Microbial-Immune Crosstalk in Elderly-Onset Inflammatory Bowel Disease: Unchartered Territory

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Abstract

Elderly-onset inflammatory bowel disease (IBD) patients exhibit a distinct natural history compared to younger IBD patients, with unique disease phenotypes, differential responses to therapy and increased surgical morbidity and mortality. Despite the foreseeable high demand for personalized medicine and specialized IBD care in the elderly, current paradigms of IBD management fail to capture the required nuances of care for elderly-onset IBD patients. Our review postulates the roles of systemic and mucosal immunosenescence, inflammaging, and a dysbiotic microbial ecosystem in the pathophysiology of elderly-onset IBD. Ultimately, a better understanding of elderly-onset IBD can lead to improved patient outcomes and the tailoring of future preventative and treatment strategies.

Keywords: Inflammatory Bowel Disease; Gut Microbiota; Immunosenescence; Intestinal Barrier Permeability; Inflammaging; Aging

Introduction

Inflammatory bowel disease (IBD), comprised of ulcerative colitis (UC) and Crohn's disease (CD), is an autoimmune condition of the gastrointestinal tract resulting from an aberrant immune response to an environmental trigger in a genetically predisposed individual[1]. While the majority of patients are diagnosed earlier in life, 10-15% are diagnosed > 60 years of age with UC being more common than CD[2]. Elderly-onset CD patients usually present with colonic disease while elderly-onset UC patients present with left-sided colitis[2] (Table 1). In comparison, pediatric and adult-onset CD patients more commonly have ileocolonic disease whereas pediatric-onset UC patients more commonly have pancolitis and adult-onset UC patients have proctitis or left-sided disease[2] (Table 1). Moreover, in pediatric-onset IBD genetics appear to play a greater role, whereas in elderly-onset IBD environmental factors seem to have a greater impact on disease pathogenesis[2,3]. While several genetic mutations have been discovered that establish a relationship between susceptibility genes and an earlier onset age for IBD, no genetic mutations have yet been identified that correlate with an older onset age in elderly IBD[4]. In contrast, there is an increased understanding that aging is associated with pathophysiologic alterations including cellular senescence, progenitor cell dysfunction, chronic inflammation, a decline in autophagic activity[5], changes in the gut microbiota composition and functionality[6], which may all contribute to an increased risk of IBD. Epidemiological studies suggest that the global incidence and prevalence of elderly-onset IBD will continue to rise[7] creating a unique challenge for healthcare providers. Though elderly-onset IBD patients typically have less complicated disease behaviour (Table 1), they have a similar risk of surgery, but a lower cumulative exposure to immunomodulators and biologics compared to adult-onset IBD patients[8]. Moreover, elderly IBD patients who require surgery for medically refractory disease, are at a greater risk for post-operative morbidity and mortality[9].

Despite the fact that individuals over the age of 60 account for up to 15% of all incident IBD cases, there is limited data available to support the management of elderly-onset IBD patients because this population is generally underrepresented in IBD clinical trials, and most of the current clinical data are based on observational data or indirect evidence[10]. Furthermore, age-specific concerns such as polypharmacy, comorbidities, malignancies, and frailty are more relevant to elderly IBD patients, requiring the clinician to provide more nuanced care to this vulnerable population[11,12]. Increasing evidence highlights that IBD across different age groups may have a distinct pathogenesis[2], which has implications for disease management. A recently

published multicenter observational study demonstrated that anti-tumour necrosis factor (anti-TNF) therapy may be less efficacious in biologic naïve elderly-onset IBD patients[13]. These findings mirror those from other retrospective studies revealing that elderly IBD patients exhibit a lower rate of short-term clinical response and an increased frequency of secondary loss of response to anti-TNF therapies[14,15].

Considering the increasing incidence and prevalence of elderly-onset IBD as well as the associated economic implications, this niche population deserves more attention to facilitate both prevention and management strategies. In this review, we explore the aging-driven factors contributing to IBD in the elderly patient population, emphasizing the role of immune remodelling (termed "immunosenescence") and aging of the gut microbiome. We propose that aging and the gut-microbiome-immune axis interact reciprocally leading to IBD in the elderly.

Table 1. A comparison of disease phenotype and behavior in pediatric-, adult- and elderly-onset inflammatory bowel disease

	Pediatric-onset IBD	Adult-onset IBD	Elderly-onset IBD
Ulcerative Colitis			
Location	Pancolitis[2,16]	Proctitis and left-sided colitis[17,18]	Left-sided colitis[19,20]
Disease Extension	29-49%[16,21,22]	10-30%[18,23]	6.6-12.3%[24]
Need for Surgery at 5 years	14-20%[16,21]	3-13%[23,25]	8-11%[8,19,25]
Crohn's Disease			
Location	Upper GI, perianal and Ileocolonic[2,26]	Ileocolonic[2]	Colonic[19,20]
Disease Behavior	Inflammatory, stricturing, penetrating[17,27]	Inflammatory, stricturing, penetrating[25]	Inflammatory[19,20]
Need for Surgery at 5 years	17-34%[26,28,29]	29-31%[25,29]	23-29%[8,20,29]

IBD, inflammatory bowel disease; GI, gastrointestinal

The hallmarks of immune aging in IBD

Biological aging, as opposed to chronological aging, reflects diminished reparative and regenerative capacity in tissues and organs, as well as remodeling of the immune system. The term "immunosenescence" refers to age-associated functional impairments or aberrant immune

responses[30]. Immunosenescence predisposes elderly people to viral and bacterial infections, autoimmunity, malignancies, and mortality[31-33]. As IBD is fundamentally a disease of chronic inflammation, elevated risks of chronic basal inflammation associated with aging (i.e.,"inflammaging") and immunosenescence together may contribute to the development and propagation of IBD in the elderly. There are several aspects of the aging immune system that overlap with characteristics of immune responses in IBD. Herein, we explore the unique cellular and molecular basis for systemic and mucosal immunosenescence and postulate their role in the pathogenesis of elderly-onset IBD.

Systemic immunosenescence and IBD

Adaptive immunosenescence and IBD immunopathogenesis

The remodelling of adaptive immunity with age can be attributed to changes in the quality and quantity of T and B cell responses[34]. Hallmarks of T cell immunosenescence include an accumulation of antigen-experienced memory T cells at the expense of antigen-inexperienced naïve T cells due to age-associated thymic involution[35] (Fig. 1). This results in a diminished response against newly encountered antigens and further restricts repertoire diversity in the elderly. Furthermore, T cell immunosenescence is accompanied by an increase in the CD4 to CD8 T cell ratio[36], an imbalance between type 1 helper (Th1) and type 2 helper (Th2) cells[37], and an increase in the ratio of pro-inflammatory type 17 helper T (Th17) cells to anti-inflammatory regulatory T (T_{reg}) cells[38] (Fig. 1). Similarly, the balance between Treg cells and effector T cells is also disrupted in patients with IBD[39], where immune tolerance is suppressed and effector T cells such as Th1, Th2, and Th17 are activated leading to IBD progression[40,41]. Moreover, an age-associated accumulation of senescent ($CD28^{-ve}$ $CD57^{+ve}$) T cells has been widely reported, particularly in the terminally differentiated EMRA cells (effector memory T cells that re-express CD45RA)[42]. These senescent T cells possess a pro-inflammatory pattern known as senescence-associated secretory phenotype (SASP) during aging[43], which secrete pro-inflammatory cytokines (IL-6 and IL-1β)[42] that play a key role in IBD pathogenesis.

