fibrosis: role of miR-21, Am. J. Physiol. -Ren. Physiol. 301 (2011) F793–F801, https://doi.org/10.1152/ajprenal.00273.2011.

[178] G. Thorlacius-Ussing, B. Schnack Nielsen, V. Andersen, K. Holmstrøm, A. E. Pedersen, Expression and localization of miR-21 and miR-126 in mucosal tissue from patients with inflammatory bowel disease, Inflamm. Bowel Dis. 23 (2017) 739–752, https://doi.org/10.1097/MIB.0000000000001086.

[179] N.J. Beres, D. Szabo, D. Kocsis, D. Szucs, Z. Kiss, K.E. Muller, G. Lendvai, A. Kiss, A. Arato, E. Sziksz, A. Vannay, A.J. Szabo, G. Veres, Role of altered expression of miR-146a, miR-155, and miR-122 in pediatric patients with inflammatory bowel disease, Inflamm. Bowel Dis. 22 (2016) 327–335, https://doi.org/10.1097/MIB.0000000000000687.

[180] W.X. Chen, L.H. Ren, R.H. Shi, Implication of miRNAs for inflammatory bowel disease treatment: Systematic review, World J. Gastrointest. Pathophysiol. 5 (2014) 63–70, https://doi.org/10.4291/wjgp.v5.i2.63.

[181] S. Moein, M. Vaghari-Tabari, D. Qujeq, M. Majidinia, S.M. Nabavi, B. Yousefi, MiRNAs and inflammatory bowel disease: An interesting new story, J. Cell. Physiol. 234 (2019) 3277–3293, https://doi.org/10.1002/jcp.27173.

[182] S. Pathak, A.R. Grillo, M. Scarpa, P. Brun, R. D'inca, L. Nai, A. Banerjee, D. Cavallo, L. Barzon, G. Palù, MiR-155 modulates the inflammatory phenotype of intestinal myofibroblasts by targeting SOCS1 in ulcerative colitis, e164-e164, Exp. Mol. Med. 47 (2015), https://doi.org/10.1038/emm.2015.21.

[183] K. Schönauen, N. Le, U. von Arnim, C. Schulz, P. Malfertheiner, A. Link, Circulating and fecal microRNAs as biomarkers for inflammatory bowel diseases, Inflamm. Bowel Dis. 24 (2018) 1547–1557, https://doi.org/10.1093/ibd/izy046.

[184] B. Cao, X. Zhou, J. Ma, W. Zhou, W. Yang, D. Fan, L. Hong, Role of MiRNAs in inflammatory bowel disease, Dig. Dis. Sci. 62 (2017) 1426–1438, https://doi.org/10.1007/s10620-017-4567-1.

[185] Y. Yang, Y. Ma, C. Shi, H. Chen, H. Zhang, N. Chen, P. Zhang, F. Wang, J. Yang, J. Yang, Overexpression of miR-21 in patients with ulcerative colitis impairs intestinal epithelial barrier function through targeting the Rho GTPase RhoB, Biochem. Biophys. Res. Commun. 434 (2013) 746–752, https://doi.org/10.1016/j.bbrc.2013.03.122.

[186] H.R. Alrafas, P.B. Busbee, M. Nagarkatti, P.S. Nagarkatti, Resveratrol downregulates miR-31 to promote T regulatory cells during prevention of TNBS-induced colitis, Mol. Nutr. Food Res 64 (2020), e1900633, https://doi.org/10.1002/mnfr.201900633.

[187] Z.-J. Lu, J.-J. Wu, W.-L. Jiang, J.-H. Xiao, K.-Z. Tao, L. Ma, P. Zheng, R. Wan, X.-P. Wang, MicroRNA-155 promotes the pathogenesis of experimental colitis by repressing SHIP-1 expression, World J. Gastroenterol. 23 (2017) 976, https://doi.org/10.3748/wjg.v23.i6.976.

[188] J.P. James, L.B. Riis, M. Malham, E. Høgdall, E. Langholz, B.S. Nielsen, MicroRNA biomarkers in IBD-differential diagnosis and prediction of colitis-associated cancer, Int J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21217893.

[189] M. Gwiggner, R.T. Martinez-Nunez, S.R. Whiteoak, V.P. Bondanese, A. Claridge, J.E. Collins, J.F. Cummings, T. Sanchez-Elsner, MicroRNA-31 and MicroRNA-155 are overexpressed in ulcerative colitis and regulate IL-13 signaling by targeting interleukin 13 receptor α-1, Genes 9 (2018) 85, https://doi.org/10.3390/genes9020085.

[190] F. Heller, P. Florian, C. Bojarski, J. Richter, M. Christ, B. Hillenbrand, J. Mankertz, A.H. Gitter, N. Bürgel, M. Fromm, Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution, Gastroenterology 129 (2005) 550–564, https://doi.org/10.1016/j.gastro.2005.05.002.

[191] S. Pathak, A.R. Grillo, M. Scarpa, P. Brun, R. D'Incà, L. Nai, A. Banerjee, D. Cavallo, L. Barzon, G. Palù, G.C. Sturniolo, A. Buda, I. Castagliuolo, MiR-155 modulates the inflammatory phenotype of intestinal myofibroblasts by targeting SOCS1 in ulcerative colitis, Exp. Mol. Med (2015), https://doi.org/10.1038/emm.2015.21 https://doi.org/10.1038/emm.2015.21.

[192] Y. Liu, F. Zhu, H. Li, H. Fan, H. Wu, Y. Dong, S. Chu, C. Tan, Q. Wang, H. He, F. Gao, X. Leng, Q. Zhou, X. Zhu, MiR-155 contributes to intestinal barrier dysfunction in DSS-induced mice colitis via targeting HIF-1α/TFF-3 axis, Aging 12 (2020) 14966–14977, https://doi.org/10.18632/aging.103555.

[193] H. Wang, K. Chao, S.C. Ng, A.H. Bai, Q. Yu, J. Yu, M. Li, Y. Cui, M. Chen, J.F. Hu, S. Zhang, Pro-inflammatory miR-223 mediates the cross-talk between the IL23 pathway and the intestinal barrier in inflammatory bowel disease, Genome Biol. 17 (2016) 58, https://doi.org/10.1186/s13059-016-0901-8.

[194] J. Tazi, C. Begon-Pescia, N. Campos, C. Apolit, A. Garcel, D. Scherrer, Specific and selective induction of miR-124 in immune cells by the quinoline ABX464: a transformative therapy for inflammatory diseases, Drug Discov. Today 26 (2021) 1030–1039, https://doi.org/10.1016/j.drudis.2020.12.019.

[195] S. Vermeire, B.E. Sands, H. Tilg, Z. Tulassay, R. Kempinski, S. Danese, I. Bunganič, J. Nitcheu, J. Santo, D. Scherrer, S. Biguenet, H.J. Ehrlich, J.-M. Steens, P. Gineste, W.J. Sandborn, ABX464 (obefazimod) for moderate-to-severe, active ulcerative colitis: a phase 2b, double-blind, randomised, placebo-controlled induction trial and 48 week, open-label extension, Lancet Gastroenterol. Hepatol. 7 (2022) 1024–1035, https://doi.org/10.1016/S2468-1253(22)00233-3.

[196] S. Vermeire, X. Hébuterne, H. Tilg, G. De Hertogh, P. Gineste, J.M. Steens, Induction and long-term follow-up with ABX464 for moderate-to-severe ulcerative colitis: results of phase IIa Trial, e2593, Gastroenterology 160 (2021) 2595–2598, https://doi.org/10.1053/j.gastro.2021.02.054.

[197] Y. Sun, Q. Li, H. Gui, D.-P. Xu, Y.-L. Yang, D.-F. Su, X. Liu, MicroRNA-124 mediates the cholinergic anti-inflammatory action through inhibiting the production of pro-inflammatory cytokines, Cell Res. 23 (2013) 1270–1283, https://doi.org/10.1038/cr.2013.116.

[198] T. Gonatopoulos-Pournatzis, V.H. Cowling, Cap-binding complex (CBC, Biochem. J. 457 (2014) 231–242, https://doi.org/10.1042/BJ20131214.

[199] A. Vautrin, L. Manchon, A. Garcel, N. Campos, L. Lapasset, A. Laaref, R. Bruno, M. Gislard, E. Dubois, D. Scherrer, J. Ehrlich, J. Tazi, Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing, Sci. Rep. 9 (2019), https://doi.org/10.1038/s41598-018-37813-y.

