Review

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The inflammation-aging axis: Shared and distinct mechanisms in physiological gut aging and IBD-associated accelerated gut aging

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SUMMARY: Inflammatory bowel disease (IBD) and physiological gut aging present with overlapping clinical features, including impaired barrier functioning, decreased nutrient absorption, and intestinal frailty. Emerging evidence indicates that even young IBD patients can exhibit gut phenotypes akin to those seen with aging. However, the two processes differ substantially in their underlying mechanisms. Gut aging is characterized by low-grade, chronic inflammation and gradual cellular senescence, whereas IBD involves persistent immune activation, cyclical tissue damage, and accelerated degenerative changes. This review systematically contrasts physiological gut aging and IBD-associated accelerated gut aging across several dimensions: cellular senescence and programmed cell death, immune cell remodeling, alterations in gut microbiota, changes in mesenteric adipose tissue, and the evolving role of the appendix. By integrating current advances in basic and translational research, this article highlights both the shared and distinct pathways driving gut dysfunction in aging and IBD, and underscores the importance of early recognition and targeted intervention for premature gut aging in clinical practice.

Keywords: gut aging, inflammatory bowel disease, cellular senescence, immune dysregulation, intestinal barrier

1. Introduction

As modern medicine has continued to advance, people's life expectancy has been increasing, and the gradual aging of various organs has brought about irreversible physiological changes (*1,2*). When the aging body cannot adapt to environmental changes, the excessive physiological burden may induce the onset and progression of diseases (*3*). Intestinal aging is a fundamental manifestation of organismal senescence. At the cellular and molecular levels, the aged gut epithelium undergoes structural remodeling, characterized by a reduced number of goblet cells, decreased expression of tight junction proteins, increased barrier permeability, and the maintenance of a chronic low-grade inflammatory microenvironment (*4-7*). Clinically, these alterations manifest as impaired nutrient absorption and intestinal dysmotility in the elderly population, highlighting the gut as a critical organ system vulnerable to aging (*8*).

Intriguingly, similar alterations are increasingly recognized in inflammatory bowel disease (IBD). Even in young patients and during clinical remission, impaired epithelial stem cell function, incomplete barrier repair, and sustained immune activation can be observed (*9-11*). Functionally, IBD patients continue to experience malabsorption, nutritional deficiencies, and delayed intestinal transit despite symptomatic remission (*12-14*). These parallels suggest that IBD represents a state of premature gut aging accelerated by chronic inflammation.

Mechanistically, both physiological gut aging and IBD involve epithelial stem cell exhaustion, immune senescence, and microbial dysbiosis. These converging processes support the concept of an "inflamm-aging axis," whereby chronic inflammation accelerates intestinal senescence and contributes to disease progression (*15,16*). Therefore, viewing IBD as "accelerated gut aging" may help emphasize the accelerated degenerative features of its disease course and provide a theoretical basis for introducing anti-aging interventions into treatment strategies (*17,18*).

Despite these similarities, existing reviews mainly emphasize inflammatory mechanisms in IBD and rarely provide a systematic comparison with physiological aging. To fill this gap, the present review offers the first multidimensional comparison of IBD-associated premature gut aging and physiological intestinal aging. By integrating evidence from cellular mechanisms, barrier functioning, immune remodeling, and clinical phenotypes, we aim to introduce the concept of the inflamm-aging axis and highlight its translational

potential in diagnosis and therapy.

2. Definition and basic characteristics of gut aging

Gut aging is an inevitable part of the organismal aging process and is primarily characterized by the gradual deterioration of cellular, tissue, and systemic functions within the intestine (*19*). Cellular senescence is one of the core mechanisms of gut aging, manifesting as the reduced proliferative capacity of epithelial cells, the accumulation of DNA damage, and the release of pro-inflammatory factors known as the senescence-associated secretory phenotype (SASP), all of which further contribute to a localized inflammatory state (*20-22*). In addition, increased oxidative stress and mitochondrial dysfunction lead to a redox imbalance and accelerate the degeneration of intestinal tissues (*23,24*). In addition, gut barrier dysfunction—such as decreased expression of tight junction proteins—renders the intestine more susceptible to invasion by external pathogens, further hastening the aging process (*25,26*). Gut microbiota dysbiosis is another key feature of gut aging, manifested as a reduction in beneficial bacteria, an increase in harmful bacteria, and abnormal levels of microbial metabolites such as short-chain fatty acids (SCFAs) (*27-29*). Finally, the impaired regenerative capacity of crypt stem cells (*30*), the decreased absorptive function of intestinal villi (*31*), progressive degeneration of the enteric nervous system (*6*), and disturbances in glucose and lipid metabolism within the gut and mesenteric fat (*32*) may all contribute, to varying degrees, to the progression of gut aging. These mechanisms do not occur in isolation; rather, their synergistic effects shape the biological changes that occur during gut aging. The multidimensional mechanisms of gut aging—including oxidative stress, chronic low-grade inflammation, stem cell exhaustion, barrier dysfunction, and microbial dysbiosis—are summarized in Figure 1, which provides an integrated overview of how these factors collectively impair intestinal homeostasis.

2.1. Active *vs.* passive patterns of immune responses

The intestinal immune system undergoes significant changes during aging, which are mainly characterized by low-grade chronic inflammation (inflammaging) and progressive immune dysfunction (immunosenescence) (*33*). During human aging, the overall number of various immune cells decreases to varying degrees, but some cell subsets increase with age, such as memory B cells, which become more abundant and exhibit increased production of pro-inflammatory cytokines (such as IL-1, IL-6, and TNF-α) (*34*). The activity of certain immune cells also declines with aging; for example, reduced dendritic cell activity weakens antigen-presenting capacity, resulting in diminished immune surveillance (*6,35*). Sustained aging leads to decreased expression of the transcription factor FoxO3 and drives macrophage polarization from the anti-inflammatory 'M2' phenotype to the pro-inflammatory 'M1' phenotype (*6*), resulting in reduced efficiency of clearing senescent cells (*36*), while phenotypic changes in muscularis macrophages may trigger disturbances in intestinal motility (*37*). In the intestines of aged mice, Dlc1+ Spock1+ intestinal macrophages decrease significantly, while Colq+ macrophages expand (*38*). Aging also reduces the deformability of T cells, leading to diminished migratory capacity (*39*). In addition, the reduction in regulatory T cells (Tregs) and the occurrence of abnormal T cell-driven cytokine and cytotoxic responses progressively impair the inhibition of pro-inflammatory responses, resulting in a mild but persistent inflammatory state in the local intestine (*40,41*).