Furthermore, chronic infection with cytomegalovirus (CMV) accelerates human T cell immunosenescence in elderly individuals[44]. Though the role of CMV infection in active IBD remains equivocal, studies have demonstrated that 20-40% of patients with severe and/or steroid-refractory IBD are seropositive for CMV infection[45]. Elderly IBD patients are also at a

higher risk for CMV reactivation[46]. In the context of aging, persistent infections with CMV may exacerbate immunosenescence by a dual immunosuppressive mechanism: occupying "immunological space" that comprises up to 50% of the total memory T cell compartment in older individuals and causing blockade of antigen-presenting cells or cytokine secretion[47]. Considering the accumulation of large numbers of CMV-specific $CD8^+$ effector T cell clones that have been demonstrated to be cytotoxic and capable of rapidly releasing proinflammatory cytokines (IFN-γ and TNF-α) in response to stimulation[48], it is a plausible hypothesis that CMV infection or reactivation may be associated with an increased risk of IBD in the elderly.

In addition, data from the human colonic mucosa transcriptome also support the hypothesis that viral infection induced autoimmunity may represent a pathogenetic mechanism for IBD, particularly CD[49]. Herpes simplex virus (HSV) infection has been identified as an upregulated pathway in CD when compared with controls[49], which involves MHC molecules that are known for the presentation of viral and self-antigens to T cells. In contrast, increased numbers of Epstein-Barr virus (EBV)-infected cells have been detected in UC as compared to CD, with elevated expression of the EBV-induced gene 3 (EBI3), a molecule belonging to the interleukin (IL)-12 family[50]. Human metagenome studies analysing virus-like particle (VLP) preparations from faecal samples obtained from patients with IBD indicate a significant expansion of *Caudovirales* bacteriophages in UC and CD patients compared with controls[51]. Nonetheless, the precise role viruses and bacteriophages play in IBD pathogenesis remains to be determined.

Alongside viruses, several bacterial species have also been positively associated with IBD [52,53]. These include *Clostridioides difficile*, *Salmonella*, *Shigella*, *Campylobacter concisus*, *Mycobacterium avium* subspecies *paratuberculosis*, enterotoxigenic *Bacteroides fragilis*, *Fusobacterium varium*, *Escherichia coli*, enteric *Helicobacter* species, and *Fusobacterium nucleatum*[52]. Overexposure of the immune system to excessive bacterial substances may lead to loss of immunological tolerance to normal commensals, eliciting intestinal inflammation and IBD development[54]. Finally, emerging evidence suggests that fungi may play a role in chronic intestinal inflammatory disorders. In this regard, a new study has shown that *Candida albicans* strains seem to dominate the colonic mucosa of patients with UC, but importantly, only some strains aggravated gut inflammation[55].

In addition to T cells, an age-associated decline in B cell lymphopoiesis and remodelling has also been observed in the B cell pool (Fig. 1). This entails a decline in B cell repertoire diversity,

a decrease in naïve B cells, an increase in antigen-experienced memory B cells and diminished humoral responses due to reduced protective antibody production, resulting in poor vaccination efficacy in older people[56,57]. Decreased antibody avidity may be attributed to down-regulated E47, a transcription factor that controls B cell function, and to a reduced activation-induced cytidine deaminase (AID) which is related to class switch recombination and Ig somatic hypermutation[58]. A further age-related change in antibody production occurs when immunoglobulin isotypes shift from IgD and IgM isotypes largely produced by naïve B cells, to increased levels of IgG or IgA isotypes produced by memory B cells[59]. Moreover, inflammatory markers occurring in the late/exhausted memory ($IgD^{-}CD27^{-}$) B cells exhibit SASP, which involves the chronic transcriptional induction and increased secretion of pro-inflammatory mediators. This includes cell cycle regulators (e.g., $p16^{INK4}$, which induces cell cycle arrest), inflammatory miRNAs (miR-155, miR-16, miR93), pro-inflammatory cytokines (TNF-α, IL-6 and IL-8), and metabolic pathways (AMPK)[57]. These factors constitute a source of chronic inflammation that may contribute to inflammaging and the development of elderly-onset IBD.

Lastly, a subset of atypical B cells, termed age-associated B cells (ABCs), secrete pro-inflammatory cytokines (e.g., TNF-α) as well as autoantibodies and accumulate with age[60]. Similarly, the accumulation of ABCs has also been observed in other autoimmune diseases such as rheumatoid arthritis in the elderly[61]. Also regulatory B cells (B_{regs}), which can resolve pro-inflammatory events by secreting anti-inflammatory IL-10, IL-35, or TGF-β[62], develop numerical and functional deficits with aging[63], increasing the risk of autoimmunity and chronic inflammation with age[64]. Notably in patients with IBD, such a numerical deficiency or decrease in B_{regs} function can propagate disease progression and severity, exacerbating the intestinal inflammation that may contribute to IBD pathogenesis[65].

Innate immunosenescence and IBD immunopathogenesis

The peripheral innate immune system, particularly the neutrophils, natural killer cells (NK), monocytes, macrophages and dendritic cells (DCs), are subject to profound changes with advancing age[66]. The dysfunction of DCs with increasing age is characterized by weakened antigen uptake and presentation as well as diminished phagocytosis of apoptotic cells[30], which prolongs self-antigen exposure and can contribute towards autoimmune responses and inflammation[67]. In addition, DCs from older adults secrete higher basal levels of pro-

inflammatory cytokines (IL-6, TNFα), accompanied by decreased levels of anti-inflammatory cytokines (IL-10)[67,68], contributing towards inflammaging. During aging, neutrophils exhibit impaired phagocytosis, defects in chemotaxis and impaired formation of neutrophil extracellular traps (NETs)[69-71], resulting in compromised pathogen clearance and an inappropriate persistence of chronic inflammation. Macrophages also demonstrate a decrease in phagocytosis with aging, which results in a delay in the resolution of inflammation[72,73]. Although an age-associated expansion of NK cells has been reported in aged individuals, these aged NK cells exhibit decreased per-cell cytotoxicity, contributing to an increased susceptibility to viral infections and possibly towards the accumulation of senescent cells[74,75]. Age-related redistribution of monocyte subsets has been observed with increased frequency of non-classical monocytes ($CD14^{+ve}CD16^{++ve}$) exhibiting SASP in a pro-inflammatory state and secreting high levels of pro-inflammatory cytokines basally[76] similar to DCs. Overall, the age-associated remodelling of the peripheral innate immune system could contribute towards a reduced clearance of senescent cells, a higher basal level of pro-inflammatory cytokines fueling inflammaging and an elevated risk of infections and autoimmune conditions, including IBD[77] (Fig. 1).

In addition to the immune cells mentioned above, innate host defense mechanisms also depend on pattern recognition receptors (PRRs)[78], inflammasomes, and autophagy[79]. The PRRs are a large family of proteins that are capable of directly recognizing pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPS), as well as apoptotic host cells and damaged senescent cells associated with aging[80]. Toll-like receptors (TLRs), the major PRRs expressed mostly by dendritic cells, macrophages and monocytes, play an important role in the innate immune response to inflammatory stimuli[81]. However, excessive activation of these receptors may lead to chronic intestinal inflammation and abnormal TLR signaling may trigger disease-related inflammation and an increased bacterial burden, hence being closely linked to the development of IBD[81]. Several members of the TLR family of receptors including TLR5, TLR8, and TLR9, are positively correlated with the presence of ulcerative colitis (UC) and the severity of endoscopic and histological inflammation, with their mRNA levels being higher in active UC in comparison to quiescent UC, as well as strongly correlated with the transcription of inflammatory cytokines (IL-6 and TNF)[82]. In particular, polymorphisms in the TLR5 gene, such as the *R392X*, *N592S* and *L616F* variants, are significantly associated with an increased risk for both UC[83] and Crohn's disease (CD)[84]. In

addition, TLR5 expression level is elevated in human monocytes from the elderly, accompanied by activation of downstream NF-κB and MAPK signaling pathways that enhance the secretion of proinflammatory mediators[85], which may contribute to the inflammatory milieu in elderly IBD.