[200] A. Vautrin, L. Manchon, A. Garcel, N. Campos, L. Lapasset, A.M. Laaref, R. Bruno, M. Gislard, E. Dubois, D. Scherrer, J.H. Ehrlich, J. Tazi, Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing, Sci. Rep. 9 (2019) 792, https://doi.org/10.1038/s41598-018-37813-y.

[201] B. Berkhout, Y.U. van der Velden, ABX464: a good drug candidate instead of a magic bullet, Retrovirology 12 (2015) 64, https://doi.org/10.1186/s12977-015-0189-x.

[202] N. Campos, R. Myburgh, A. Garcel, A. Vautrin, L. Lapasset, E.S. Nadal, F. Mahuteau-Betzer, R. Najman, P. Fornarelli, K. Tantale, E. Basyuk, M. Seveno, J. P. Venables, B. Pau, E. Bertrand, M.A. Wainberg, R.F. Speck, D. Scherrer, J. Tazi, Long lasting control of viral rebound with a new drug ABX464 targeting Rev - mediated viral RNA biogenesis, Retrovirology 12 (2015) 30, https://doi.org/10.1186/s12977-015-0159-3.

[203] T. Hammer, E. Langholz, The epidemiology of inflammatory bowel disease: balance between East and West? A narrative review, Dig. Med. Res. 3 (2020), https://doi.org/10.21037/dmr-20-1.

[204] P. Behzadi, E. Behzadi, R. Ranjbar, The incidence and prevalence of Crohn's disease in global scale, SOJ Immunol. 3 (2015) 1–6, https://doi.org/10.15226/soji/3/2/00125.

[205] S.S. Krishnachaitanya, M. Liu, K. Fujise, Q. Li, MicroRNAs in inflammatory bowel disease and its complications, Int J. Mol. Sci. (2022) **23**, https://doi.org/10.3390/ijms23158751.

[206] H. Jung, J.S. Kim, K.H. Lee, K. Tizaoui, S. Terrazzino, S. Cargnin, L. Smith, A. Koyanagi, L. Jacob, H. Li, S.H. Hong, D.K. Yon, S.W. Lee, M.S. Kim, P. Wasuwanich, W. Karnsakul, J.I. Shin, A. Kronbichler, Roles of microRNAs in inflammatory bowel disease, Int J. Biol. Sci. 17 (2021) 2112–2123, https://doi.org/10.7150/ijbs.59904.

[207] A. Nijhuis, P. Biancheri, A. Lewis, C.L. Bishop, P. Giuffrida, C. Chan, R. Feakins, R. Poulsom, A. Di Sabatino, G.R. Corazza, In Crohn's disease fibrosis-reduced expression of the miR-29 family enhances collagen expression in intestinal fibroblasts, Clin. Sci. 127 (2014) 341–350, https://doi.org/10.1042/CS20140048.

[208] Santacroce G., Lenti M.V. and Di Sabatino A. (2022) Therapeutic Targeting of Intestinal Fibrosis in Crohn's Disease. Cells 11:429. https://doi.org/10.3390/cells11030429.

[209] Y. Chen, W. Ge, L. Xu, C. Qu, M. Zhu, W. Zhang, Y. Xiao, miR-200b is involved in intestinal fibrosis of Crohn's disease, Int. J. Mol. Med. 29 (2012) 601–606, https://doi.org/10.3892/ijmm.2012.894.

[210] A. Lewis, A. Nijhuis, S. Mehta, T. Kumagai, R. Feakins, J.O. Lindsay, A. Silver, Intestinal fibrosis in Crohn's disease: role of microRNAs as fibrogenic modulators, serum biomarkers, and therapeutic targets, Inflamm. bowel Dis. 21 (2015) 1141–1150, https://doi.org/10.1097/MIB.0000000000000298.

[211] N. Zidar, E. Boštjančič, M. Jerala, N. Kojc, D. Drobne, B. Štabuc, D. Glavač, Down-regulation of microRNAs of the miR-200 family and up-regulation of Snail and Slug in inflammatory bowel diseases - hallmark of epithelial-mesenchymal