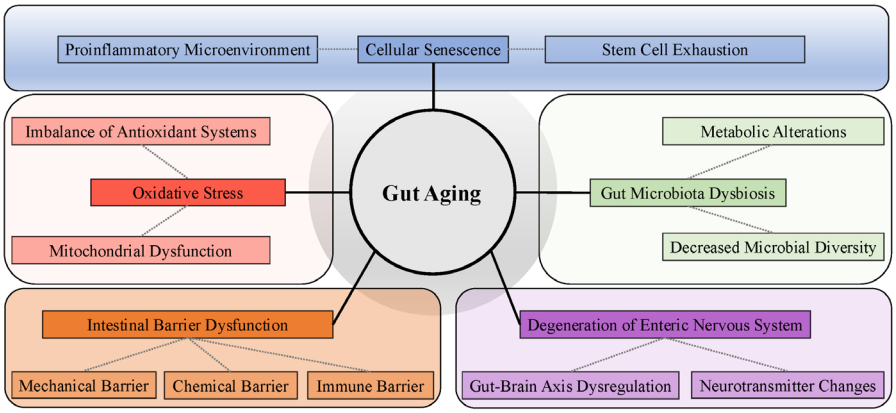

Figure 1. Multidimensional mechanisms underlying gut aging. This diagram summarizes the major pathological processes involved in gut aging, including oxidative stress driven by mitochondrial dysfunction and an antioxidant system imbalance, a chronic proinflammatory microenvironment, stem cell exhaustion, cellular senescence, and gut microbiota dysbiosis with decreased microbial diversity and metabolic alterations. Gut aging is also characterized by progressive intestinal barrier dysfunction affecting mechanical, chemical, and immune barriers and degeneration of the enteric nervous system, leading to gut-brain axis dysregulation and neurotransmitter changes. These interconnected mechanisms collectively contribute to impaired gut homeostasis and age-related vulnerability to gastrointestinal disorders.

This is accompanied by a weakening of the intestinal immune barrier, and such immune dysregulation not only exacerbates microbial imbalance but also facilitates invasion by external pathogens (*42*). Single-cell analyses show that in the intestines of aged mice, CD4+ naïve T cells decrease with age—a trend consistent with other organs—whereas the abundance of CD8+ T cells increases, mainly in the form of the CD8+ Gzmb+ T cell subset, uniquely in the gut, suggesting that the aging intestine possesses a distinct immune environment (*38*). Alongside age-related T cell expansion, various B cell and plasma cell subsets also expand significantly during gut aging. Notably, there is a marked increase in Mki67+ Mybl1+ germinal center B cells in the aging gut. IgA+ plasma cells and memory B cell subsets highly expressing Fcgbp are abundantly clustered in the aged intestinal mucosa, maintaining mucosal immune function (*38*). Although innate lymphoid cells have no significant regulatory effect on the aging process, marked enrichment of ILC3s can still be observed in the aging gut (*38*). Immune disorders linked to aging may also cause the translocation of intestinal bacteria, bacterial metabolites, and inflammatory mediators into mesenteric fat and even to distant organs *via* the systemic circulation (*43*). Due to age-related gut aging, a defective immune system accelerates the accumulation of unresolved inflammation in the intestine; however, this is not entirely irreversible. Time-restricted eating (TRE) can increase the abundance of anti-inflammatory bacteria and probiotics in the gut, elevate the proportion of Treg cells, and upregulate anti-aging serum metabolites, helping to reverse the aging state of the gut (*44*). A reasonable diet and eating habits can improve the inflammaging state associated with gut aging and even further reverse the decline of the immune system (*45,46*).

In contrast, intestinal immune changes in IBD are characterized by intense immune activation alternating with chronic inflammation, and these changes are difficult to reverse (*47*). Compared to gut aging, macrophages in the intestines of IBD patients are excessively activated, with significant increases in both M1 and M2 macrophage subsets, and widely infiltrate the tissue. An elevated M1/M2 macrophage ratio is associated with disease activity (*48,49*). Pro-inflammatory cell populations dominated by Th1 and Th17 cells are abnormally active in IBD patients, accompanied by high levels of pro-inflammatory cytokines such as IL-17 and IFN-γ (*50*). The proportion of Treg cells decreases significantly in IBD, and an increased Th17/Treg ratio predicts more severe colitis (*51,52*). This pathological hyperactivation of the immune system leads to severe damage to the intestinal barrier and massive colonization by pathogenic bacteria, resulting in a vicious cycle of inflammation, tissue destruction, and immune activation. In the early stages of IBD, there is a dysregulation of mucosal ILCs, manifesting as a reduction in ILC3s (*53*) and an increase in ILC2s (*54*). These lymphocyte changes are unable to suppress the chronic intestinal inflammation mediated by IL-23 in IBD (*55*). Activated dendritic cells accelerate antigen presentation, leading to the recruitment of large numbers of neutrophils to sites of intestinal injury (*56*). In the later stages of IBD, immunosenescence-like changes can also occur, with progressive decline in immune cell function and long-term damage caused by immune remodeling (*33*). Unlike the gradual immunosenescence of physiological gut aging, which mainly manifests as impaired absorption, immunosenescence in IBD progresses more rapidly, is accompanied by stronger inflammation and a more complex molecular network, and often leads to a restricted diet and more severe nutritional deficiency than in the elderly. Nutrition is a key determinant of immune function and the gut microbiota; micronutrients such as vitamins C, D, and E, as well as zinc and selenium, play important roles in supporting the function of many types of immune cells (*57*).

Although there are differences in their manifestations, there are still certain similarities in the fundamental features of the immune imbalance between physiological gut aging and IBD-associated accelerated gut aging. Both gut aging and IBD are characterized by disruption of immune homeostasis, such as the reduced function of Tregs, overexpression of pro-inflammatory factors, and weakening of the intestinal immune barrier. However, gut aging is more prone to low-grade chronic inflammation, mainly driven by immune cell exhaustion, stem cell decline, and endogenous metabolic alterations, and can be defined as "passive" immunosenescence. In contrast, IBD predominantly involves abnormally active pro-inflammatory cell populations, an excessively activated immune system, and high-grade inflammation driven by exogenous microbial dysbiosis, which can be regarded as "active" immunosenescence. Table 1 summarizes the phenotypic and functional changes in key intestinal immune cell subsets during physiological gut aging and IBD-associated accelerated gut aging, highlighting their distinct and overlapping roles. The immunological characteristics of both conditions not only provide important contrasts for disease research but also offer new insights for the development of specific therapeutic targets for different pathological states.

2.2. Similarities and differences in cellular mechanisms

2.2.1. Cell death

In both the aging gut and the IBD gut, cellular mechanisms are central drivers of tissue degeneration and disease progression. Telomere shortening and DNA damage serve as initiating factors. Oxidative stress and mitochondrial dysfunction are driving forces. In addition, restricted clearance of senescent cells and persistent SASP act as key maintenance factors. Cellular senescence is regarded as one of the hallmarks of aging and is defined as stable growth arrest mainly mediated by cell cycle

Table 1. Immune cell alterations in physiological gut aging *vs.* IBD-associated accelerated gut aging