Inflammasomes are multiprotein complexes assembled by PRRs that orchestrate proinflammatory responses and participate in innate responses by sensing microbial motifs, endogenous signals, and environmental irritants[86,87]. NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3), one of the better studied inflammasomes, activates when stress signals from PAMPs or DAMPs are present[88]. This results in a series of proinflammatory responses, including the secretion of proinflammatory cytokines such as IL-1β and IL-18, as well as the initiation of pyroptosis (a proinflammatory type of programmed cell death)[88]. Furthermore, recent studies have highlighted the role of the NLRP3 inflammasome contributing to age-related inflammation or "inflammaging" and the pathogenesis of a wide variety of age-related diseases[86], as well as IBD[89].

In particular, inflammasome activation has been shown to interact and reciprocally influence autophagy[90]. While activation of the inflammasome can trigger autophagy, autophagy in turn can inhibit excessive inflammasome activation via autophagic engulfment to maintain homeostasis[91]. A number of IBD susceptibility genes have been discovered to regulate crosstalk between autophagy and inflammasome activation, including autophagy-related 16-like 1 (ATG16L1) and immune-related GTPase M (IRGM)[92]. With respect to aging, it is noteworthy that autophagy could minimize aging effects by removing endogenous DAMPs; however, autophagy activity is downregulated with aging[5], resulting in unrestricted inflammasome activation and consequent inflammation[93].

Inflammaging and IBD pathogenesis

"Inflammaging", a chronic low-grade systemic inflammation that increases with age, is another hallmark of immune aging[68]. It is speculated that an increased asymptomatic pro-inflammatory state (conceptualized as a proclivity of the innate immunity system to confront pathogens) may have evolutionary advantages, leading to beneficial adaptations in the aging process which maintain homeostasis[94]. The inflammation factor has been found to be a significant contributor to successful aging in super semi-centenarians[95]. Nevertheless, as shown by the antagonistic pleiotropic theory of aging[96], these protective effects over time can

lead to detrimental outcomes in the absence of adequate compensatory mechanisms. Inflammaging results from an imbalance between pro-inflammatory and anti-inflammatory networks[66]. It is characterized by a heightened pro-inflammatory environment associated with a subclinical accumulation of pro-inflammatory factors including IL-6, IL-1β, IL-18, IL-22, and TNFα without an effective counter-regulation by anti-inflammatory molecules such as IL-10, IL-4 and TGF-β1[66,94,97]. This contributes to the development of frailty and increased mortality in the elderly[97,98], as well as chronic age-related diseases[99].

Similar to inflammaging, an imbalanced inflammatory and anti-inflammatory equilibrium as well as remodeling of cytokine networks have also been demonstrated to contribute to the pathogenesis of IBD, which accordingly provides a rationale for the development of tailored cytokine-targeted therapies for IBD. These strategies aim to block pro-inflammatory cytokine signaling mediated by TNFα, IL-1β, IL-6, IL-12, IL-17, and IL-23, and/or to enhance anti-inflammatory pathways through IL-2, IL-10, or TGF-β1[81,100]. Interestingly, inflammaging occurs concurrently with immunosenescence[101,102]. Moreover, inflammaging is triggered by chronic repeated activation of the innate immune system, which exhausts the adaptive immune system, and in turn exacerbates immunosenescence[103]. Therefore, immunosenescence and inflammaging may function reciprocally to shape IBD in the elderly.

It is proposed that the chronic proinflammatory state of inflammaging is mediated by a number of molecular mechanisms including (Fig. 1): cellular senescence SASP factors[104], mitochondrial dysfunction such as mitochondrial DNA (mtDNA) damage[105], a decline in autophagy capacity that compromises cellular housekeeping and immune 'rejuvenation'[106], accumulation of damage-associated molecular patterns (DAMPs)[107], dysregulation of the ubiquitin-proteasome system (UPS)[108], activation of inflammasomes[109], telomere shortening[110] and activation of the DNA damage response (DDR)[111]. In addition to these factors, gut microbiota dysbiosis is of particular importance since the gut microbiota closely interacts with the diet, intestinal barrier, metabolism, and systemic inflammation[102,112,113], as well as being subject to profound remodeling with advancing age as discussed in section 3.

It is notable that studies in IBD demonstrate great promise for utilizing frailty and sarcopenia, which are interrelated concepts with inflammaging, as a risk stratification tool for IBD patients at the greatest risk of experiencing adverse outcomes[12,114]. Furthermore, it has been reported

that 41.6% of patients with IBD have sarcopenia[115], a condition characterized by progressive loss of muscle mass and function associated with aging and considered to be a key component of frailty[116]. Although the pathogenesis of frailty and sarcopenia is still poorly understood, an emerging theory ties the two together because of inflammaging and immunosenescence[117,118]. Particularly, the inflammatory cytokine components of inflammaging (e.g., TNFα, IL-1β, and IL-6) contribute to muscle wasting, either directly by increasing protein degradation and catabolism, or indirectly by promoting anabolic resistance by inhibiting the expression and activity of growth hormone and insulin-like growth factor 1[119,120].

There are still many unknowns about the intricacies of the aging body and its clinical implications for IBD. It is generally believed that aging induces systemic immune dysfunction, pro-inflammatory cytokine responses and an accumulation of senescent cells, leading to immunosenescence and inflammaging. If this combination persists to increase the imbalance between pro-inflammatory and anti-inflammatory responses without effective counter-regulation, it may provide favorable conditions that lead to IBD in the elderly (Fig. 1).