transition, J. Cell Mol. Med 20 (2016) 1813–1820, https://doi.org/10.1111/jcmm.12869.
[212] A.S. Collins, C.E. McCoy, A.T. Lloyd, C. O'Farrelly, N.J. Stevenson, miR-19a: an effective regulator of SOCS3 and enhancer of JAK-STAT signalling, PLoS One 8 (2013), e69090, https://doi.org/10.1371/journal.pone.0069090.
[213] X. Cheng, X. Zhang, J. Su, Y. Zhang, W. Zhou, J. Zhou, C. Wang, H. Liang, X. Chen, R. Shi, K. Zen, C.Y. Zhang, H. Zhang, miR-19b downregulates intestinal SOCS3 to reduce intestinal inflammation in Crohn's disease, Sci. Rep. 5 (2015) 10397, https://doi.org/10.1038/srep10397.
[214] H. Wang, H. Xing, Y. Xia, Y. Zhou, J. Zhou, L. Li, W. Tao, Q. Liu, Y. Wang, J. Zhao, Y. Yuan, C. Zhang, W. Zhu, PLGA microspheres carrying miR-20a-5p improved intestinal epithelial barrier function in patients with Crohn's disease through STAT3-mediated inhibition of Th17 differentiation, Int. Immunopharmacol. 110 (2022), 109025, https://doi.org/10.1016/j.intimp.2022.109025.
[215] C. He, Y. Shi, R. Wu, M. Sun, L. Fang, W. Wu, C. Liu, M. Tang, Z. Li, P. Wang, Y. Cong, Z. Liu, miR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-α in IBD, Gut 65 (2016) 1938–1950, https://doi.org/10.1136/gutjnl-2015-309389.
[216] Z. Huang, T. Shi, Q. Zhou, S. Shi, R. Zhao, H. Shi, L. Dong, C. Zhang, K. Zeng, J. Chen, J. Zhang, miR-141 Regulates colonic leukocytic trafficking by targeting CXCL12β during murine colitis and human Crohn's disease, Gut 63 (2014) 1247–1257, https://doi.org/10.1136/gutjnl-2012-304213.
[217] K. Zhao, C. Wang, Y. Liu, Y. Li, T. Hui, G. Wang, X. Zhang, X. Xue, J. Kang, G. Feng, Deficiency of microRNA-10b promotes DSS-induced inflammatory response via impairing intestinal barrier function, Biochem. Biophys. Res. Commun. 636 (2022) 48–54, https://doi.org/10.1016/j.bbrc.2022.10.096.
[218] C. Apolit, N. Campos, A. Vautrin, C. Begon-Pescia, L. Lapasset, D. Scherrer, P. Gineste, H. Ehrlich, A. Garcel, J. Santo, J. Tazi, ABX464 (Obefazimod) upregulates miR-124 to reduce proinflammatory markers in inflammatory bowel diseases, Clin. Transl. Gastroenterol. 14 (2023), e00560, https://doi.org/10.14309/ctg.0000000000000560.
[219] C.J. Black, A.C. Ford, Global burden of irritable bowel syndrome: trends, predictions and risk factors, Nat. Rev. Gastroenterol. Hepatol. 17 (2020) 473–486, https://doi.org/10.1038/s41575-020-0286-8.
[220] H.Y. Tang, A.J. Jiang, X.Y. Wang, H. Wang, Y.Y. Guan, F. Li, G.M. Shen, Uncovering the pathophysiology of irritable bowel syndrome by exploring the gut-brain axis: a narrative review, Ann. Transl. Med 9 (2021) 1187, https://doi.org/10.21037/atm-21-2779.
[221] D.J. Gracie, J.P. Hamlin, A.C. Ford, Longitudinal impact of IBS-type symptoms on disease activity, healthcare utilization, psychological health, and quality of life in inflammatory bowel disease, Off. J. Am. Coll. Gastroenterol. | ACG 113 (2018), https://doi.org/10.1038/s41395-018-0021-z.
[222] L.A. Bravo-Vazquez, I. Medina-Rios, L.D. Marquez-Gallardo, J. Reyes-Munoz, F. I. Serrano-Cano, S. Pathak, A. Banerjee, A. Bandyopadhyay, A.K. Duttaroy, S. Paul, Functional implications and clinical potential of microRNAs in irritable bowel syndrome: a concise review, Dig. Dis. Sci. 68 (2023) 38–53, https://doi.org/10.1007/s10620-022-07516-6.
[223] S. Mahurkar-Joshi, L. Chang, Epigenetic mechanisms in irritable bowel syndrome, Front. Psychiatry (2020) **11**, https://doi.org/10.3389/fpsyt.2020.00805.
[224] Q. Zhou, G.N. Verne, miRNA-based therapies for the irritable bowel syndrome, Expert Opin. Biol. Ther. 11 (2011) 991–995, https://doi.org/10.1517/14712598.2011.577060.
[225] R. Nakov, V. Snegarova, D. Dimitrova-Yurukova, T. Velikova, Biomarkers in irritable bowel syndrome: biological rationale and diagnostic value, Dig. Dis. 40 (2022) 23–32, https://doi.org/10.1159/000516027.
[226] M. Camilleri, H. Halawi, I. Oduyebo, Biomarkers as a diagnostic tool for irritable bowel syndrome: where are we, Expert Rev. Gastroenterol. Hepatol. 11 (2017) 303–316, https://doi.org/10.1080/17474124.2017.1288096.
[227] Q. Zhou, W.W. Souba, C.M. Croce, G.N. Verne, MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome, Gut 59 (2010) 775–784, https://doi.org/10.1136/gut.2009.181834.
[228] Q. Zhou, S. Costinean, C.M. Croce, A.R. Brasier, S. Merwat, S.A. Larson, S. Basra, G.N. Verne, MicroRNA 29 targets nuclear Factor-κB–repressing factor and claudin 1 to increase intestinal permeability, e158, Gastroenterology 148 (2015) 158–169, https://doi.org/10.1053/j.gastro.2014.09.037.
[229] S. Mahurkar-Joshi, C.R. Rankin, E.J. Videlock, A. Soroosh, A. Verma, A. Khandadash, D. Iliopoulos, C. Pothoulakis, E.A. Mayer, L. Chang, The colonic mucosal microRNAs, MicroRNA-219a-5p, and MicroRNA-338-3p are downregulated in irritable bowel syndrome and are associated with barrier function and MAPK signaling, e2419, Gastroenterology 160 (2021) 2409–2422, https://doi.org/10.1053/j.gastro.2021.02.040.
[230] Y. Xing, S. Xue, J. Wu, J. Zhou, F. Xing, T. Li, X. Nie, Serum exosomes derived from irritable bowel syndrome patient increase cell permeability via regulating miR-148b-5p/RGS2 signaling in human colonic epithelium cells, Gastroenterol. Res. Pract. 2021 (2021) 6655900, https://doi.org/10.1155/2021/6655900.
[231] Q. Zhou, L. Yang, S. Larson, S. Basra, S. Merwat, A. Tan, C. Croce, G.N. Verne, Decreased miR-199 augments visceral pain in patients with IBS through translational upregulation of TRPV1, Gut 65 (2016) 797, https://doi.org/10.1136/gutjnl-2013-306464.
[232] M.H. Farzaei, R. Bahramsoltani, M. Abdollahi, R. Rahimi, The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments, J. Neurogastroenterol. Motil. 22 (2016) 558–574, https://doi.org/10.5056/jnm16001.
[233] C. Manzella, M. Singhal, M. Ackerman, W.A. Alrefai, S. Saksena, P.K. Dudeja, R. K. Gill, Serotonin transporter untranslated regions influence mRNA abundance and protein expression, Gene Rep. 18 (2020), 100513, https://doi.org/10.1016/j.genrep.2019.100513.
[234] X.-J. Liao, W.-M. Mao, Q. Wang, G.-G. Yang, W.-J. Wu, S.-X. Shao, MicroRNA-24 inhibits serotonin reuptake transporter expression and aggravates irritable bowel syndrome, Biochem. Biophys. Res. Commun. 469 (2016) 288–293, https://doi.org/10.1016/j.bbrc.2015.11.102.
[235] L. Fei, Y. Wang, microRNA-495 reduces visceral sensitivity in mice with diarrhea-predominant irritable bowel syndrome through suppression of the PI3K/AKT signaling pathway via PKIB, IUBMB Life 72 (2020) 1468–1480, https://doi.org/10.1002/iub.2270.
[236] E. Balsells, T. Shi, C. Leese, I. Lyell, J. Burrows, C. Wiuff, H. Campbell, M.H. Kyaw, H. Nair, Global burden of Clostridium difficile infections: a systematic review and meta-analysis, J. Glob. Health 9 (2019), 010407, https://doi.org/10.7189/jogh.09.010407.
[237] PH E (2021(June 2019).) Quarterly epidemiological commentary: mandatory MRSA, MSSA, Gram-negative bacteraemia and C. difficile infections data, Public Health England.
[238] J.R. Beard, A. Officer, I.A. de Carvalho, R. Sadana, A.M. Pot, J.P. Michel, P. Lloyd-Sherlock, J.E. Epping-Jordan, G. Peeters, W.R. Mahanani, J.A. Thiyagarajan, S. Chatterji, The World report on ageing and health: a policy framework for healthy ageing, Lancet 387 (2016) 2145–2154, https://doi.org/10.1016/S0140-6736(15)00516-4.
[239] J. Czepiel, M. Dróżdż, H. Pituch, E.J. Kuijper, W. Perucki, A. Mielimonka, S. Goldman, D. Wultańska, A. Garlicki, G. Biesiada, Clostridium difficile infection: review, Eur. J. Clin. Microbiol. Infect. Dis. 38 (2019) 1211–1221, https://doi.org/10.1007/s10096-019-03539-6.
[240] L. Zhang, D. Dong, C. Jiang, Z. Li, X. Wang, Y. Peng, Insight into alteration of gut microbiota in Clostridium difficile infection and asymptomatic C. difficile colonization, Anaerobe 34 (2015) 1–7, https://doi.org/10.1016/j.anaerobe.2015.03.008.
[241] T.M. Monaghan, A.M. Seekatz, N.O. Markham, T.O. Yau, M. Hatziapostolou, T. Jilani, N. Christodoulou, B. Roach, E. Birli, O. Pomenya, Fecal microbiota transplantation for recurrent Clostridioides difficile infection associates with functional alterations in circulating microRNAs, e254, Gastroenterology 161 (2021) 255–270, https://doi.org/10.1053/j.gastro.2021.03.050.
[242] T.M. Monaghan, N.A. Duggal, E. Rosati, R. Griffin, J. Hughes, B. Roach, D. Y. Yang, C. Wang, K. Wong, L. Saxinger, M. Pučić-Baković, F. Vučković, F. Klicek, G. Lauc, P. Tighe, B.H. Mullish, J.M. Blanco, J.A.K. McDonald, J.R. Marchesi, N. Xue, T. Dottorini, A. Acharjee, A. Franke, Y. Li, G.K. Wong, C. Polytarchou, T. O. Yau, N. Christodoulou, M. Hatziapostolou, M. Wang, L.A. Russell, D.H. Kao, A multi-factorial observational study on sequential fecal microbiota transplant in patients with medically refractory clostridioides difficile infection, Cells 10 (2021), https://doi.org/10.3390/cells10113234.
[243] T.M. Monaghan, A.M. Seekatz, B.H. Mullish, C.C.E.R. Moore-Gillon, L.F. Dawson, A. Ahmed, D. Kao, W.C. Chan, Clostridioides difficile: innovations in target discovery and potential for therapeutic success, Expert Opin. Ther. Targets 25 (2021) 949–963, https://doi.org/10.1080/14728222.2021.2008907.
[244] T.M. Monaghan, C. Polytarchou, D. Kao, C. Alexander, P. Gurnani, Therapeutic potential of miRNAs in Clostridioides difficile infection, Future Microbiol 17 (2022) 315–318, https://doi.org/10.2217/fmb-2021-0311.
[245] T.M. Monaghan, A. Ugun-Klusek, M. Finelli, P. Gurnani, L. Chakrabarti, D. Kao, C. Alexander, C. Polytarchou, Connecting inflammatory bowel and neurodegenerative diseases: microRNAs as a shared therapeutic intervention, Gut (2023) 2022–327301, https://doi.org/10.1136/gutjnl-2022-327301. :gutjnl-.
[246] A.A. Vinithakumari, P. Padhi, B. Hernandez, S.J. Lin, A. Dunkerson-Kurzhumov, L. Showman, M. Breitzman, C. Stokes, Y. Sulaiman, C. Tangudu, D.A. Kuttappan, M.S. Muyyarikkandy, A.A. Willette, G.J. Phillips, V. Anantharam, A. Perera, B. A. Sponseller, A. Kanthasamy, S. Mooyottu, Clostridioides difficile infection dysregulates brain dopamine metabolism, Microbiol Spectr. 10 (2022), e0007322, https://doi.org/10.1128/spectrum.00073-22.
[247] W.R. Russell, S.H. Duncan, L. Scobbie, G. Duncan, L. Cantlay, A.G. Calder, S. E. Anderson, H.J. Flint, Major phenylpropanoid-derived metabolites in the human gut can arise from microbial fermentation of protein, Mol. Nutr. Food Res. 57 (2013) 523–535, https://doi.org/10.1002/mnfr.201200594.
[248] Y. Saito, T. Sato, K. Nomoto, H. Tsuji, Identification of phenol-and p-cresol-producing intestinal bacteria by using media supplemented with tyrosine and its metabolites, fiy125, FEMS Microbiol. Ecol. 94 (2018), https://doi.org/10.1093/femsec/fiy125.
[249] T. Pascucci, M. Colamartino, E. Fiori, R. Sacco, A. Coviello, R. Ventura, S. Puglisi-Allegra, L. Turriziani, A.M. Persico, P-cresol alters brain dopamine metabolism and exacerbates autism-like behaviors in the BTBR mouse, Brain Sci. 10 (2020) 233, https://doi.org/10.3390/brainsci10040233.
[250] P. Bermudez-Martin, J.A.J. Becker, N. Caramello, S.P. Fernandez, R. Costa-Campos, J. Canaguier, S. Barbosa, L. Martinez-Gili, A. Myridakis, M.E. Dumas, A. Bruneau, C. Cherbuy, P. Langella, J. Callebert, J.M. Launay, J. Chabry, J. Barik, J. Le Merrer, N. Glaichenhaus, L. Davidovic, The microbial metabolite p-Cresol induces autistic-like behaviors in mice by remodeling the gut microbiota, Microbiome 9 (2021) 157, https://doi.org/10.1186/s40168-021-01103-z.
[251] K. Fettucciari, L. Macchioni, M. Davidescu, P. Scarpelli, C. Palumbo, L. Corazzi, A. Marchegiani, M. Cerquetella, A. Spaterna, P. Marconi, G. Bassotti, Clostridium difficile toxin B induces senescence in enteric glial cells: A potential new mechanism of Clostridium difficile pathogenesis, Biochim. Biophys. Acta BBA Mol. Cell Res. 1865 (2018) 1945–1958, https://doi.org/10.1016/j.bbamcr.2018.10.007.