Immune Cell	Subtype	Physiological Gut Aging	IBD-associated Accelerated Gut Aging	*Ref.*
T cell	Treg	↑ Quantity ↑ Proportion ↑ Suppression	↓ Stability or dysfunction ↓ Regulatory capacity	(*169,170*)
	CD4+	↓ Slight decrease ↓ Tends to result in functional exhaustion	↑ Th1/Th17 bias ↑ Activation	(*38,171*)
	CD8+	↓ Quantity ↑ Suppressive phenotype e.g., PD-1+	↑ Cytotoxicity ↑ Inflammatory function	(*38,147*)
B cell	-	↓ Antibody production ↓ Repertoire diversity	↑ IgA hypersecretion Altered Breg ratio	(*34,172*)
Macrophage	M1	↑ Mild activation ↑ Inflammatory signals	↑ Strong polarization ↑ Proinflammatory cytokines	(*6,36,38*)
	M2	↑ Reparative function	↓ Imbalance or suppressive dysfunction	(*36,38*)
	LLMs	↑ Number ↑ Anti-inflammatory bias	Unclear function Limited evidence	(*173,174*)
NK cell	-	↓ Total number ↓ Killing capacity	↑ Total number ↑ Pro-inflammatory activity	(*10,147*)
Dendritic cell	-	↓ Antigen presentation ↑ Tolerance induction	↑ CD83/CD86 expression ↑ Activation markers	(*6,35,175*)
Neutrophil	-	↓ Chemotaxis ↓ Inflammatory mediator release	↑ Aggregation ↑ NETs/ROS production	(*88,176*)
Innate Lymphoid Cells	ILC3	↓ Abundance ↓ IL-22 secretion ↓ Barrier support	↓ Number ↑ Aberrant activation ↑ ILC1-like shift	(*69*)

regulators such as p53, p21, and p16 (*58*). Under normal conditions, the clearance of senescent cells is often accompanied by the activation of programmed cell death (PCD) mechanisms, such as apoptosis and autophagy. In gut aging, however, dysregulation of intrinsic PCD can lead to restricted removal of senescent cells, and excessive accumulation of senescent cells further accelerates gut aging (*59*). Under physiological conditions, the shedding and renewal of intestinal epithelial cells (IECs) is closely related to the balance between cellular senescence and apoptosis. In the context of gut aging, genes regulating apoptosis are downregulated, while those regulating senescence are upregulated, indicating that senescent cells may not directly undergo apoptosis, but rather enter a SASP state to maintain chronic intestinal inflammation (*60*). Elevated levels of autophagy can induce cell death, whereas insufficient autophagy may trigger cellular senescence (*61*). The lysosome is the key regulator that maintains the balance between cellular senescence and cell death. Autophagic impairment due to lysosomal dysfunction is an important feature of oxidative stress-induced senescence (*62*). Senescent cells exhibit lysosomal amplification and dysfunction (*63*), and the age-dependent decline of lysosome processing and adaptation systems (LYPAS) may inevitably trigger senescence and/or cell death (*64*). In addition, senescent T cells in the gut of elderly individuals can activate the PAR1 signaling pathway, resulting in increased apoptosis of colonic epithelial cells, and also activate the PAR2 pathway, leading to the release of IL-8 by IECs and maintenance of a chronic inflammatory microenvironment (*65*).

Excessive activation of regulated cell death is a hallmark of IBD (*66*). Figure 2 integrates current evidence, highlighting the involvement of multiple modalities—including apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagy—in IBD-associated intestinal injury. These interconnected pathways exacerbate epithelial barrier disruption, sustain chronic inflammation, and drive mucosal immune dysregulation, thereby linking cellular dysfunction with disease progression. Under normal circumstances, X-linked inhibitor of apoptosis protein (XIAP) suppresses TNF-driven intestinal inflammation and dysbiosis by promoting the innate immune responses of Paneth cells and dendritic cells (*67*). In IBD, an XIAP deficiency leads to increased expression of caspase-8, which not only activates extrinsic apoptosis but also promotes GSDMD processing and NLRP3 activation, thereby inducing pyroptosis (*68*). TNF is a key mediator of intestinal inflammation in IBD, and various TNF inhibitors are mainstream therapies for IBD (*69*). TNF drives cell death in the intestines of IBD patients through tumor necrosis factor receptor 1 (TNFR1)-mediated