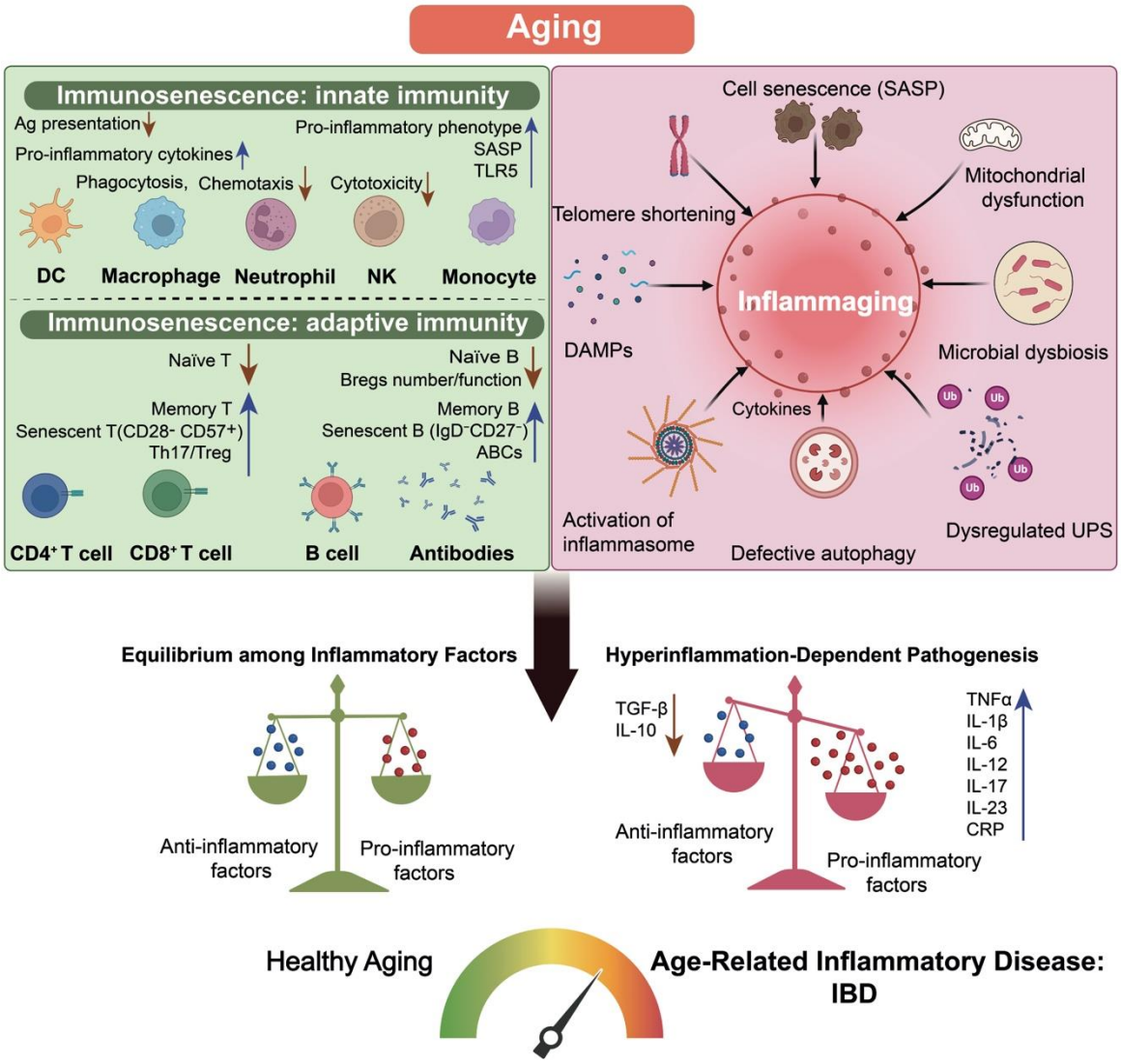

Figure 1. ***Hallmarks of immunosenescence, inflammaging, and susceptibility to IBD.*** During aging, immunosenescence (remodeling of the innate and adaptive immune systems) and inflammaging (low-grade inflammation) both contribute to promoting pro-inflammatory responses in the elderly. If this pro-inflammatory milieu is not adequately counteracted by anti-inflammatory mediators, it may provide the ideal circumstances for the development of IBD in the elderly. ABCs, age-associated B cells; Bregs, regulatory B cells; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; NK, natural killer cells; PRR, pattern recognition receptors; SASP, senescent-associated secretory phenotype; TLR, Toll-like receptor; Treg, regulatory T cell; UPS, ubiquitin-proteasome system. Blue arrow: increase; Red arrow: decrease. The diagram was created with BioRender.com.

Mucosal immunosenescence and IBD

It is well established in IBD that the mucosal barrier is compromised and that both the mucosal barrier and the local immune system play a prominent role in the pathophysiology of disease[121-123]. Emerging data illustrates an overall decline in the integrity of the intestinal epithelial barrier of the elderly, with the first signs of aging in the gut immune system occurring at mucosal surfaces earlier than in the systemic immune compartment[124]. Along with systemic immune disorders, age-associated changes in the local mucosal immune system may disrupt the integrity of the epithelial barrier, leading to a leaky gut and initiating the onset of IBD. An integrated series of changes occur at the mucosal interface of aging guts including physical changes (intestinal epithelial cells and tight junctions)[125-129], immunological changes (secretory IgA and mucosal immune cells)[124,130-135], biochemical changes (mucus layer and anti-microbial peptides, AMPs)[136-139], as well as microbial changes[124,140,141]. A summary of mucosal immune changes in the elderly that may represent a pathogenesis link to IBD is displayed in Table 2.

Table 2. Aging-associated changes of the intestinal epithelial barrier and mucosal immune system that parallel the pathophysiology of IBD

Mucosal barrier components	Hallmarks of aging	Studied changes in IBD	Implication in IBD pathogenesis
Physical barrier: IECs	ISCs: Regenerative capacity ↓ [142,143] Proliferation ↓ [128] Cellular motion ↓ [143]		Altered architecture; Impaired function of intestinal barrier
	Paneth cells: Secretory function ↓ [141,142] Wnt signalling ↓ [142,144] Wnt antagonist ↑ [144]	Dysfunctional Paneth cells with reduced secretion of AMPs [145]	
	Enterocytes: Apoptosis ↑ Cell function ↓ [128]	Somatic mutations in UC [146,147] and CD [147]	
	M cells: Mature cells ↓ Antigen uptake ↓ [148]		
Physical barrier: TJs	E-cadherin ↓ [149] Occludin ↓ [149,150]; ZO-1 ↓ [150]; JAM-A ↓ [150] Claudin-2 ↑ [150,151]	Occludin in CD ↓ [152] and UC ↓ [153] Claudin-2 in CD ↑ [152] and UC ↑ [154]	Increased intestinal permeability
Mucosal immunity	Ag-specific SIgA response ↓ [124,131]		Attenuated antigen-presentation and protection against pathogens
	T cell priming by DCs ↓ [133] Oral toleration to antigen ↓ [130]		
	ILCs: ILC2 ↑ [135]; ILC3 ↓ [134]	Frequencies of ILC2 in CD ↑ [155]; ILC3 in UC ↓ [156]	
Biochemical barrier: Mucus layer	Thickness of the colonic mucus layer ↓ [157,158]	Mucus thickness in UC ↓ [159]	Defects in mucus barrier leading to increased bacterial penetration
Biochemical barrier: AMPs	Reg3β ↑; Reg3γ ↑ β-defensin 1 ↑; angiogenin-4 ↑; Relmβ ↑ [136]; α-defensin 5 ↓ [160]	α-defensin 5 in ileal CD ↓ [161]	Reduced mucosal antimicrobial activity

Ag, antigen; AMPs, antimicrobial peptides; CD, Crohn's disease; IECs, intestinal epithelial cells; ILCs, innate lymphoid cells; ISCs, intestinal stem cells; JAM-A, junctional adhesion molecule-A; SIgA, secretory IgA; TJs, tight junctions; UC, ulcerative colitis.

Physical changes in the intestinal barrier with aging

The integrity of the gut epithelium is compromised with age in humans[149,151] as well as in various model organisms such as *C. elegans*[129], *Drosophila*[129,162], mice[149] and monkeys[163]. The aging process may negatively impact the physical barrier of the gut epithelium by affecting two key components of intestinal barrier function: intestinal epithelial cells (IECs), and cell-cell junctional complexes known as tight junctions (TJs), which are implicated in the pathogenesis of IBD[41,122].