[252] B.H. Mullish, Letter: improvements in mental health after faecal microbiota transplantation-an underexplored treatment-related benefit? Aliment Pharm. Ther. 47 (2018) 1562–1563, https://doi.org/10.1111/apt.14626.
[253] S.H. Park, J.H. Lee, J.S. Kim, T.J. Kim, J. Shin, J.H. Im, B. Cha, S. Lee, K.S. Kwon, Y.W. Shin, S.B. Ko, S.H. Choi, Fecal microbiota transplantation can improve cognition in patients with cognitive decline and Clostridioides difficile infection, Aging 14 (2022) 6449–6466, https://doi.org/10.18632/aging.204230.
[254] Ea Dorsey, R. Constantinescu, J. Thompson, K. Biglan, R. Holloway, K. Kieburtz, F. Marshall, B. Ravina, G. Schifitto, A. Siderowf, Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030, Neurology 68 (2007) 384–386, https://doi.org/10.1212/01.wnl.0000247740.47667.03.
[255] L.V. Kalia, A.E. Lang, Parkinson's disease, Lancet 386 (2015) 896–912, https://doi.org/10.1016/S0140-6736(14)61393-3.
[256] L. Leggio, S. Vivarelli, F. L'Episcopo, C. Tirolo, S. Caniglia, N. Testa, B. Marchetti, N. Iraci, microRNAs in parkinson's disease: from pathogenesis to novel diagnostic and therapeutic approaches, Int J. Mol. Sci. 18 (2017), https://doi.org/10.3390/ijms18122698.
[257] S.S. Titze-de-Almeida, C. Soto-Sánchez, E. Fernandez, J.B. Koprich, J.M. Brotchie, R. Titze-de-Almeida, The promise and challenges of developing miRNA-based therapeutics for Parkinson's disease, Cells 9 (2020), https://doi.org/10.3390/cells9040841.
[258] V. Dobricic, M. Schilling, I. Farkas, D.O. Gveric, O. Ohlei, J. Schulz, L. Middleton, S.M. Gentleman, L. Parkkinen, L. Bertram, C.M. Lill, Common signatures of differential microRNA expression in Parkinson's and Alzheimer's disease brains, Brain Commun. (2022), https://doi.org/10.1093/braincomms/fcac274, 4: fcac274.
[259] B. Evans, H.At Furlong, A. de Lencastre, Parkinson's disease and microRNAs - Lessons from model organisms and human studies, Exp. Gerontol. 155 (2021), 111585, https://doi.org/10.1016/j.exger.2021.111585.
[260] S.Y. Goh, Y.X. Chao, S.T. Dheen, E.K. Tan, S.S. Tay, Role of microRNAs in parkinson's disease, Int J. Mol. Sci. (2019) **20**, https://doi.org/10.3390/ijms20225649.
[261] A. Fragkouli, E. Doxakis, miR-7 and miR-153 protect neurons against MPP+-induced cell death via upregulation of mTOR pathway, Front. Cell. Neurosci. 8 (2014) 182, https://doi.org/10.3389/fncel.2014.00182.
[262] M.T. Milner, M. Maddugoda, J. Götz, S.S. Burgener, K. Schroder, The NLRP3 inflammasome triggers sterile neuroinflammation and Alzheimer's disease, Curr. Opin. Immunol. 68 (2021) 116–124, https://doi.org/10.1016/j.coi.2020.10.011.
[263] Q. Sun, S. Wang, J. Chen, H. Cai, W. Huang, Y. Zhang, L. Wang, Y. Xing, MicroRNA-190 alleviates neuronal damage and inhibits neuroinflammation via Nlrp3 in MPTP-induced Parkinson's disease mouse model, J. Cell Physiol. 234 (2019) 23379–23387, https://doi.org/10.1002/jcp.28907.
[264] Z. Mao, C. Liu, S. Ji, Q. Yang, H. Ye, H. Han, Z. Xue, The NLRP3 Inflammasome is Involved in the Pathogenesis of Parkinson's Disease in Rats, Neurochem. Res. 42 (2017) 1104–1115, https://doi.org/10.1007/s11064-017-2185-0.
[265] E. Doxakis, Post-transcriptional regulation of alpha-synuclein expression by mir-7 and mir-153, J. Biol. Chem. 285 (2010) 12726–12734, https://doi.org/10.1074/jbc.M109.086827.
[266] Y. Zhou, M. Lu, R.H. Du, C. Qiao, C.Y. Jiang, K.Z. Zhang, J.H. Ding, G. Hu, MicroRNA-7 targets Nod-like receptor protein 3 inflammasome to modulate neuroinflammation in the pathogenesis of Parkinson's disease, Mol. Neurodegener. 11 (2016) 28, https://doi.org/10.1186/s13024-016-0094-3.
[267] D. Yang, T. Li, Y. Wang, Y. Tang, H. Cui, Y. Tang, X. Zhang, D. Chen, N. Shen, W. Le, miR-132 regulates the differentiation of dopamine neurons by directly targeting Nurr1 expression, J. Cell Sci. 125 (2012) 1673–1682, https://doi.org/10.1242/jcs.086421.
[268] K.F. Hansen, K. Sakamoto, G.A. Wayman, S. Impey, K. Obrietan, Transgenic miR132 alters neuronal spine density and impairs novel object recognition memory, PloS One 5 (2010), e15497, https://doi.org/10.1371/journal.pone.0015497.
[269] G. Lungu, G. Stoica, A. Ambrus, MicroRNA profiling and the role of microRNA-132 in neurodegeneration using a rat model, Neurosci. Lett. 553 (2013) 153–158, https://doi.org/10.1016/j.neulet.2013.08.001.
[270] E. Jia, Y. Zhou, Z. Liu, L. Wang, T. Ouyang, M. Pan, Y. Bai, Q. Ge, Transcriptomic profiling of circular RNA in different brain regions of parkinson's disease in a mouse model, Int J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21083006.
[271] D. Li, F.L. Mastaglia, S. Fletcher, S.D. Wilton, Progress in the molecular pathogenesis and nucleic acid therapeutics for Parkinson's disease in the precision medicine era, Med Res Rev. 40 (2020) 2650–2681, https://doi.org/10.1002/med.21718.
[272] N. Kanagaraj, H. Beiping, S. Dheen, S. Tay, Downregulation of miR-124 in MPTP-treated mouse model of Parkinson's disease and MPP iodide-treated MN9D cells modulates the expression of the calpain/cdk5 pathway proteins, Neuroscience 272 (2014) 167–179, https://doi.org/10.1016/j.neuroscience.2014.04.039.
[273] J. Yang, X. Zhang, X. Chen, L. Wang, G. Yang, Exosome mediated delivery of miR-124 promotes neurogenesis after ischemia, Mol. Ther. -Nucleic Acids 7 (2017) 278–287, https://doi.org/10.1016/j.omtn.2017.04.010.
[274] C. Saraiva, J. Paiva, T. Santos, L. Ferreira, L. Bernardino, MicroRNA-124 loaded nanoparticles enhance brain repair in Parkinson's disease, J. Control. Release 235 (2016) 291–305, https://doi.org/10.1016/j.jconrel.2016.06.005.
[275] D. Li, H. Yang, J. Ma, S. Luo, S. Chen, Q. Gu, MicroRNA-30e regulates neuroinflammation in MPTP model of Parkinson's disease by targeting Nlrp3, Hum. Cell 31 (2018) 106–115, https://doi.org/10.1007/s13577-017-0187-5.