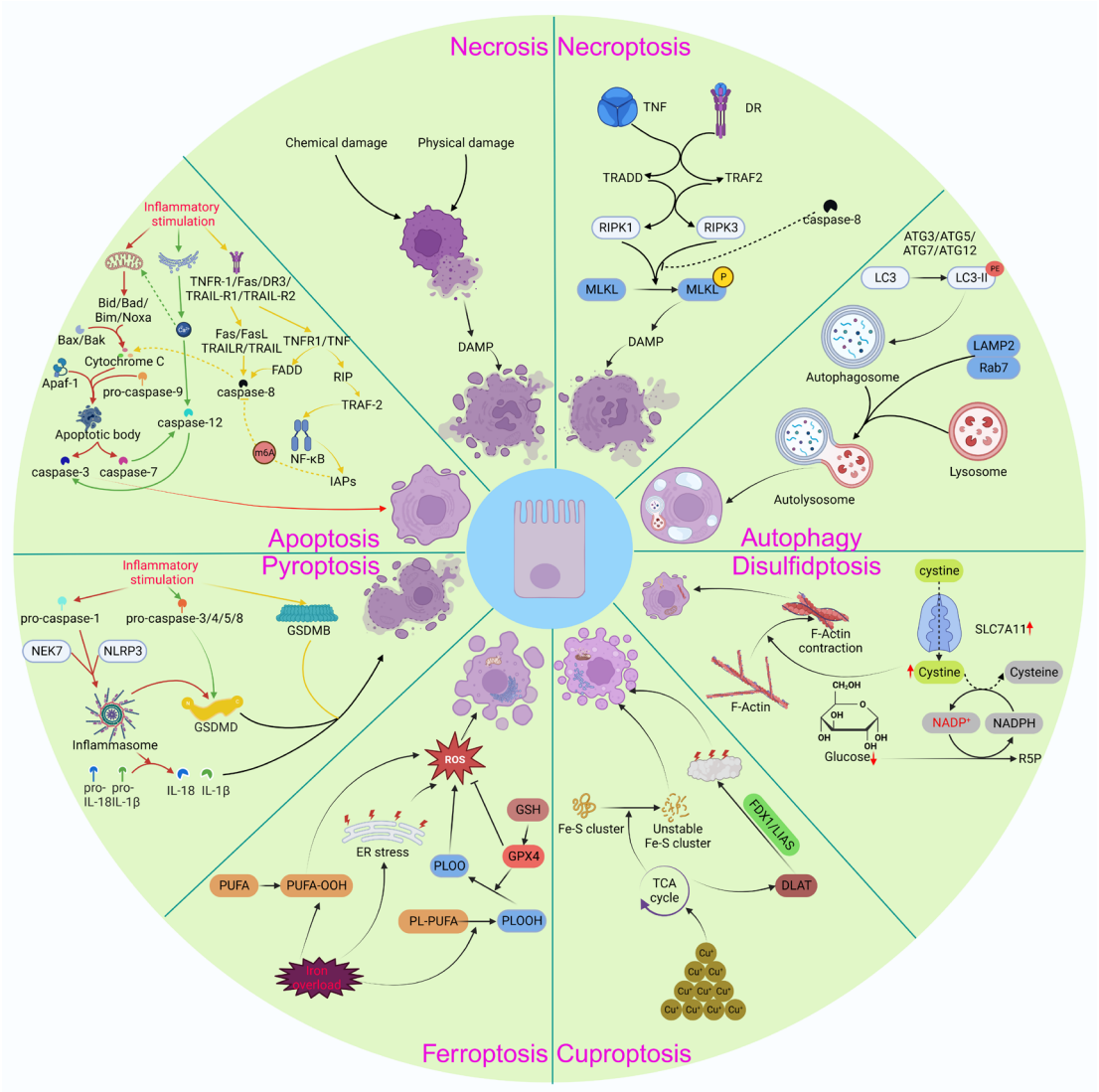

Figure 2. Roles and pathogenic mechanisms of various regulated cell death modalities in inflammatory bowel disease (IBD). This schematic illustrates the involvement and crosstalk of major forms of RCD — including apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagy — in the pathogenesis of IBD. Key molecular pathways, such as caspase-dependent apoptosis, RIPK3/MLKL-mediated necroptosis, inflammasome- and gasdermin D–dependent pyroptosis, ferroptosis characterized by iron-driven lipid peroxidation, and impaired autophagy, contribute to epithelial barrier disruption, chronic inflammation, and mucosal immune dysregulation. Dysregulated cell death pathways may trigger excessive epithelial cell loss, release of damage-associated molecular patterns (DAMPs), and perpetuation of intestinal inflammation, thereby promoting disease progression in both ulcerative colitis and Crohn's disease.

activation of multiple signaling pathways; it can induce caspase-8- and caspase-3-mediated apoptosis as well as RIPK3-dependent necroptosis (*70,71*), and can also activate the NF-κB pathway, which promotes the binding of NEK7 to the NLRP3 inflammasome, leading to pyroptosis (*72*). Moreover, aberrant activation of the TNF/NF-κB signaling pathway in IBD not only regulates lipid peroxidation and GPX4 activity to induce ferroptosis (*73*) but also affects cellular metabolism and copper ion homeostasis to trigger cuproptosis (*74*) and can further enhance oxidative stress and metabolic disorders to promote disulfidptosis (*75*). In summary, unlike cell death in gut aging, cell death mechanisms in IBD patients are not simply single pathological processes but rather display diverse and interacting patterns—such as alternating activation of apoptotic and necrotic pathways or combined activation of autophagy and apoptosis—with distinct differences in the activation strength of common cell death modalities between IBD and gut aging (Figure 3). The diversity and frequent alternation of these mechanisms exacerbate immune system instability and make intestinal cells more susceptible to damage and clearance. Notably, the excessive activation of various forms of regulated cell death in the IBD gut does not appear to be aimed at clearing senescent cells, but rather represents an immune response by the body to cope with recurrent chronic inflammation.

2.2.2. Mitochondria

The SASP is a characteristic feature of cellular senescence, and the release of mitochondrial double-stranded RNA

(mt-dsRNA) into the cytosol is a common phenomenon in senescent cells. The mt-dsRNA/MAVS/MFN1 axis is a key driver of the SASP (*76*). Mitochondrial dysfunction inhibits the production of chylomicrons and the transport of dietary lipids in IECs, thereby impairing the gut's ability to absorb lipids (*77*). The pro-senescent effects of mitochondria are mainly mediated by inflammation and oxidative stress; the reactive oxygen species (ROS) they generate induce DNA damage response (DDR), accelerate telomere shortening, and trigger signaling networks that maintain the senescent phenotype, thus promoting the onset of senescence (*78*). Of course, the human body also has intrinsic anti-aging mechanisms — for example, Prohibitin 1 responds to mitochondrial ROS under oxidative stress by promoting Nix localization to mitochondria, thereby initiating mitophagy (*79*). These mechanisms influence gut health by promoting the decline of cellular function and weakening tissue functionality. Oxidative stress and mitochondrial dysfunction play critical roles in this process, leading to the accumulation of DNA damage, telomere shortening, and instability of cellular signaling pathways, thus exacerbating cellular senescence and the activation of PCD mechanisms.

Unlike the general process of gut aging, the loss of mitophagy in IBD not only disrupts the homeostasis of epithelial cells but can also lead to more severe pathological changes, such as Paneth cell dysfunction and mitochondrial accumulation (*79*). Recurrent chronic inflammation in the intestines of IBD patients can cause mitochondrial DNA damage (with mtDNA released extracellularly), activate the cGAS-STING pathway, and trigger innate immune responses, thereby further aggravating inflammation (*80,81*). Aberrant activation of the STING signaling pathway, by affecting mitochondrial stress and mitophagy, contributes to intestinal barrier disruption (*82*). High levels of ROS resulting from mitochondrial dysfunction exacerbate tissue injury in the IBD gut and lead to cell death, such as ferroptosis and necroptosis (*83,84*). Mitochondrial dysfunction in immune cells is also an important driver of inflammation in IBD. Dysregulated mitophagy in macrophages (such as disruption of the PINK1/Parkin pathway) results in excessive ROS production, drives pro-inflammatory responses of M1 macrophages, promotes the secretion of more TNF-α and IL-6, and worsens intestinal tissue damage (*85*). Mitochondrial metabolic disorders in T cells can disrupt immune homeostasis by causing an imbalance between effector T cells (Teff) and Tregs