The intestinal epithelium barrier comprises specialized cells with diverse functions that emerge from intestinal stem cells (ISCs) at the base of crypts[164]. However, ISCs are highly prone to stem cell exhaustion, an integrative hallmark of aging[105], as evidenced by a reduced tissue regenerative capacity after damage and a slower turnover of the epithelium with aging[142,143]. The current emerging molecular mechanisms underlying ISC exhaustion may be related to increased DNA damage and an age-related dysfunction of the DDR[165], increased apoptosis[128] and a decline in stemness maintaining Wnt signalling[142,144]. As the gut ages, the reduced mitotic rate[142] coupled with an increased level of apoptosis in active ISCs[128] lead to decreased cell proliferation within the crypt, and the ROCK pathway-dependent cellular motion of ISCs is also impaired in aging crypts[143] (Table 2). Of note, the regenerative potential of human and mouse intestinal epithelium declines with age not only due to defects in stem cells themselves, but also in their niche, which supports and regulates ISCs[144,166]. Transcriptomic data suggests that this functional decline may be caused by a decrease in the canonical Wnt signalling, particularly *Wnt3,* mainly secreted by ISCs and their neighbouring Paneth cells and subepithelial mesenchymal cells in aged intestinal crypts[142,144].

IECs have an essential role in maintaining homeostasis of the intestinal epithelial barrier by modulating responses to the gut microbiota[167]. Several types of specialized IECs including absorptive enterocytes, Paneth cells, goblet cells and microfold cells (M cells) are negatively affected by aging, especially with respect to their function and composition[126,168,169] (Table 2). Generally, proteomic analysis demonstrates that aging affects epithelial immunity, metabolism, and cell proliferation as well as the composition of the epithelium changes region-dependently in aged mice[170], which could account for the altered architecture and dysfunction of the aging gut. To date, it is unclear what role each epithelial cell subtype plays in the breakdown of the epithelial barrier that underlies IBD. However, aberrant IEC responses to IBD-associated microbial sensing, TNF stimulation, and dysregulated inflammatory pathways in IECs (such

as interferon-γ, NF-κB, RIPK, and ER stress)[171-173] may compromise intestinal barrier integrity, thereby promoting intestinal inflammation.

The TJ barrier defects, characterized by discontinuous tight junction strands, have been implicated in the pathogenesis of IBD[41]. The underlying cellular mechanisms include altered expression of TJ proteins including occludin, claudins, zonula occludens (ZOs), and junctional adhesion molecule (JAM)[167]. In aged humans, colonic tissue exhibits discontinued TJ strands accompanied by a decline in E-cadherin and occludin levels[149] as well as an increase in claudin-2[151], resulting in a profound decrease in transepithelial electrical resistance (TEER) which indicates impaired integrity of the epithelial barrier[151]. The remodeling of the intestinal epithelial tight junction proteins in aged non-human animals such as mice and baboons exhibits a similar pattern, with reduced levels of E-cadherin[149], occludin[149,150], ZO-1[150], and JAM-A[150], and increased levels of claudin-2[150]. In particular, occludin downregulation in patients with IBD[152,153], and claudin-2 upregulation in both CD[152] and UC[154] patients is known to result in enhanced tight junction permeability for cations, providing the molecular basis for leaky gut (Table 2). The altered intestinal TJ permeability may result from the accumulation of pro-inflammatory cytokines such as TNF-α, IL-1β, IFN-γ, and IL-6 secreted by IECs, which modulate TJ protein expression and function, or activate regulatory pathways linked to the TJs complex[174-176]. Interestingly, pro-inflammatory cytokine levels tend to increase with advancing age because of inflammaging.

Immunological changes in the intestinal barrier with aging

The GI tract is generally acknowledged as the largest immunologic organ with regards to lymphocyte numbers, as the gut-associated lymphoid tissue (GALT) accommodates nearly 70% of the total immune cells in the body[177]. Aging is also associated with progressive alterations in mucosal immune responses driven by both impaired immune cells and gut mucosal regulatory immunity, referred to as mucosal immunosenescence[178], which is functionally distinct from its systemic counterpart.

The major change seen in the aged mucosa is a failure to elicit an antigen (Ag)-specific secretory IgA (SIgA) antibody (Ab) response, which forms the first line of local defense against potentially invasive microorganisms and is central to the normal function of the GI tract as an immune barrier[179]. Although conflicting results have been reported on the magnitude of IgA-mediated responses in aging[126], Ag-specific mucosal SIgA Ab responses, which are particularly

supported by the GALT inductive immune system, are markedly lower in aged animals[124,131], suggesting that Ag-specific mucosal immune responses are attenuated. Further, adoptive transfer of adipose tissue-derived mesenchymal stem cells from young donors restored a youthful Ag-specific SIgA Ab response in aged mice[132]. These findings suggest a possible failure of induction of SIgA Ab responses for protection in aging.

The mechanisms underlying the impaired Ag-specific SIgA Ab responses as well as lack of oral tolerance induction that occur in the aging state have been proposed to involve decreased DCs and follicular DC functions in Peyer's patches, in addition to impaired T cell responses[130]. Aging deficits in mucosal DCs derived from the small intestine are characterized by a diminished capacity to prime T cell responses, failure to stimulate TGF-β secretion and differentiation of CD4+ LAP+ T_{reg} cells[133]. In addition, mucosal innate lymphoid cells (ILCs) are a heterogeneous group of innate immune cells that have been implicated in the pathogenesis of chronic intestinal inflammation in IBD[122,123], by playing a critical role in maintaining the integrity of the mucosal barrier. In aged humans, intestinal group 3 ILC3 (ILC3) that produce the Th17 cell-associated cytokines decrease with aging, whereas classical NK cells exhibit a compensatory increase[134]. Parallel to this aging-related change, ILC3 levels have been shown to decrease in colonic mucosa samples of patients with UC[156]. Furthermore, intestinal samples from CD patients have shown increased frequencies of ILC2[155], which is also consistent with age-associated increases in ILC2[135]. A dysregulated mucosal immune response is the central driver of IBD, and aberrant functions of mucosal DCs and ILCs may contribute to elderly-onset IBD.

Biochemical changes in the intestinal barrier with aging

The intestinal mucus layer, which is formed by glycoprotein mucins secreted by goblet cells, coats IECs and functions as a biochemical defense barrier against microbial invasion[180]. In aged mice or accelerated aging mice models, the colonic mucus layer becomes thinner or absent[157,158,181], which may be due to a lack of mucus-secreting goblet cells in the colonic crypts[158]. Aging-induced deterioration of the protective mucus layer is associated with increased bacterial penetrability, alterations in immunity and microbiota composition, as well as increased susceptibility to colonic inflammation[158]. In line with this, active UC is associated with thinner colonic mucus layers that are more permeable to bacteria[159], along with a decrease

in core mucus components such as MUC2 and FCGBP, a decrease in sentinel goblet cells and a reduced secretory response to microbes[182], contributing to the development of UC.