[276] D.-M. Wu, S. Wang, X. Wen, X.-R. Han, Y.-J. Wang, M. Shen, S.-H. Fan, J. Zhuang, Z.-F. Zhang, Q. Shan, Inhibition of microRNA-200a upregulates the expression of striatal dopamine receptor D2 to repress apoptosis of striatum via the cAMP/PKA signaling pathway in rats with Parkinson's disease, Cell. Physiol. Biochem. 51 (2018) 1600–1615, https://doi.org/10.1159/000495649.
[277] A.D. Thome, A.S. Harms, L.A. Volpicelli-Daley, D.G. Standaert, microRNA-155 regulates alpha-synuclein-induced inflammatory responses in models of Parkinson disease, J. Neurosci. 36 (2016) 2383–2390, https://doi.org/10.1523/JNEUROSCI.3900-15.2016.
[278] I.A. Babar, C.J. Cheng, C.J. Booth, X. Liang, J.B. Weidhaas, W.M. Saltzman, F. J. Slack, Nanoparticle-based therapy in an in vivo microRNA-155 (miR-155)-dependent mouse model of lymphoma, Proc. Natl. Acad. Sci. USA 109 (2012) E1695–E1704, https://doi.org/10.1073/pnas.1201516109.
[279] C.A. Lane, J. Hardy, J.M. Schott, Alzheimer's disease, Eur. J. Neurol. 25 (2018) 59–70, https://doi.org/10.1111/ene.13439.
[280] B. Martinez, P.V. Peplow, MicroRNAs as diagnostic and therapeutic tools for Alzheimer's disease: advances and limitations, Neural Regen. Res 14 (2019) 242–255, https://doi.org/10.4103/1673-5374.244784.
[281] H. Walgrave, L. Zhou, B. De Strooper, E. Salta, The promise of microRNA-based therapies in Alzheimer's disease: challenges and perspectives, Mol. Neurodegener. 16 (2021) 76, https://doi.org/10.1186/s13024-021-00496-7.
[282] M.J. Millan, Linking deregulation of non-coding RNA to the core pathophysiology of Alzheimer's disease: An integrative review, Prog. Neurobiol. 156 (2017) 1–68, https://doi.org/10.1016/j.pneurobio.2017.03.004.
[283] C.Y. Lee, I.S. Ryu, J.H. Ryu, H.J. Cho, miRNAs as therapeutic tools in Alzheimer's disease, Int J. Mol. Sci. (2021) **22**, https://doi.org/10.3390/ijms222313012.
[284] E. Salta, A. Sierksma, E. Vanden Eynden, B. De Strooper, miR-132 loss de-represses ITPKB and aggravates amyloid and TAU pathology in Alzheimer's brain, EMBO Mol. Med. 8 (2016) 1005–1018, https://doi.org/10.15252/emmm.201606520.
[285] P.Y. Smith, J. Hernandez-Rapp, F. Jolivette, C. Lecours, K. Bisht, C. Goupil, V. Dorval, S. Parsi, F. Morin, E. Planel, miR-132/212 deficiency impairs tau metabolism and promotes pathological aggregation in vivo, Hum. Mol. Genet. 24 (2015) 6721–6735, https://doi.org/10.1093/hmg/ddv377.
[286] H. Walgrave, S. Balusu, S. Snoeck, E. Vanden Eynden, K. Craessaerts, N. Thrupp, L. Wolfs, K. Horré, Y. Fourne, A. Ronisz, E. Silajdžić, A. Penning, G. Tosoni, Z. Callaerts-Vegh, R. D'Hooge, D.R. Thal, H. Zetterberg, S. Thuret, M. Fiers, C. S. Frigerio, B. De Strooper, E. Salta, Restoring miR-132 expression rescues adult hippocampal neurogenesis and memory deficits in Alzheimer's disease, e1808, Cell Stem Cell 28 (2021) 1805–1821, https://doi.org/10.1016/j.stem.2021.05.001.
[287] G. Yang, Y. Song, X. Zhou, Y. Deng, T. Liu, G. Weng, D. Yu, S. Pan, MicroRNA-29c targets β-site amyloid precursor protein-cleaving enzyme 1 and has a neuroprotective role in vitro and in vivo, Mol. Med. Rep. 12 (2015) 3081–3088, https://doi.org/10.3892/mmr.2015.3728.
[288] Y. Jiang, B. Xu, J. Chen, Y. Sui, L. Ren, J. Li, H. Zhang, L. Guo, X. Sun, Micro-RNA-137 inhibits tau hyperphosphorylation in Alzheimer's disease and targets the CACNA1C gene in transgenic mice and human neuroblastoma SH-SY5Y cells, Med. Sci. Monit.: Int. Med. J. Exp. Clin. Res. 24 (2018) 5635, https://doi.org/10.12659/MSM.908765.
[289] J. Jia, C. Liu, Y. Han, H. Han, M. Zhong, Y. Gao, miR-146a alleviates the apoptosis of hippocampal neurons induced by microglia activation via targeting TRAF6, Hum. Exp. Toxicol. 39 (2020) 1650–1660, https://doi.org/10.1177/0960327120930069.
[290] H. Mai, W. Fan, Y. Wang, Y. Cai, X. Li, F. Chen, X. Chen, J. Yang, P. Tang, H. Chen, T. Zou, T. Hong, C. Wan, B. Zhao, L. Cui, Intranasal administration of miR-146a agomir rescued the pathological process and cognitive impairment in an AD mouse model, Mol. Ther. Nucleic Acids 18 (2019) 681–695, https://doi.org/10.1016/j.omtn.2019.10.002.
[291] K. Lee, H. Kim, K. An, O.B. Kwon, S. Park, J.H. Cha, M.H. Kim, Y. Lee, J.H. Kim, K. Cho, H.S. Kim, Replenishment of microRNA-188-5p restores the synaptic and cognitive deficits in 5XFAD Mouse Model of Alzheimer's Disease, Sci. Rep. 6 (2016) 34433, https://doi.org/10.1038/srep34433.
[292] Q. Qian, J. Zhang, F.-P. He, W.-X. Bao, T.-T. Zheng, D.-M. Zhou, H.-Y. Pan, H. Zhang, X.-Q. Zhang, X. He, B.-G. Sun, B.-Y. Luo, C. Chen, G.-P. Peng, Down-regulated expression of microRNA-338-5p contributes to neuropathology in Alzheimer's disease, FASEB J. 33 (2019) 4404–4417, https://doi.org/10.1096/fj.201801846R.
[293] K. Vasudeva, A. Munshi, miRNA dysregulation in ischaemic stroke: Focus on diagnosis, prognosis, therapeutic and protective biomarkers, Eur. J. Neurosci. 52 (2020) 3610–3627, https://doi.org/10.1111/ejn.14695.
[294] M. Katan, A. Luft, Global burden of stroke, Semin Neurol. 38 (2018) 208–211, https://doi.org/10.1055/s-0038-1649503.
[295] (2019) Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18:439–458. https://doi.org/10.1016/s1474-4422(19)30034–1.
[296] E.S. Donkor, Stroke in the 21(st) century: a snapshot of the burden, epidemiology, and quality of life, Stroke Res Treat (2018), https://doi.org/10.1155/2018/3238165, 2018:3238165.
[297] F. Lanas, P. Seron, Facing the stroke burden worldwide, Lancet Glob. Health 9 (2021) e235–e236, https://doi.org/10.1016/s2214-109x(20)30520-9.
[298] A.G. Thrift, T. Thayabaranathan, G. Howard, V.J. Howard, P.M. Rothwell, V. L. Feigin, B. Norrving, G.A. Donnan, D.A. Cadilhac, Global stroke statistics, Int. J. Stroke 12 (2017) 13–32, https://doi.org/10.1177/1747493016676285.
[299] R.R.A. Kadir, M. Alwjwaj, U. Bayraktutan, MicroRNA: an emerging predictive, diagnostic, prognostic and therapeutic strategy in ischaemic stroke, Cell Mol. Neurobiol. 42 (2022) 1301–1319, https://doi.org/10.1007/s10571-020-01028-5.
[300] M. Qu, J. Pan, L. Wang, P. Zhou, Y. Song, S. Wang, L. Jiang, J. Geng, Z. Zhang, Y. Wang, MicroRNA-126 regulates angiogenesis and neurogenesis in a mouse