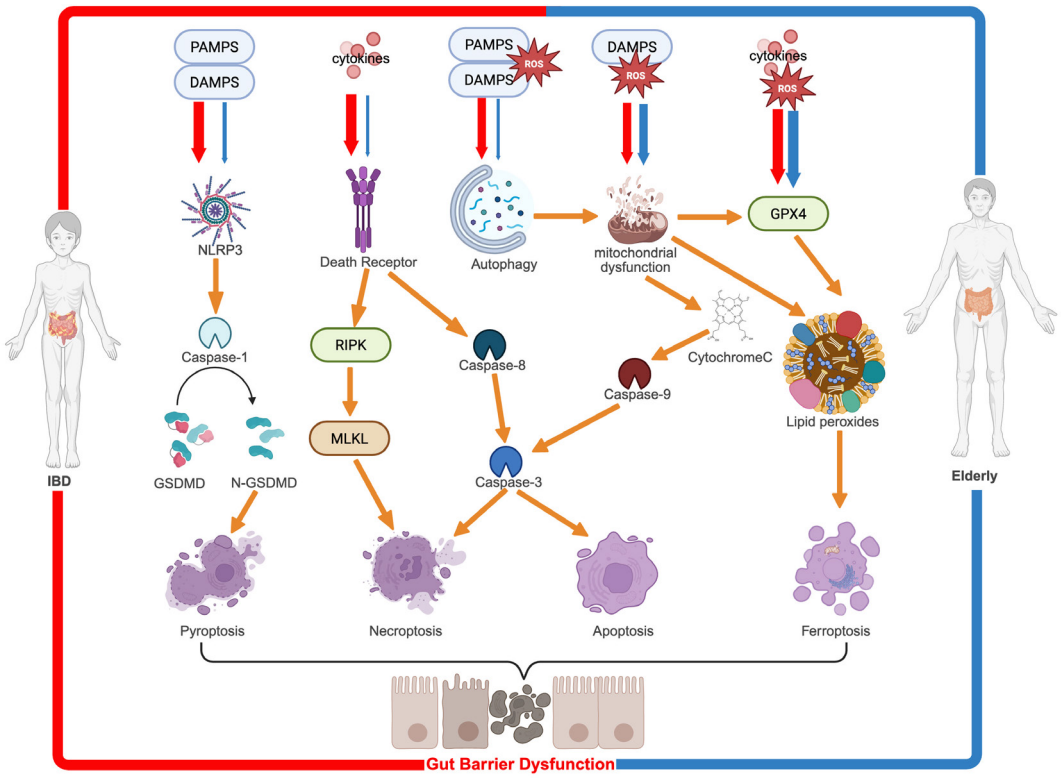

Figure 3. Schematic summary of regulated epithelial cell death pathways in the gut with inflammatory bowel disease (IBD), indicated by red arrows, versus aging, indicated by blue arrows, with arrow thickness indicating relative pathway strength. IBD prominently activates pyroptosis via the inflammasome–caspase-1–gasdermin D axis, promoting inflammation and barrier damage; necroptosis, driven by RIPK and MLKL, contributes to epithelial necrosis and leaky barrier integrity; and ferroptosis, characterized by iron accumulation, ROS-mediated lipid peroxidation, and GPX4 inactivation, plays a pivotal role in chronic IBD progression and mucosal erosion. Aging exacerbates mitochondrial dysfunction and oxidative stress, impairs autophagy/mitophagy, and diminishes GPX4 defense — thus potentiating apoptosis, necroptosis, and especially ferroptosis. The combined result of these distinct and overlapping death processes culminates in epithelial cell loss, tight junction disruption, mucosal thinning, and ultimately gut barrier dysfunction.

(*86,87*). In addition, the large amounts of ROS generated by neutrophils not only directly damage intestinal tissue but also promote cell death (such as ferroptosis and necroptosis) through ROS signaling, further aggravating inflammation (*88*). In addition, mitochondrial dysfunction is also associated with gut microbiota dysbiosis; for example, SCFAs, a class of gut microbial metabolites, can regulate mitochondrial function and thereby modulate cellular metabolism in intestinal epithelial and immune cells (*89*).

2.2.3. Intestinal stem cells (ISCs)

Stem cell exhaustion is a key mechanism in gut aging. As the function of crypt stem cells declines, the regenerative capacity of the tissue is significantly suppressed, impairing the ability of the gut to repair and renew itself; this may be closely related to age-dependent nonlinear DNA methylation (*90*). In the intestines of aged mice, mTORC1 drives ISC senescence through the p38 MAPK-p53 pathway, accelerating villus aging and resulting in defective intestinal nutrient absorption (*31*). The aging state of the intestine alters the structure of the small intestinal crypts and villi as well as crypt cell proliferation. Notum, produced by Paneth cells within the crypts, weakens the regenerative capacity of the aging intestinal epithelium *in vivo* by reducing Wnt activity in stem cells (*91,92*). Single-cell analysis has revealed that marker genes of specific ISC subpopulations in the aged small intestine are associated with negative regulation of the cell cycle and activation of apoptotic signaling pathways, further restricting the gut's repair capacity (*93*).

In IBD, the repeated chronic inflammatory environment has a unique impact on ISC function. Genetic factors, such as polymorphisms in autophagy-related genes (*e.g.*, ATG16L1), together with persistent inflammatory conditions, can lead to mitochondrial autophagy dysfunction in IECs, thereby affecting the homeostasis of ISCs (*79*). Dysregulation of ISC functioning may result in the reduced regenerative capacity of the crypts and trigger severe pathological changes, including Paneth cell dysfunction and cell death. Paneth cell dysfunction further exacerbates ISC depletion, while the interactions between ISCs and immune cells, as well as the pro-inflammatory signals (such as TNF-α and IL-6) they secrete, may further impair the reparative ability of stem cells *via* the inflammatory microenvironment (*94*). In addition, interactions between ISCs and gut microbiota have been found to be critical to ISC functioning. In IBD, the reduction in SCFAs further weakens the metabolic activity of ISCs, limiting their regenerative capacity (*81*).

2.3. Commonalities and divergences in barrier functioning and microbiota

Beyond cellular mechanisms such as cell death and stem cell exhaustion, alterations in the gut barrier and microbiota also represent pivotal points of divergence and convergence between physiological aging and IBD. The intestinal barrier and gut microbiota are the two core factors in maintaining gut health, and both are significantly affected in the pathological states of gut aging and IBD. The aging gut is characterized by a chronic, progressive decline in barrier functioning and dysbiosis, while IBD is marked by recurrent intestinal inflammation, accompanied by barrier damage and microbiota disturbances (*95*). Although the underlying mechanisms in these two conditions differ, there are certain similarities in the interactions between the barrier and the microbiota.

Both gut aging and IBD present with structural and functional damage to the intestinal barrier, resulting in increased intestinal permeability that allows microbes and their metabolic toxins to cross the barrier and trigger systemic inflammatory responses (*96*). In both conditions, there is a reduction in the expression of tight junction proteins (such as decreased levels of claudin and occludin), a decrease in mucus layer thickness, and reduced expression of antimicrobial peptides (such as β-defensins) (*97*). Excessive ROS in both gut aging and IBD directly impair barrier functioning by inducing the apoptosis or necroptosis of epithelial cells (*98,99*). Additionally, dysregulation of autophagy (such as ATG16L1 dysfunction) is also common in both settings, further weakening barrier repair capacity (*79*). Although the phenotypes of barrier dysfunction are similar in both conditions, there are differences in the driving factors of barrier damage and the mechanisms of barrier repair. In gut aging, barrier dysfunction is mainly driven by chronic oxidative stress, telomere shortening, and the decreased regenerative capacity of epithelial cells (*100*). In IBD, chronic inflammation induces the excessive release of pro-inflammatory cytokines, such as IL-17 and TNF-α, which activate the innate immune system of the gut, leading to epithelial injury and a rapid deterioration in barrier functioning (*101*). Dysregulation of intestinal mesenchymal cells further impairs the mechanical barrier by secreting pro-inflammatory cytokines and chemokines (*50*). As oxidative stress persists and the functioning of stem cells declines, this process is further exacerbated—not only affecting the physical and immune functions of the gut barrier but also limiting its self-repair capability. In the aging gut, the slower repair of the barrier is mainly due to the decreased proliferation and differentiation capacity of crypt stem cells (*16*). In IBD, repair may be characterized by immature or abnormal reconstruction due to excessive activation of inflammatory responses and may even lead to fibrosis (*102*).