The antimicrobial peptides (AMPs), produced by Paneth cells[41], are another major component of the biochemical barrier as they localize to the mucus layer and act in conjunction with the mucus layer to prevent bacterial attachment and invasion[180,183,184]. In addition, intestinal AMPs can influence treatment outcomes, as anti-TNF therapy responders and non-responders in UC patients exhibit distinct patterns of mucosal AMP expression[138]. In aged mice, the transcript levels of Paneth cell-derived AMPs such as ileal α-defensin and lysozyme are decreased, while other AMP genes are increased, including regenerating islet-derived protein (Reg)-3β and -3γ, β-defensin 1, angiogenin-4, and resistin-like molecule beta (Relmβ)[136]. The mechanism underlying the age-related up-regulation of AMPs may be mediated by cytokines[137]. In contrast to the observations in aged mice, a study of elderly people suggests that several serum AMPs levels are not affected by aging, as elder individuals produce comparable levels of cathelicidin (LL-37) and β-defensin-2 (hBD-2) as healthy young adults[139]. However, it is noteworthy that the secretion of human α-defensin 5 is lower in the elderly than in middle-aged individuals[160]. This parallels the reduced expression of α-defensin 5 shown in patients with ileal CD, which compromises mucosal host defenses and predisposes patients to CD[161].

Aging gut microbiome and IBD

The gut is home to the largest microbial community of the body and is the most diverse and well-studied commensal ecosystem. However, a disrupted ('dysbiotic') gut microbiome, has been extensively characterized in IBD, where it is closely associated with a reduction in the total number, and diversity of microbial species[41,185-187]. Furthermore, dysbiosis is a hallmark of aging. The microbiota profile of older adults is different from that of young adults for several reasons associated with senescence, including aging-related changes in lifestyle and dietary intake, decreased locomotion, weakened immune strength, altered gut morphology and physiology, recurrent infections, hospitalizations, polypharmacy and frailty[140,188-191]. The causal relationship between changes in the microbiome and host aging has yet to be determined. The substantial alteration of the microbiome in aging may negatively impact gut physiology by leading to reduced gut motility, decreased mucus secretion, and impaired intestinal barrier dysfunction[140]. This results in a cascade of inflammatory events that enhance the risk of

developing aging-associated pathologies including frailty, neurodegeneration, type-2 diabetes, cancer, and cardiovascular disease[192]. It is likely that overlapping or shared microbiome alterations across these aging-linked disorders are, in part, a consequence of general physiological decline, including inflammation and loss of mucosal barrier, which have been summarised by DeJong et al[193]. Importantly, Ghosh et al have demonstrated that cross-disease microbiome alterations overlap with those changes associated with healthy aging and unhealthy aging [190,194].

Although dysbiosis likely contributes to IBD pathogenesis[41,123], the cause-effect relationship between microbial dysbiosis and IBD has not yet been fully elucidated[195,196]. In IBD, microbial dysbiosis manifests as an overall decrease in bacterial diversity, along with decreased protective bacteria [Bacteroidetes (*Bacteroides fragilis*), Firmicutes (*Lactobacillus, F. prausnitzii* and *Clostridium* strains)], and Actinobacteria [(*Bifidobacterium*)][122,197-200] and increased pathogenic species [Proteobacteria (*Gamma proteobacteria*, and *Escherichia coli*) and Fusobacteria (*Fusobacterium nucleatum*)][122,197,201]. Furthermore, multi-omics approaches applied in cross-sectional and longitudinal studies have revealed that metagenomic, metatranscriptomic and stool metabolomic profiles are disrupted during IBD activity[202]. Dysbiosis in IBD involves an increase in facultative anaerobes at the expense of obligate anaerobes, disruptions of microbial transcription, and a decrease in beneficial metabolite pools, including short-chain fatty acids (SCFAs) such as butyrate and propionate, as well as secondary bile acids (lithocholate and deoxycholate)[202,203].

Similarly, aging is associated with a decrease in the diversity of intestinal commensal microbes, manifested by a loss of beneficial commensal bacteria, and an increase in opportunistic and potentially pathogenic commensal microbes. Generally, the composition of the intestinal microbiota in older adults (>65 years) is extremely variable between individuals and differs from the core microbiota and diversity levels in younger adults[204]. Particularly, the intestinal commensal bacteria (*bifidobacteria, lactobacilli, bacteroides*) that are responsible for maintaining immune tolerance are reported to be reduced in the elderly, while Proteobacteria is elevated[188,191,205-207] mirroring changes noted in IBD patients[122,197,198]. Furthermore, the aging-associated changes in gut commensals are also accompanied by a decrease in microbiome-associated metabolites such as vitamin B12, vitamin B7, creatine, butyrate, as well as their respective microbial metabolic pathways, thus contributing to muscle atrophy and increasing frailty[208,209].

To date, there is a lack of human research exploring the interaction between IBD-microbiome associations and aging. However, a recent study reveals that aging influences microbiome composition as well as microbiome-disease signatures in IBD[194]. In this study based on gut microbiomes derived from over 2,500 individuals, age was identified as a strong covariate of disease signatures across multiple diseases, including IBD. In particular, IBD was associated with distinct bacterial species across three age groups [young (20-39), middle-aged (40-59), and elderly (above 60)] with a decrease in the prevalence of *Clostridium*, *Lachnospiraceae*, *Escherichia*, *Blautia producta* and *Streptococci* in the elderly with IBD compared to the young[194]. Currently, the relationship between the IBD-associated gut microbiome and disease pathogenesis in elderly-onset IBD is poorly understood due to a lack of direct evidence and relatively small sample sizes in existing studies.

Aging microbial-immune crosstalk in the initiation of elderly-onset IBD

The advancements in genomics over the past few years have revealed how the host immune system contributes to the determination of the gut microbiota and, in turn, how the microbiota modulates the immune system[210]. The interplay between the immune system and the microbiome is balanced for the maintenance of homeostasis, however abnormalities in these tightly controlled regulatory circuits could be linked to aging-related disorders. Although the exact pathogenesis of IBD remains unknown, IBD is believed to be associated with a breakdown in intestinal homeostasis pathways due to a dysfunctional communication between the epithelial barrier, intestinal flora, and immune system[81,211].

During aging, immunosenescence and an aging gut microbiome develop as both the immune system and the intestinal microbial ecosystem undergo profound remodeling. As such, it raises the question of whether immunosenescence and age-related changes in the microbiota are causally related. Recent studies have demonstrated the role of the microbiota in the regulation of immunosenescence using microbiome modulation. Fecal microbiota transplantation (FMT) has been demonstrated to be an effective tool for manipulating the aging processes, by reversing aging-associated dysbiosis and restoring secondary bile acids in progeroid mice, thereby counteracting the aging process and extending lifespan[212]. In a multi-omics human study, reversal of immunosenescence features was observed in patients with severe or

fulminant *Clostridioides difficile* infection undergoing successful FMT treatment[213], suggesting that changes in the gut microbiome may influence immunosenescence pathways. Similarly, in middle-aged mice, syringaresinol (SYR), a polyphenolic lignan, reverses immunosenescence through enhancing beneficial bacteria (*Lactobacillus* and *Bifidobacterium*) while reducing opportunistic pathogens (*Akkermansia*), suggesting that SYR contributes to the reversal of immunosenescence via modulation of gut integrity and microbiota diversity[214]. In addition, transferring gut microbiota from old to young mice promotes inflammation in the small intestine, upregulates inflammation-associated immune pathways (PRRs, Th cell differentiation, B cell development), and enhances leakage of inflammatory bacterial components into the circulation, indicating that aged microbiota contributes to inflammaging[215]. These findings suggest that the restoration of a youthful microbiome promotes the rejuvenation of an aged host by counteracting immunosenescence and inflammaging, which may slow down aging and its associated diseases.