model of focal cerebral ischemia, Mol. Ther. -Nucleic Acids 16 (2019) 15–25, https://doi.org/10.1016/j.omtn.2019.02.002.
[301] H.Y. Cheng, Y.S. Wang, P.Y. Hsu, C.Y. Chen, Y.C. Liao, S.H. Juo, miR-195 has a potential to treat ischemic and hemorrhagic stroke through neurovascular protection and neurogenesis, Mol. Ther. Methods Clin. Dev. 13 (2019) 121–132, https://doi.org/10.1016/j.omtm.2018.11.011.
[302] Z. Wang, Y. Yuan, Z. Zhang, K. Ding, Inhibition of mi RNA-27b enhances neurogenesis via AMPK activation in a mouse ischemic stroke model, FEBS Open Bio 9 (2019) 859–869, https://doi.org/10.1002/2211-5463.12614.
[303] E. Caballero-Garrido, J.C. Pena-Philippides, T. Lordkipanidze, D. Bragin, Y. Yang, E.B. Erhardt, T. Roitbak, In vivo inhibition of miR-155 promotes recovery after experimental mouse stroke, J. Neurosci. 35 (2015) 12446–12464, https://doi.org/10.1523/JNEUROSCI.1641-15.2015.
[304] X. Zuo, J. Lu, A. Manaenko, X. Qi, J. Tang, Q. Mei, Y. Xia, Q. Hu, MicroRNA-132 attenuates cerebral injury by protecting blood-brain-barrier in MCAO mice, Exp. Neurol. 316 (2019) 12–19, https://doi.org/10.1016/j.expneurol.2019.03.017.
[305] Y. Li, L. Mao, Y. Gao, S. Baral, Y. Zhou, B. Hu, MicroRNA-107 contributes to post-stroke angiogenesis by targeting Dicer-1, Sci. Rep. 5 (2015) 1–13, https://doi.org/10.1038/srep13316.
[306] C.M. Stary, L. Xu, X. Sun, Y.-B. Ouyang, R.E. White, J. Leong, J. Li, X. Xiong, R. G. Giffard, MicroRNA-200c contributes to injury from transient focal cerebral ischemia by targeting Reelin, Stroke 46 (2015) 551–556, https://doi.org/10.1161/STROKEAHA.114.007041.
[307] M. Li, W.-D. Chen, Y.-D. Wang, The roles of the gut microbiota–miRNA interaction in the host pathophysiology, Mol. Med. 26 (2020) 101, https://doi.org/10.1186/s10020-020-00234-7.
[308] B. Zhang, H.E. Wang, Y.-M. Bai, S.-J. Tsai, T.-P. Su, T.-J. Chen, Y.-P. Wang, M.-H. Chen, Inflammatory bowel disease is associated with higher dementia risk: a nationwide longitudinal study, Gut 70 (2021) 85, https://doi.org/10.1136/gutjnl-2020-320789.
[309] M.N. Zhang, Y.D. Shi, H.Y. Jiang, The risk of dementia in patients with inflammatory bowel disease: a systematic review and meta-analysis, Int J. Colorectal Dis. 37 (2022) 769–775, https://doi.org/10.1007/s00384-022-04131-9.
[310] N. Liu, Y. Wang, L. He, J. Sun, X. Wang, H. Li, Inflammatory bowel disease and risk of dementia: An updated meta-analysis, Front. Aging Neurosci. 14 (2022), https://doi.org/10.3389/fnagi.2022.962681.
[311] F. Zhang, Y. Yao, N. Miao, N. Wang, X. Xu, C. Yang, Neuroprotective effects of microRNA 124 in Parkinson's disease mice, Arch. Gerontol. Geriatr. 99 (2022), 104588, https://doi.org/10.1016/j.archger.2021.104588.
[312] A.D. Thome, A.S. Harms, L.A. Volpicelli-Daley, D.G. Standaert, microRNA-155 regulates alpha-synuclein-induced inflammatory responses in models of parkinson disease, J. Neurosci. 36 (2016) 2383–2390, https://doi.org/10.1523/jneurosci.3900-15.2016.
[313] H. Li, L. Yu, M. Li, X. Chen, Q. Tian, Y. Jiang, N. Li, MicroRNA-150 serves as a diagnostic biomarker and is involved in the inflammatory pathogenesis of Parkinson's disease, Mol. Genet Genom. Med 8 (2020), e1189, https://doi.org/10.1002/mgg3.1189.
[314] A. Gámez-Valero, J. Campdelacreu, D. Vilas, L. Ispierto, R. Reñé, R. Álvarez, M. P. Armengol, F.E. Borràs, K. Beyer, Exploratory study on microRNA profiles from plasma-derived extracellular vesicles in Alzheimer's disease and dementia with Lewy bodies, Transl. Neurodegener. 8 (2019) 31, https://doi.org/10.1186/s40035-019-0169-5.
[315] C. Ma, Y. Peng, H. Li, W. Chen, Organ-on-a-chip: a new paradigm for drug development, Trends Pharm. Sci. 42 (2021) 119–133, https://doi.org/10.1016/j.tips.2020.11.009.
[316] C.G. Williams, H.J. Lee, T. Asatsuma, R. Vento-Tormo, A. Haque, An introduction to spatial transcriptomics for biomedical research, Genome Med. 14 (2022) 68, https://doi.org/10.1186/s13073-022-01075-1.
[317] M.S. Thomsen, K.B. Johnsen, K. Kucharz, M. Lauritzen, T. Moos, Blood-brain barrier transport of transferrin receptor-targeted nanoparticles, Pharmaceutics 14 (2022), https://doi.org/10.3390/pharmaceutics14102237.
[318] C. Diener, A. Keller, E. Meese, Emerging concepts of miRNA therapeutics: from cells to clinic, Trends Genet. 38 (2022) 613–626, https://doi.org/10.1016/j.tig.2022.02.006.
[319] N. Benderska, A.L. Dittrich, S. Knaup, T.T. Rau, C. Neufert, S. Wach, F. B. Fahlbusch, M. Rauh, R.M. Wirtz, A. Agaimy, S. Srinivasan, V. Mahadevan, P. Rummele, E. Rapti, M. Gazouli, Hartmann A and Schneider-Stock R, miRNA-26b overexpression in ulcerative colitis-associated carcinogenesis, Inflamm. Bowel Dis. 21 (2015) 2039–2051, https://doi.org/10.1097/MIB.0000000000000453.
[320] D. Macartney-Coxson, K. Danielson, J. Clapham, M.C. Benton, A. Johnstone, A. Jones, O. Shaw, R.D. Hagan, E.P. Hoffman, M. Hayes, MicroRNA profiling in adipose before and after weight loss highlights the role of miR-223–3p and the NLRP3 inflammasome, Obesity 28 (2020) 570–580, https://doi.org/10.1002/oby.22722.
[321] X. Wu, S. Pan, W. Luo, Z. Shen, X. Meng, M. Xiao, B. Tan, K. Nie, T. Tong, X. Wang, Roseburia intestinalis-derived flagellin ameliorates colitis by targeting miR-223–3p-mediated activation of NLRP3 inflammasome and pyroptosis, Mol. Med. Rep. 22 (2020) 2695–2704, https://doi.org/10.3892/mmr.2020.11351.
[322] H. Wang, K. Chao, S.C. Ng, A.H. Bai, Q. Yu, J. Yu, M. Li, Y. Cui, M. Chen, J.-F. Hu, Pro-inflammatory miR-223 mediates the cross-talk between the IL23 pathway and the intestinal barrier in inflammatory bowel disease, Genome Biol. 17 (2016) 1–15, https://doi.org/10.1186/s13059-016-0901-8.
[323] M. Li, J. Zhao, M. Cao, R. Liu, G. Chen, S. Li, Y. Xie, J. Xie, Y. Cheng, L. Huang, Mast cells-derived MiR-223 destroys intestinal barrier function by inhibition of CLDN8 expression in intestinal epithelial cells, Biol. Res. 53 (2020) 1–11, https://doi.org/10.1186/s40659-020-00279-2.