The bidirectional relationship between barrier dysfunction and a microbiota imbalance forms a "vicious cycle" that jointly drives both gut aging and IBD (*103*). Barrier damage leads to increased translocation of microbes and their metabolic products (such as LPS) into the systemic circulation, triggering immune responses, while dysbiosis further impairs the barrier

by reducing beneficial metabolites (such as SCFAs) and increasing harmful ones (*104*). Both gut aging and IBD are characterized by the reduced diversity of gut microbiota and an increase in pathogenic bacteria (such as Escherichia coli), a dysbiosis that diminishes the protection of barrier functioning by the microbiota while enhancing pro-inflammatory properties (*105*). The patterns of a gut microbiota imbalance differ between the two pathological states: in gut aging, dysbiosis is mainly driven by host factors such as immunosenescence, dietary changes, and reduced gut motility (*106*), whereas in IBD, dysbiosis is usually induced by the inflammatory environment and long-term use of medications such as antibiotics and proton pump inhibitors (*107*). Additionally, in the aging gut, certain commensal bacteria (such as Bacteroides) may increase in abundance but display reduced metabolic capacity (*108*). In contrast, IBD is characterized by the excessive proliferation and colonization of mucosa-associated pathogens, such as adherent-invasive Escherichia coli (*109*). In IBD patients, chronic unhealed mucosal ulceration cannot be effectively repaired, and persistent tissue injury leads to ongoing epithelial damage and a significant reduction in intestinal absorptive function (*110,111*). The decline in absorptive function impairs both nutrient uptake and the elimination of bacterial metabolites, further aggravating the microbial imbalance, increasing the colonization of harmful strains, and reducing beneficial bacteria. In summary, this cycle of barrier weakening and microbiota dysbiosis progresses more slowly and cumulatively in gut aging but is far more intense in the IBD gut. Table 2 presents representative gut microbiota taxa altered in gut aging and IBD, along with their associations with inflammation, cellular senescence, and changes in relative abundance. Beyond cellular pathways, barrier dysfunction, and microbial imbalance, aging and IBD also induce organ-specific changes in the gut. These alterations, exemplified by mesenteric fat and the appendix, highlight how inflamm-aging manifests at the tissue level and extends beyond the mucosal interface.

3. Tissue and organ-specific changes in gut aging and IBD

3.1. Functional differences in mesenteric fat

Mesenteric adipose tissue (MAT) is a unique fat depot surrounding the intestines within the abdominal cavity and can be regarded as a special "organ" that is closely related to gut health, inflammation regulation, and immune responses. As the human body ages, there is an increase in and redistribution of adipose tissue, and NF-κB serves as an important regulatory factor in cellular senescence and the development of SASP within adipose tissue (*112*). Acute and dramatic changes in gene expression in MAT occur only in late life, but certain plasma proteins are highly correlated with gene expression in visceral MAT, including Postn, which is associated with lipid metabolism, and Thrombospondin-4, which promotes synapse formation (*113*). During gut aging, MAT reduces inflammatory responses and protects the intestinal barrier by secreting anti-inflammatory adipokines such as adiponectin (*114*). Decreased insulin sensitivity of adipose tissue may weaken its metabolic regulatory capacity and increase the risk of low-grade chronic inflammation (*115*). In aged MAT, immune cell infiltration increases, with M2 macrophages predominating. As gut aging progresses, however, macrophages gradually shift from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype, which further exacerbates intestinal barrier dysfunction, manifesting as epithelial barrier impairment (*116*). In addition, fibrosis within adipose tissue and reduced local blood microcirculation further weaken its metabolic support (*117*). The latest UK Biobank study found that visceral adipose tissue progressively increases with age, rising by approximately 8.2% per decade in men and 5.3% in women (*118*). In elderly individuals, excessive accumulation of mesenteric fat may represent a potential driver of accelerated intestinal ageing.

Similarly, in IBD, excessive deposition of visceral fat—and particularly mesenteric fat—is commonly observed. Our study found that a higher ratio of visceral to subcutaneous fat (mesenteric fat index, or MFI) predicts an increased likelihood of requiring surgical intervention (*119*). In the early stages of IBD, MAT primarily plays a protective role (*120*). As intestinal barrier functioning

Table 2. Gut microbiota and associated functions in physiological gut aging and IBD-associated accelerated gut aging

Gut Microbiota	Metabolites	Inflammation	Cell Senescence	Abundance in Aging	Abundance in IBD	*Ref.*
Faecalibacterium prausnitzii	Butyrate	↓	↓	↓	↓	(*157,177,178*)
Akkermansia muciniphila	Mucin enzymes	→	↓	↑	↓	(*157,179*)
Roseburia spp.	Butyrate	↓	↓	↓	↓	(*180,181*)
Bilophila wadsworthia	Secondary bile acids	↑	↑	↑	↑	(*182,183*)
Bacteroides fragilis	Polysaccharides	↑	→	→	↑	(*184,185*)
Lactobacillus spp.	Lactate	↓	↓	↓	↓	(*186,187*)
Escherichia coli	Lipopolysaccharide	↑	↑	→	↑	(*178,188*)
Methanobrevibacter smithii	Methane	→	→	↑	→	(*189,190*)
Parabacteroides spp.	SCFAs	↓	↓	↓	↓	(*178,191*)

Note: The symbols ↑, ↓, and → respectively indicate an increase, a decrease, or no consistent or significant change in functional effects or abundance based on current evidence. Abbreviations: SCFAs, Short-chain fatty acids; ROS, Reactive oxygen species; IEC, Intestinal epithelial cell.

declines, adipocytes in MAT proliferate and secrete anti-inflammatory factors (such as adiponectin) to alleviate inflammation. Adipokines like adiponectin can inhibit the release of pro-inflammatory cytokines (such as TNF-α) and enhance the immune barrier functioning of the gut (*114*). Adipose tissue can also isolate damaged intestinal segments to reduce the spread of bacteria and their toxins, and proliferating adipocytes form "creeping fat" that covers the injured intestinal wall, providing a physical barrier (*121*). As IBD progresses, the role of MAT shifts from protective to pathological. An increasing mesenteric-to-abdominal fat ratio is associated with a worse prognosis in IBD (*122*). Persistent inflammation leads to further increases in intestinal permeability, resulting in the translocation of large numbers of intestinal bacteria into the MAT and excessive activation of the immune system (macrophages and T cells), which in turn promotes adipose tissue hyperplasia (*123*). Creeping fat secretes pro-inflammatory factors (such as IL-6 and CCL2) and fibrotic signaling molecules (such as TGF-β and fibroblast growth factors), thereby aggravating local inflammation, leading to intestinal fibrosis and strictures and ultimately causing intestinal obstruction (*124,125*). Additionally, the MAT exhibits insulin resistance and dysregulated secretion of adipokines (such as leptin and adiponectin) in IBD patients. These metabolic abnormalities may indirectly impair intestinal barrier functioning by enhancing immune cell activity (*126*). In summary, functioning of the MAT differs markedly between the aging gut and IBD: it can serve as a protector of the barrier but may also exacerbate pathological changes through abnormal adipose tissue proliferation.

3.2. Functional differences in the appendix

As a special immune organ within the gut, the appendix plays a potentially important role in both gut aging and IBD. First, the appendix is rich in gut-associated lymphoid tissue, which supports the differentiation and activation of immune cells and regulates the mucosal immune balance in the intestine (*127*). The appendix also provides a stable "refuge" for gut microbes, allowing the restoration of the intestinal ecosystem by releasing healthy microbiota, especially after disruptions such as antibiotic use (*128*). During gut aging, the reduction in lymphoid tissue in the appendix leads to a gradual weakening of its role in immune regulation of the gut (*129*). This immunosenescence-related change may decrease the appendix's support for gut microbiota homeostasis and increase the risk of a microbial imbalance. The levels of anti-inflammatory cytokines (such as IL-10) and Tregs in the appendix may also decrease, leading to the aggravation of chronic low-grade inflammation (*130*). The appendix's role as a sanctuary for commensal bacteria may diminish with aging, particularly as overall microbial diversity in the gut declines, further exacerbating dysbiosis (*131*).