The 'leaky gut', or increased intestinal permeability, is one of the key consequences of aging-onset dysbiosis. The age-related deterioration of intestinal barrier function is proposed to lead to the leakage of gut microbes into the systemic circulation, thus increasing systemic inflammation and hyper-inflammatory responses, which ultimately increases the host's susceptibility to various age-related diseases[113,216]. In turn, the translocation of microbes and their by-products, identified as microbe-associated molecular patterns (MAMPs) or PAMPs, may contribute to inflammaging[112,113]. Mice with aging gut microbiomes produce more pro-inflammatory cytokines, such as IL-6 and TNFα as well as a breakdown of the intestinal barrier[113]. Dysbiosis with advancing age is also linked with a reduction in commensal bacteria-derived metabolites, such as SCFAs and bile acids. In parallel, dysbiosis in IBD patients is associated with a decrease in the number of SCFAs and butyrate-producing bacteria, in particular the members of the *Firmicutes* phylum[217,218]. Butyrate, a key SCFA, is a beneficial mediator of intestinal barrier integrity, as it promotes epithelial cell proliferation and increases the expression of tight junction components such as occludin, ZO-1 and claudin-2[219]. Moreover, butyrate and secondary bile acids (3β-hydroxydeoxycholic acid, isoDCA) play a vital role in reducing intestinal inflammation through promoting the expansion of T_{regs}[220,221] or regulating B_{reg} functions[222]. Therefore, age-related loss of SCFAs and bile acids may further lead to the breakdown of the intestinal barrier and bacterial translocation, and subsequently chronic intestinal inflammation.

There is a reciprocal relationship between immunosenescence, the aging gut microbiome, and an impaired intestinal barrier. In the past decade, research has focused on the complex interactions between the microbiome, host immunity, and intestinal epithelial barrier, revealing a wide range of mechanisms involved in the crosstalk between these three entities, and how aberrations within this communication network may contribute to the molecular etiology of a number of multifactorial diseases, including IBD[211,223-225]. During aging, this immune-microbiota-intestinal barrier cross-talk may be largely mediated by PRRs [i.e., TLRs, nucleotide-binding oligomerization (NOD)-like receptors (NLRs), and the RIG-like receptors], which sense signals derived from microbial products (such as PAMPs and MAMPs) to initiate immune responses and elicit protective barrier responses[81,211,226]. For example, the Crohn's disease-associated PRR NOD2 triggers a series of immune responses when activated by bacteria-derived muramyl-dipeptide (MDP), including the activation of NF-κB, autophagy, and production of AMPs and pro-inflammatory mediators[224,227,228]. Moreover, PRR signals modulate epithelial barrier function by inducing proliferative and growth factors (COX2, PGE2, and amphiregulin) as well as strengthening tight junctions between IECs[229,230]. PRRs also play an important role in limiting bacterial colonization and translocation by stimulating IEC production of AMPs such as defensins and Reg3γ[225,231]. Particularly, the PRR members associated with IBD susceptibility play an important role in controlling dysbiosis and colon inflammation, including NOD2[232], TLR5[233], NLRP6[234], and NLRP12[235]. However, chronic activation of PRRs by microbial exposure, which increases with aging, can drive systemic and local inflammatory responses resulting in a multitude of pro-inflammatory molecules, thus fueling inflammaging[81,211,236]. Inflammaging underpins microbial dysbiosis and has been linked to increased gut permeability[237,238]. In addition, recent research has suggested that a "gut-muscle axis" exists in IBD patients, wherein inflammation, gut dysbiosis, and malnutrition interact leading to frailty and sarcopenia[239]. Nestled within this concept is a vital role of the aging gut microbiome, as physical frailty and sarcopenia are marked by a loss of microbial diversity and the depletion of specific microbes such as saccharolytic and butyrate-producing bacteria[118,240]. It is speculated that gut dysbiosis may alter the immune response and host metabolism, promoting inflammaging which up-regulates several molecular pathways that are associated with sarcopenia and frailty[239], and in turn could contribute to disease pathogenesis in elderly-onset IBD patients.

In summary, advancing age is accompanied by modifications in the microbiome, host immune system, and intestinal barrier, which are inextricably linked. Although we are still unable to

ascertain the specific causal relationships between these events associated with aging, a vicious cycle is hypothesized in which immunosenescence, inflammaging, and an ageing microbiome form part of a feed-forward feedback mechanism which could contribute to the pathogenesis of elderly-onset IBD (Fig. 2).