[324] D. Sun, C. Wang, S. Long, Y. Ma, Y. Guo, Z. Huang, X. Chen, C. Zhang, J. Chen, J. Zhang, C/EBP-β-activated microRNA-223 promotes tumour growth through targeting RASA1 in human colorectal cancer, Br. J. Cancer 112 (2015) 1491–1500, https://doi.org/10.1038/bjc.2015.107.
[325] H. Zhou, J. Xiao, N. Wu, C. Liu, J. Xu, F. Liu, L. Wu, MicroRNA-223 regulates the differentiation and function of intestinal dendritic cells and macrophages by targeting C/EBPβ, Cell Rep. 13 (2015) 1149–1160, https://doi.org/10.1016/j.celrep.2015.09.073.
[326] V. Butin-Israeli, T.M. Bui, H.L. Wiesolek, L. Mascarenhas, J.J. Lee, L.C. Mehl, K. R. Knutson, S.A. Adam, R.D. Goldman, A. Beyder, L. Wiesmuller, S.B. Hanauer, R. Sumagin, Neutrophil-induced genomic instability impedes resolution of inflammation and wound healing, J. Clin. Invest 129 (2019) 712–726, https://doi.org/10.1172/JCI122085.
[327] P. Gasparini, F. Lovat, M. Fassan, L. Casadei, L. Cascione, N.K. Jacob, S. Carasi, D. Palmieri, S. Costinean, C.L. Shapiro, Protective role of miR-155 in breast cancer through RAD51 targeting impairs homologous recombination after irradiation, Proc. Natl. Acad. Sci. 111 (2014) 4536–4541, https://doi.org/10.1073/pnas.1402604111.
[328] M. Xu, D. Zuo, X. Liu, H. Fan, Q. Chen, S. Deng, Z. Shou, Q. Tang, J. Yang, Z. Nan, MiR-155 contributes to Th17 cells differentiation in dextran sulfate sodium (DSS)-induced colitis mice via Jarid2, Biochem. Biophys. Res. Commun. 488 (2017) 6–14, https://doi.org/10.1016/j.bbrc.2017.04.143.
[329] W.-H. Liu, S.G. Kang, Z. Huang, C.-J. Wu, H.Y. Jin, C.J. Maine, Y. Liu, J. Shepherd, M. Sabouri-Ghomi, A. Gonzalez-Martin, A miR-155–Peli1–c-Rel pathway controls the generation and function of T follicular helper cells, J. Exp. Med. 213 (2016) 1901–1919, https://doi.org/10.1084/jem.20160204.
[330] F. Zhu, H. Li, Y. Liu, C. Tan, X. Liu, H. Fan, H. Wu, Y. Dong, T. Yu, S. Chu, miR-155 antagomir protect against DSS-induced colitis in mice through regulating Th17/Treg cell balance by Jarid2/Wnt/β-catenin, Biomed. Pharmacother. 126 (2020), 109909, https://doi.org/10.1016/j.biopha.2020.109909.
[331] R.T. Martinez-Nunez, F. Louafi, T. Sanchez-Elsner, The interleukin 13 (IL-13) pathway in human macrophages is modulated by microRNA-155 via direct targeting of interleukin 13 receptor α1 (IL13Rα1), J. Biol. Chem. 286 (2011) 1786–1794, https://doi.org/10.1074/jbc.M110.169367.
[332] C. He, T. Yu, Y. Shi, C. Ma, W. Yang, L. Fang, M. Sun, W. Wu, F. Xiao, F. Guo, MicroRNA 301A promotes intestinal inflammation and colitis-associated cancer development by inhibiting BTG1, e1415, Gastroenterology 152 (2017) 1434–1448, https://doi.org/10.1136/gutjnl-2015-309389.
[333] C. He, Y. Shi, R. Wu, M. Sun, L. Fang, W. Wu, C. Liu, M. Tang, Z. Li, P. Wang, miR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-α in IBD, Gut 65 (2016) 1938–1950, https://doi.org/10.1136/gutjnl-2015-309389.
[334] R. Perdigao-Henriques, F. Petrocca, G. Altschuler, M. Thomas, M. Le, S. Tan, W. Hide, J. Lieberman, miR-200 promotes the mesenchymal to epithelial transition by suppressing multiple members of the Zeb2 and Snail1 transcriptional repressor complexes, Oncogene 35 (2016) 158–172, https://doi.org/10.1038/onc.2015.69.
[335] N. Zidar, E. Boštjančič, M. Jerala, N. Kojc, D. Drobne, B. Štabuc, D. Glavač, Down-regulation of micro RNA s of the miR-200 family and up-regulation of Snail and Slug in inflammatory bowel diseases—hallmark of epithelial– mesenchymal transition, J. Cell. Mol. Med. 20 (2016) 1813–1820, https://doi.org/10.1111/jcmm.12869.
[336] Y. Liu, J. Yin, W. Abou-Kheir, P. Hynes, O. Casey, L. Fang, M. Yi, R. Stephens, V. Seng, H. Sheppard-Tillman, MiR-1 and miR-200 inhibit EMT via Slug-dependent and tumorigenesis via Slug-independent mechanisms, Oncogene 32 (2013) 296–306, https://doi.org/10.1038/onc.2012.58.
[337] J.-a Li, Y.-d Wang, K. Wang, Z.-l Wang, D.-y Jia, B.-y Yang, C.-b Xiong, Downregulation of miR-214-3p may contribute to pathogenesis of ulcerative colitis via targeting STAT6, BioMed. Res. Int. 2017 (2017), https://doi.org/10.1155/2017/8524972.
[338] C. Polytarchou, D.W. Hommes, T. Palumbo, M. Hatziapostolou, M. Koutsioumpa, G. Koukos, A.E. van der Meulen-de, A. Oikonomopoulos, W.K. van Deen, C. Vorvis, MicroRNA214 is associated with progression of ulcerative colitis, and inhibition reduces development of colitis and colitis-associated cancer in mice, e911, Gastroenterology 149 (2015) 981–992, https://doi.org/10.1053/j.gastro.2015.05.057.
[339] Q. Zhang, S. Zhang, miR-214 promotes radioresistance in human ovarian cancer cells by targeting PETN, Biosci. Rep. 37 (2017), https://doi.org/10.1042/BSR20170327.
[340] W. Wu, Y. He, X. Feng, S. Ye, H. Wang, W. Tan, C. Yu, J. Hu, R. Zheng, Y. Zhou, MicroRNA-206 is involved in the pathogenesis of ulcerative colitis via regulation of adenosine A3 receptor, Oncotarget 8 (2017) 705, https://doi.org/10.18632/oncotarget.13525.
[341] Y. Ando, L. Mazzurana, M. Forkel, K. Okazaki, M. Aoi, P.T. Schmidt, J. Mjosberg, F. Bresso, Downregulation of MicroRNA-21 in colonic CD3+ T cells in UC remission, Inflamm. Bowel Dis. 22 (2016) 2788–2793, https://doi.org/10.1097/MIB.0000000000000969.
[342] C. Shi, Y. Yang, Y. Xia, Y. Okugawa, J. Yang, Y. Liang, H. Chen, P. Zhang, F. Wang, H. Han, Novel evidence for an oncogenic role of microRNA-21 in colitis-associated colorectal cancer, Gut 65 (2016) 1470–1481, https://doi.org/10.1136/gutjnl-2014-308455.
[343] L.-H. Sun, D. Tian, Z.-C. Yang, J.-L. Li, Exosomal miR-21 promotes proliferation, invasion and therapy resistance of colon adenocarcinoma cells through its target PDCD4, Sci. Rep. 10 (2020) 1–8, https://doi.org/10.1038/s41598-020-65207-6.