The appendix has a dual role in IBD: in the early stages of IBD, it can assist in restoring gut microbial diversity and alleviate inflammation by secreting anti-inflammatory cytokines such as IL-10 (*132*). However, repeated episodes of IBD may lead to excessive activation of immune responses in the appendix, resulting in inflammatory cascades (*133*). Large numbers of Th17 cells in the appendix can aggravate intestinal inflammation by secreting pro-inflammatory cytokines such as IL-17 (*134,135*). Mendelian randomization studies have shown that simple appendicitis does not increase the risk of IBD, and IBD is associated with a reduced risk of simple appendicitis (*136*). Real-world studies indicate that appendectomy in adulthood may be associated with an increased risk of developing IBD, suggesting that the appendix has a protective role (*133*). Conversely, a nationwide cohort study from Sweden found that appendectomy due to appendicitis during adolescence was associated with a reduced risk of adult IBD, further indicating the dual role of the appendix (*137*). Crohn's disease (CD) patients who had undergone an appendectomy tend to have higher postoperative recurrence rates, which may be related to the higher incidence of penetrating disease (*138*). Unlike with CD, appendectomy has a positive effect on the clinical course of ulcerative colitis (UC), but it may increase the risk of colorectal tumors, suggesting that the appendix may play a greater role in pro-inflammatory responses and cancer linked to chronic inflammation in UC (*139*). The roles of the appendix differ in CD and UC, which can be attributed to the clinical characteristics of these diseases. In CD, intestinal inflammation is characterized by segmental, skip lesions, often involving the terminal ileum and the appendix; appendectomy may disrupt gut immune homeostasis and trigger systemic inflammation (*138*). In UC, inflammation is continuously distributed along the colonic mucosa, and appendectomy may reduce the source of pro-inflammatory factors from distal intestinal sites (such as the ileum and appendix), thereby providing some relief from colonic inflammation (*140*). In individuals with a higher genetic susceptibility, appendectomy may affect immune and microbial stability in the gut, potentially triggering CD (*141*). In UC, genetic background may result in a more pronounced pro-inflammatory role of the appendix, so appendectomy can protect against the risk of UC (*142*). Taken together, organ-specific changes such as those occurring in mesenteric fat and the appendix not only reflect premature aging features in IBD but also create a pro-inflammatory microenvironment. These alterations may ultimately converge on tumorigenic pathways, thereby bridging inflamm-aging and the transition to cancer.

4. Inflammation-to-cancer transition

The ultimate outcome of the inflammatory pathological states of gut aging and IBD is not intestinal fibrosis, but

rather malignant transformation of the inflamed tissue (*60*). In the aging gut, carcinogenesis typically results from the gradual accumulation of chronic low-grade inflammation that promotes tumor formation (*143*). Reduced telomerase activity in the aging gut renders cells more susceptible to DNA double-strand breaks and chromosomal instability (*144*). Telomere dysfunction not only mediates the release of various pro-inflammatory cytokines but also enhances tumorigenesis (*145*). In elderly patients with colorectal cancer, significant telomere shortening and dysfunction can be observed at the tumor sites (*146*). Additionally, as age increases, immunosenescence leads to the decreased cytotoxicity of NK cells and CD8+ T cells to tumor cells (*147*). Mitochondrial dysfunction and metabolic disorders also raise ROS levels, exacerbating DNA damage and abnormal cell proliferation (*148*). In summary, telomere dysfunction, immunosenescence, and mitochondrial impairment act synergistically to drive chronic inflammation, DNA damage, and loss of control over cell proliferation, ultimately promoting carcinogenesis in the aging gut.

Colitis-associated cancer (CAC) and sporadic colorectal cancer (sCRC) exhibit significant differences in epidemiology and molecular mechanisms. Epidemiological data show that the risk of CRC in patients with UC is 2%, 8%, and 18% after 10, 20, and 30 years, respectively, while the risk of CRC in patients with CD is about 4-6% after 20 years (*149*). Mechanistically, CAC is mainly driven by chronic inflammation, with sustained activation of the IL-6/STAT3 and NF-κB pathways in the inflammatory environment leading to COX-2 overexpression, inhibition of epithelial cell apoptosis, and the induction of early p53 mutations by ROS and RNS, thereby promoting carcinogenesis (*150*). In contrast, sCRC is primarily driven by an adenoma-carcinoma sequence mediated by APC mutations and is more likely to exhibit MSI-H-related DNA repair defects (*151*).

In clinical practice, patients with IBD-associated cancer often have a poorer prognosis and earlier distant metastasis, which may be related to the enhanced pro-carcinogenic effects of the gut microbiota and the inflammatory microenvironment. Studies have found that Fusobacterium nucleatum is significantly enriched in CAC tissues, and its FadA adhesin promotes epithelial proliferation by activating β-catenin and enhances the expression of genes driving the epithelial-mesenchymal transition (EMT), thereby increasing cancer cell invasiveness (*152,153*). In addition, certain toxic strains of Escherichia coli (pks^+ E. coli) produce colibactin, which can induce DNA breaks and increase the risk of carcinogenesis in IBD patients (*154*). Compared to sCRC, CAC is characterized by the absence of a typical adenoma stage, a high burden of inflammation-mediated mutations, a worse prognosis, and a higher risk of early metastasis, all of which may influence the screening and treatment strategies for IBD-associated cancer (*155*). As shown in Figure 4, IBD-associated colorectal cancer (shown on the left) arises from persistent NF-κB, STAT3, and COX-2 activation, which leads to DNA damage, early TP53 mutations, and rapid tumor progression. In contrast, aging-associated colorectal cancer (shown on the right) follows a slower trajectory characterized by telomere and mitochondrial dysfunction and the classical APC-KRAS-TP53 mutation sequence. This comparison highlights the mechanistic differences between carcinogenesis promoted by inflammation and that associated with aging. These findings underscore the clinical need to translate mechanistic insights into actionable biomarkers for improved disease management.

5. From biomarkers to clinical use

Given the complex interplay between chronic inflammation, aging-related tissue changes, and carcinogenesis, the identification of robust biomarkers has become essential. Gut aging is a natural process, and its diagnosis is based on the gradual decline in intestinal barrier functioning and alterations in cellular mechanisms. Researchers commonly assess gut aging by measuring biomarkers, including tight junction proteins (such as occludin and zonulin), mucus layer thickness, and the expression of antimicrobial peptides (such as β-defensins). Other indicators, such as telomere length, cell cycle assessment, and mitochondrial function assays, are also used to evaluate age-related decline in cellular functioning. Decreased gut microbiota diversity (such as a lower Shannon index) is closely associated with inflamm-aging, and changes in the abundance of specific bacteria — such as reduced levels of anti-inflammatory species like Faecalibacterium prausnitzii and increased abundance of potential pathogens like Eggerthella lenta — can serve as key biomarkers (*156,157*). In addition, measuring microbial metabolites (such as SCFAs) and using ecological indicators (such as the microbiome aging index) to quantify the aging state can provide precise biological evidence for gut aging (*157,158*). Imaging studies can also be used to detect gut aging; for example, intestinal MRI can be used to identify changes in intestinal wall thickness, decreased blood flow, and early signs of fibrosis (*159*). Functional tests, such as stool transit time and nutrient absorption efficiency, are used to assess intestinal physiological function (*160*).