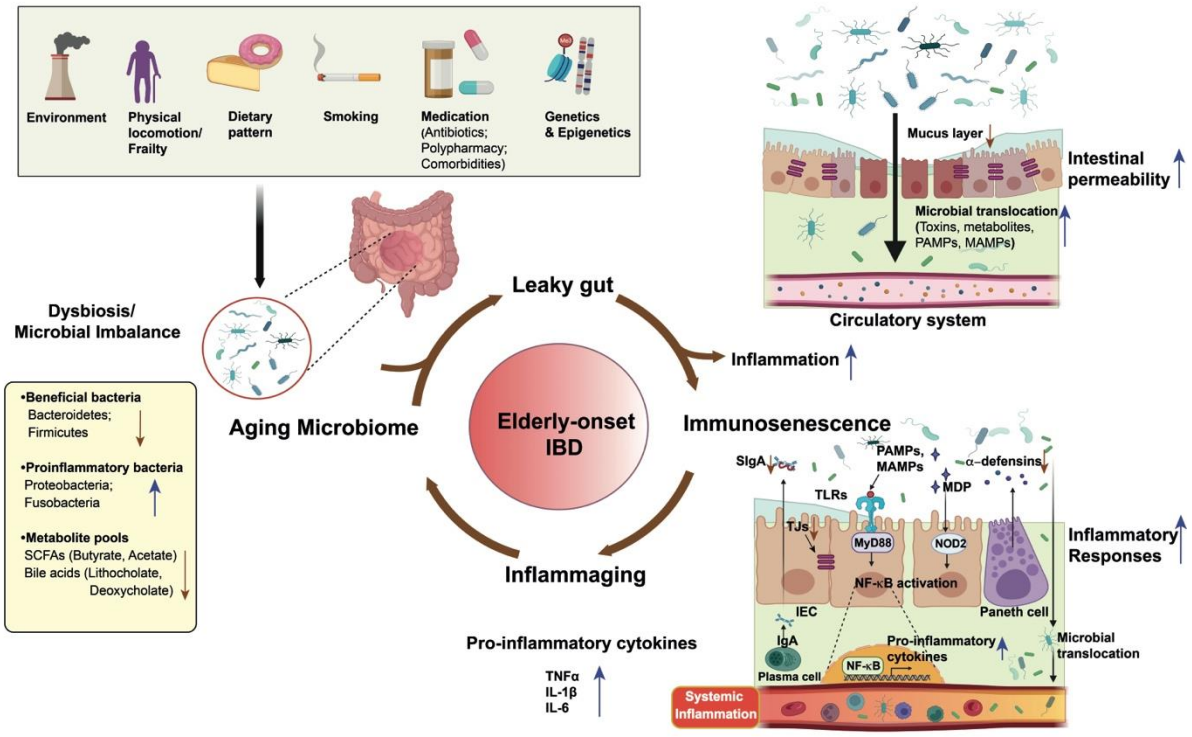

Figure 2. ***Immunosenescence, the aging microbiome, and leaky gut - a vicious cycle in IBD.*** Aging has a detrimental effect on the microbiome through multiple factors, including an urban environment, diet, medications, smoking, decreased movement, frailty, and genetic and epigenetic factors, causing a decrease in gut microbial diversity and function. Dysbiosis with aging is accompanied by deterioration of bacterial-epithelial cell interactions. A reduced mucus layer and defects in TJ proteins together lead to an increased intestinal permeability ('leaky gut'), resulting in continuous translocation of microbial products from the lumen into the circulation. This leads to the sustained release of pro-inflammatory factors, which in turn trigger local and systemic inflammation (inflammaging). The dysbiotic microbiome further influences the immune system through microbial signaling, accompanied by immunosenescence. Reduced production of SIgA by plasma cells decreases the ability of the mucosal barrier to prevent microbial penetration. Moreover, defects in immune cells, such as defects in Paneth cells that subsequently result in a reduced secretion of α-defensins, lead to a diminished ability to mount an adequate mucosal and systemic immune response. In addition, the excessive bacterial sensing PRR responses (e.g., NOD2, TLRs) and antimicrobial pathways may exacerbate the chronic local and systemic inflammation. MAMPs, microbe-associated molecular patterns; MDP, muramyl dipeptide; MyD88, myeloid differentiation factor 88; PAMPs, pathogen-associated molecular patterns; PRR, pattern recognition receptors; SCFAs, short-chain fatty acids; SIgA, secretory Immunoglobulin A; TLRs, Toll-like receptors; TJs, tight junctions. Blue arrow: increase; Red arrow: decrease. The diagram was created with BioRender.com.

Contribution of other factors to IBD pathogenesis in the elderly

Aging is an extremely complex, multifactorial process encompassing a wide spectrum of factors that contribute to diminished function and increased risk of morbidity and mortality. In

addition to immunosenescence, inflammaging and the aging microbiome, other variables may also predispose to elderly-onset IBD including epigenetic modifications, glycosylation, and environmental exposures.

Emerging evidence from cohort studies of the elderly suggests that age-associated changes in epigenetic signatures may contribute to inflammaging and immunosenescence, and hence could be associated with aging-related pathologies. Epigenetic and transcriptomic analyses have linked aging-related changes in DNA methylation at cytosine-phospho-guanine (CpG) sites with circulating levels of inflammaging biomarkers, such as IL-6[241], C-reactive protein (CRP)[242], TNF, IL-8 or IL-10[243]. Epigenetic mechanisms also influence immunosenescence by manipulating the plasticity of immune cells during the aging process[244]. Likewise, altered epigenetic methylation patterns of IBD-associated genes have been observed in blood and tissue samples from IBD patients[245-248], in particular genes involved in inflammation and immune response, such as *α-defensin 5* (*DEFA5*) and *TNF*[246] which are implicated in IBD pathogenesis. In addition, there is evidence that IBD patients have dysregulated miRNA levels[249-251], and miRNAs may influence specific IBD characteristics, such as the loss of barrier integrity and dysregulation of the immune system[252-255], implying that therapeutics based on miRNAs may be beneficial to patients[256].

Glycosylation, one of the most common post-translational modifications of proteins, also undergoes profound changes associated with aging, cancer and inflammatory conditions[257]. *N*-glycome has been found to be closely associated with the clinical characterization of IBD, including disease localization, activity, and response to therapy[258,259], and may therefore play a role in disease pathophysiology. In CD and UC patients, a wide range of *N*-glycosylation patterns in plasma differ from those found in healthy controls, including fucosylation, bisection, galactosylation, and sialylation[258]. Moreover, the intestinal mucus of patients with IBD is characterized by decreased glycosylation levels and impaired mucin synthesis, resulting in barrier dysfunction[260]. Also, changes in the glycosylation of IgG antibodies have been associated with IBD[259,261]. Specifically, a decrease in IgG galactosylation and sialylation in IBD has been linked to a more pro-inflammatory antibody-mediated immune response and advanced disease severity[259,261]. Interestingly this change in IgG glycosylation also occurs with aging, shifting towards a pro-inflammatory glycotype and potentially contributing to inflammaging[262-264]. Thus, the IgG glycopattern and total glycosylation patterns in the elderly may predispose to the development of inflammatory diseases such as IBD.

Lastly, a variety of other influences may add to the complexity of understanding the pathogenesis of elderly-onset IBD. Smoking and smoking cessation[265,266], dietary pattern and nutritional intake[267-269], and vascular endothelial dysfunction[270], as well as environmental triggers such as air pollution[271,272], antibiotics[273], infections/vaccinations[274], and non-steroidal anti-inflammatory drugs (NSAIDs)[275], may contribute to dysbiosis and aberrant immune responses in the elderly. In addition, over 240 genes have been linked with IBD susceptibility[276,277], including those involved in bacteria-sensing (e.g., *NOD2*), the autophagy pathway for microbe clearance (e.g., *ATG16L1, IRGM,* and *LRRK2),* epithelial barrier function (e.g., *ECM1),* innate and adaptive immunity regulation (e.g., *IL23R* and *IL10*), and integrity of the mucus layer (*MUC2*); however, genetic predisposition is less likely to be a major contributor to elderly-onset IBD as compared to early-onset IBD[2].

Summary and future perspectives

This is the first review which has theorized potential mechanisms for the pathogenesis of elderly-onset IBD. There is mechanistic evidence that inflammaging, immune remodelling and alterations in the gut microbiota with aging may lead to an unyielding cycle that contributes to elderly-onset IBD. Admittedly, our knowledge in this nascent field is limited, and many unknowns remain regarding the complicated crosstalk between aging and the gut-microbiome-immune axis that results in either healthy aging or IBD in advanced age. Although clear differences have been demonstrated in both the systemic and mucosal immune systems as well as the gut microbiome between the young and elderly, the impact of these changes on the development of IBD has yet to be explored. Irrespective of the age of onset, aberrant immune responses appear to be crucial to the development of IBD, and while in pediatric-onset IBD this is driven primarily by genetics, in elderly-onset IBD we propose that the immunologic changes arise primarily from immunosenescence and inflammaging. It is imperative to bridge the knowledge gap between pediatric-onset, adult-onset and elderly-onset IBD regarding the different risk factors and pathophysiological mechanisms at play. For this to be achieved, future longitudinal studies across various geographies and nationalities should utilize multi-omics platforms for high-throughput profiling on humans[202,278,279], integrating multiple layers of data on immune modifications, gut microbial composition and function, environmental exposures, genetics, epigenetics, and clinical phenotype. By leveraging various omics signatures[280] together with humanized gnotobiotic rodent models that allow functional validation, we can

obtain multidimensional insights into the molecular pathways and risk factors associated with elderly-onset IBD.

Furthermore, upon better understanding the pathogenesis of elderly-onset IBD, pharmacologic treatments based on the advances in molecular pathways involved in the reciprocal interactions between immunosenescence and the aging microbiome, such as those discussed in this review, may help personalize therapeutic options. Non-biologic or small molecule therapies including microbiota-targeted dietary and probiotic interventions[190,267,281], FMT[281], metabolite-based treatments[282], microbial engineering[283], epigenetic reprogramming[284-287] or even senolytic drugs[288] are areas that warrant further investigation. There are also promising prospects for developing aging-driven biomarkers as potential predictors of disease or prognosticators of suboptimal clinical outcomes. Though elderly-onset IBD patients comprise a niche population within IBD, obtaining a better understanding of their disease pathogenesis should prove valuable for improving the care for all elderly IBD patients.

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Conflicts of Interest

The authors declare no competing interests.

Author contributions

All authors contributed to the conceptualization, writing, preparation of figures, and review and editing of the manuscript.

Data Availability Statement

No data were analysed in this work.

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