[344] M. Hu, Y. Lu, H. Zeng, Z. Zhang, S. Chen, Y. Qi, Y. Xu, F. Chen, Y. Tang, M. Chen, MicroRNA-21 maintains hematopoietic stem cell homeostasis through sustaining the nuclear factor-B signaling pathway in mice, Haematologica 106 (2021) 412, https://doi.org/10.3324/haematol.2019.236927.
[345] Y. Zhu, L. Gu, Y. Li, X. Lin, H. Shen, K. Cui, L. Chen, F. Zhou, Q. Zhao, J. Zhang, miR-148a inhibits colitis and colitis-associated tumorigenesis in mice, Cell Death Differ. 24 (2017) 2199–2209, https://doi.org/10.1038/cdd.2017.151.
[346] A. Raso, E. Dirkx, L.E. Philippen, A. Fernandez-Celis, F. De Majo, V. Sampaio-Pinto, M. Sansonetti, R. Juni, H. El Azzouzi, M. Calore, Therapeutic delivery of miR-148a suppresses ventricular dilation in heart failure, Mol. Ther. 27 (2019) 584–599, https://doi.org/10.1016/j.ymthe.2018.11.011.
[347] V. Zafari, M. Asadi, N. Bakhtiyari, M. Sadeghzadeh, M. Khalili, H. Zarredar, S. Bornehdeli, E. Seyedrezazadeh, Regulatory effect of let-7f transfection in non-small cell lung cancer on its candidate target genes, Iran. Biomed. J. 26 (2022) 209–218, https://doi.org/10.52547/ibjhy.26.3.209.
[348] Z.H. Li, Y.F. Wang, D.D. He, X.M. Zhang, Y.L. Zhou, H. Yue, S. Huang, Z. Fu, L. Y. Zhang, Z.Q. Mao, S. Li, C.Y. Zhang, X. Chen, J. Fu, Let-7f-5p suppresses Th17 differentiation via targeting STAT3 in multiple sclerosis, Aging 11 (2019) 4463–4477, https://doi.org/10.18632/aging.102093.
[349] F. Wu, M. Zikusoka, A. Trindade, T. Dassopoulos, M.L. Harris, T.M. Bayless, S. R. Brant, S. Chakravarti, J.H. Kwon, MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2α, e1624, Gastroenterology 135 (2008) 1624–1635, https://doi.org/10.1053/j.gastro.2008.07.068.
[350] J.P. Wang, L.N. Dong, M. Wang, J. Guo, Y.Q. Zhao, MiR-146a regulates the development of ulcerative colitis via mediating the TLR4/MyD88/NF-κB signaling pathway, Eur. Rev. Med Pharm. Sci. 23 (2019) 2151–2157, https://doi.org/10.26355/eurrev_201903_17260.
[351] J. Feng, Y. Zhu, L. Chen, M. Wang, Clinical significance of microRNA-146a in patients with Ulcerative Colitis, Ann. Clin. Lab Sci. 50 (2020) 463–467.
[352] I.K.M. Law, K. Bakirtzi, C. Polytarchou, A. Oikonomopoulos, D. Hommes, D. Iliopoulos, C. Pothoulakis, Neurotensin—regulated miR-133α is involved in proinflammatory signalling in human colonic epithelial cells and in experimental colitis, Gut 64 (2015) 1095–1104, https://doi.org/10.1136/gutjnl-2014-307329.
[353] I.K.M. Law, D. Jensen, N.W. Bunnett, C. Pothoulakis, Neurotensin-induced miR-133α expression regulates neurotensin receptor 1 recycling through its downstream target aftiphilin, Sci. Rep. 6 (2016) 1–14, https://doi.org/10.1038/srep22195.
[354] J. Pekow, K. Meckel, U. Dougherty, Y. Huang, X. Chen, A. Almoghrabi, R. Mustafi, F. Ayaloglu-Butun, Z. Deng, H.I. Haider, miR-193a-3p is a key tumor suppressor in ulcerative colitis–associated colon cancer and promotes carcinogenesis through upregulation of IL17RDRole of miR-193a-3p in UC-associated neoplasia, Clin. Cancer Res. 23 (2017) 5281–5291, https://doi.org/10.1158/1078-0432.CCR-17-0171.
[355] H.M. Yu, C. Wang, Z. Yuan, G.L. Chen, T. Ye, B.W. Yang, LncRNA NEAT1 promotes the tumorigenesis of colorectal cancer by sponging miR-193a-3p, Cell Prolif. 52 (2019), e12526, https://doi.org/10.1111/cpr.12526.
[356] B. Chen, S. She, D. Li, Z. Liu, X. Yang, Z. Zeng, F. Liu, Role of miR-19a targeting TNF-alpha in mediating ulcerative colitis, Scand. J. Gastroenterol. 48 (2013) 815–824, https://doi.org/10.3109/00365521.2013.800991.
[357] G. Koukos, C. Polytarchou, J.L. Kaplan, A. Morley–Fletcher, B. Gras–Miralles, E. Kokkotou, M. Baril–Dore, C. Pothoulakis, H.S. Winter, D. Iliopoulos, MicroRNA-124 regulates STAT3 expression and is down-regulated in colon tissues of pediatric patients with ulcerative colitis, e842, Gastroenterology 145 (2013) 842–852, https://doi.org/10.1053/j.gastro.2013.07.001.
[358] S. Lin, Q. Liu, J. Wen, K. Bai, Y. Guo, J. Wang, Mir-124 attenuates STAT3-mediated TH17 differentiation in colitis-driven colon cancer, Front Oncol. 10 (2020), 570128, https://doi.org/10.3389/fonc.2020.570128.
[359] M. Cai, S. Chen, W. Hu, MicroRNA-141 is involved in ulcerative colitis pathogenesis via aiming at CXCL5, J. Interferon Cytokine Res. 37 (2017) 415–420, https://doi.org/10.1089/jir.2017.0019.
[360] H. Zhang, W. Li, microRNA-15 activates NF-κB pathway via down regulating expression of adenosine A2 receptor in ulcerative colitis, Cell. Physiol. Biochem. 51 (2018) 1932–1944, https://doi.org/10.1159/000495718.
[361] J.R. Pekow, U. Dougherty, R. Mustafi, H. Zhu, M. Kocherginsky, D.T. Rubin, S. B. Hanauer, J. Hart, E.B. Chang, A. Fichera, L.J. Joseph, M. Bissonnette, miR-143 and miR-145 are Downregulated in Ulcerative Colitis: Putative Regulators of Inflammation and Protooncogenes, Inflamm. Bowel Dis. 18 (2011) 94–100, https://doi.org/10.1002/ibd.21742.
[362] Z. Bian, L. Li, J. Cui, H. Zhang, Y. Liu, C.Y. Zhang, K. Zen, Role of miR-150-targeting c-Myb in colonic epithelial disruption during dextran sulphate sodium-induced murine experimental colitis and human ulcerative colitis, J. Pathol. 225 (2011) 544–553, https://doi.org/10.1002/path.2907.
[363] J. Zhou, J. Liu, Y. Gao, L. Shen, S. Li, S. Chen, miRNA-based potential biomarkers and new molecular insights in ulcerative Colitis, Front. Pharmacol. 12 (2021), https://doi.org/10.3389/fphar.2021.707776.
[364] A. Vishnoi, S. Rani, MiRNA biogenesis and regulation of diseases: an overview, in: S. Rani (Ed.), MicroRNA Profiling: Methods and Protocols, Springer, New York, New York, NY, 2017, pp. 1–10, https://doi.org/10.1007/978-1-4939-6524-3_1.
[365] Y.-K. Kim, V.N. Kim, Processing of intronic microRNAs, EMBO J. 26 (2007) 775–783, https://doi.org/10.1038/sj.emboj.7601512.
[366] S. Lin, R.I. Gregory, MicroRNA biogenesis pathways in cancer, Nat. Rev. Cancer 15 (2015) 321–333, https://doi.org/10.1038/nrc3932.
[367] C. Okada, E. Yamashita, S.J. Lee, S. Shibata, J. Katahira, A. Nakagawa, Y. Yoneda, T. Tsukihara, A high-resolution structure of the Pre-microRNA nuclear export machinery, Science 326 (2009) 1275–1279, https://doi.org/10.1126/science.1178705.
[368] M. Sarshar, D. Scribano, C. Ambrosi, A.T. Palamara, A. Masotti, Fecal microRNAs as innovative biomarkers of intestinal diseases and effective players in host-microbiome interactions, Cancers 12 (2020), https://doi.org/10.3390/cancers12082174.
[369] J. O'Brien, H. Hayder, Y. Zayed, C. Peng, Overview of MicroRNA biogenesis, mechanisms of actions, and circulation, Front. Endocrinol. 9 (2018), https://doi.org/10.3389/fendo.2018.00402.
[370] J.G. Ruby, C.H. Jan, D.P. Bartel, Intronic microRNA precursors that bypass Drosha processing, Nature 448 (2007) 83–86, https://doi.org/10.1038/nature05983.
[371] K. Okamura, J.W. Hagen, H. Duan, D.M. Tyler, E.C. Lai, The mirtron pathway generates microRNA-class regulatory RNAs in Drosophila, Cell 130 (2007) 89–100, https://doi.org/10.1016/j.cell.2007.06.028.
[372] M. Xie, M. Li, A. Vilborg, N. Lee, M.-D. Shu, V. Yartseva, N. Šestan, J.A. Steitz, Mammalian 5′-capped microRNA precursors that generate a single microRNA, Cell 155 (2013) 1568–1580, https://doi.org/10.1016/j.cell.2013.11.027.