Unlike gut aging, premature intestinal aging in IBD patients is caused by chronic inflammation and immune dysregulation, making its mechanisms more complex. In addition to the methods of detecting gut aging mentioned previously, significantly increased expression of pro-inflammatory cytokines and fecal calprotectin are also specific diagnostic markers for IBD-associated accelerated gut aging. A marked increase in pro-inflammatory bacteria such as adherent-invasive Escherichia coli (AIEC) and Enterococcus spp. also provides valuable guidance for diagnosing accelerated

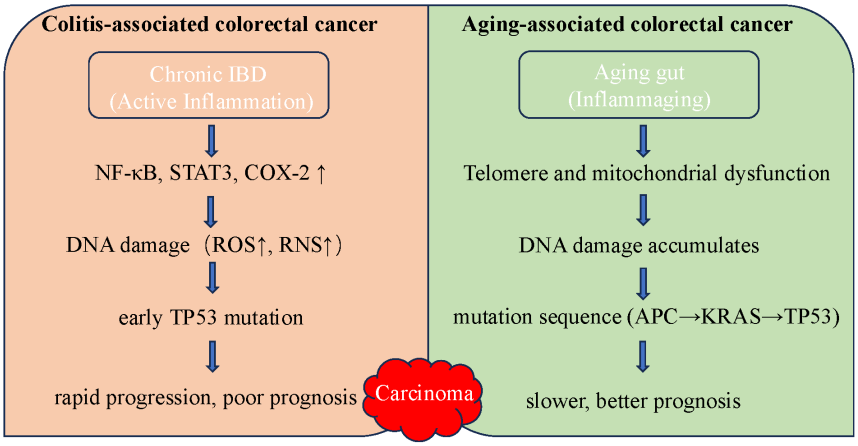

Figure 4. Distinct mechanistic pathways leading to colorectal cancer in IBD-associated and aging-associated contexts. The left side of the diagram shows the development of colitis-associated colorectal cancer, where chronic active inflammation in IBD drives persistent activation of the NF-κB, STAT3, and COX-2 pathways, leading to increased oxidative and nitrosative stress ROS↑, RNS↑, DNA damage, and early TP53 mutations. This results in rapid cancer progression and a poor prognosis. The right side depicts aging-associated colorectal cancer, in which the aging gut microenvironment inflammaging is characterized by telomere and mitochondrial dysfunction, gradual accumulation of DNA damage, and the classical sequence of the mutations APC→KRAS→TP53. This process is generally slower and associated with a better prognosis.

gut aging in IBD (*161*). Therefore, a future direction would be to develop comprehensive scoring tools (such as the Gut Aging Index) that combine biomarkers, functional assessments, and imaging technologies to diagnose accelerated gut aging (*162*). Current IBD assessment indices (such as CRP, fecal calprotectin, and endoscopy) primarily reflect the inflammatory burden and tissue injury but lack evaluation of long-term tissue degeneration, barrier dysfunction, and depletion of ISCs (*18*). When inflammation improves only in the short term, it may mask the progression of premature gut aging and ultimately result in a poor long-term prognosis for patients. Recurrent chronic inflammation leads to accelerated tissue degeneration (such as stem cell dysfunction and dysbiosis), and these "premature aging" features have significant effects on disease chronicity and treatment resistance but have not yet been incorporated into existing evaluation systems. Incorporating gut aging-related indicators into the assessment of IBD disease activity will help provide a more comprehensive understanding of disease biology and offer new directions for optimizing therapy. In addition, therapeutic strategies targeting premature gut aging may complement existing anti-inflammatory treatments, thereby improving long-term outcomes and reducing the risk of disease relapse in IBD patients.

The value of using anti-aging therapies to treat gut aging lies mainly in slowing functional decline and reducing the accumulation of inflammation, while these therapies are more auxiliary in IBD-associated accelerated gut aging, aiming to alleviate chronic damage and improve overall health. mTOR inhibitors (such as sirolimus) promote autophagy, protect ISC functioning, and reduce pro-inflammatory states, thus helping to delay the degeneration of crypt stem cells and barrier dysfunction (*31*). NAD^+ supplements (NMN or NR) restore NAD^+ levels, improve mitochondrial function, enhance cellular antioxidant capacity, and promote metabolic homeostasis (*163*). Spermidine (a natural polyamine) reduces inflammation by modulating autophagy pathways and repairing the intestinal barrier (*164*). Senolytics (senescent cell-clearing drugs) remove accumulated senescent cells, reducing functional decline caused by chronic inflammation (*165*). AMP activators (such as metformin and tedizolid) regulate cellular energy metabolism by activating AMPK signaling, reduce aging-related inflammation, and improve gut barrier functioning (*166*). IL-6/STAT3 inhibitors (such as tocilizumab) suppress pro-inflammatory signaling and reduce the inhibition of cellular regeneration by inflammation (*167*). In addition to these conventional anti-aging strategies, combining biologics with anti-aging therapies in clinical IBD management may help protect and restore prematurely aged intestinal function. Mesenchymal stem cells and fecal microbiota transplantation also have the potential for broad applicability in refractory IBD patients, especially due to their unique advantages in promoting tissue repair, restoring the microbiota balance, and modulating immune responses (*168*).

6. Conclusion

Aging of the intestine and IBD-associated premature gut aging share striking similarities at the cellular, molecular, and functional levels, including intestinal barrier dysfunction, immune dysregulation, and altered microbial homeostasis. These converging features support the concept of an "inflamm-aging axis," in which chronic inflammation accelerates tissue senescence and contributes to disease progression.

As a first step, future studies should determine

whether gut aging biomarkers — such as epithelial senescence signatures, tight junction protein decline, and microbiome aging indices — can be incorporated into IBD assessment systems to improve patient stratification and personalized therapy. Second, the possibility of using anti-aging interventions in IBD, including senolytics, autophagy modulators, and microbiome-targeted therapies, represents a promising adjunctive strategy beyond conventional anti-inflammatory treatments. Moreover, systematic comparisons of immune cell lineage remodeling between physiological aging and IBD are still lacking, and the contribution of organ-specific aging, such as the MAT and the appendix, to chronic inflammation and carcinogenesis needs to be explored further. Longitudinal and multi-omics studies need to be conducted to address these gaps.

In summary, by systematically contrasting IBD-associated premature gut aging with physiological intestinal aging, this review has introduced the concept of the inflamm-aging axis and highlighted its translational potential. Combining mechanistic insights with clinical use will not only deepen our understanding of intestinal pathophysiology but also inspire innovative diagnostic and therapeutic strategies for IBD.

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