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Senescence-Associated Secretory Phenotype as a Key Driver of Intestinal Aging: A Narrative Review

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ABSTRACT

Population aging is accompanied by progressive deterioration of intestinal structure and function, leading to impaired epithelial regeneration, increased intestinal permeability, chronic inflammation, and gut microbiota dysbiosis. Emerging evidence has identified the senescence-associated secretory phenotype (SASP) as a major mediator linking cellular senescence to intestinal aging; however, current evidence remains fragmented. This narrative review aimed to synthesize recent findings regarding the role of SASP in intestinal aging, with particular emphasis on its molecular mechanisms, biological consequences, and potential therapeutic strategies. A literature search was conducted in PubMed using the keywords ("senescence-associated secretory phenotype" OR SASP) AND (gut OR intestin* OR gastrointestin*) AND aging. The initial search identified 113 publications. After title and abstract screening, 60 articles were retained, and the exclusion of review articles and other non-original publications resulted in 28 original studies. Following full-text assessment, 26 articles were included for qualitative synthesis. The available evidence indicates that SASP contributes to intestinal aging by promoting chronic inflammation, impairing intestinal stem cell function, disrupting epithelial barrier integrity, remodeling the extracellular matrix, and altering gut microbiota composition. These interconnected mechanisms create a self-amplifying cycle that accelerates intestinal dysfunction and the loss of tissue homeostasis. Furthermore, emerging senotherapeutic approaches, including senolytics, senomorphics, and microbiota-targeted interventions, show promise in mitigating SASP-mediated intestinal aging. Overall, SASP represents both a key mechanistic driver and a promising therapeutic target for preserving intestinal homeostasis and promoting healthy aging.

INTRODUCTION

Population aging is a rapidly growing global phenomenon that poses significant challenges to healthcare systems due to the increasing prevalence of chronic diseases and functional decline among older adults. Aging is characterized by the progressive deterioration of cellular and tissue functions, resulting in impaired regenerative capacity, loss of homeostasis, and increased vulnerability to disease. Recent advances in geroscience have identified cellular senescence as a central hallmark of aging that contributes to tissue dysfunction and chronic inflammation across multiple organ systems (Di Micco et al., 2021; Schmauck-Medina et al., 2022).

Cellular senescence is a stable state of cell-cycle arrest induced by various stressors, including DNA damage, oxidative stress, mitochondrial dysfunction, telomere shortening, and oncogenic activation. While senescence serves as an important physiological mechanism for tumor suppression and tissue repair, the persistent accumulation of senescent cells during aging

can have detrimental consequences. Senescent cells remain metabolically active and develop a distinctive secretory profile known as the senescence-associated secretory phenotype (SASP), which consists of pro-inflammatory cytokines, chemokines, growth factors, proteases, extracellular matrix-remodeling enzymes, and extracellular vesicles (Basisty et al., 2020; Kumari & Jat, 2021). Key SASP factors, including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), and matrix metalloproteinases (MMPs), contribute to local and systemic inflammatory responses that characterize aging tissues (Yue et al., 2022).

Increasing evidence indicates that SASP is a major mediator of the pathological effects of cellular senescence. Through autocrine and paracrine signaling, SASP reinforces senescence, induces dysfunction in neighboring cells, alters tissue microenvironments, and promotes chronic low-grade inflammation, commonly referred to as inflammaging (Fafián-Labora et al., 2021; Saul et al., 2022). Persistent SASP signaling has been implicated in the development of numerous age-related disorders, including cardiovascular disease, metabolic dysfunction, neurodegenerative diseases, and cancer. Consequently, SASP has emerged as a promising therapeutic target for interventions aimed at extending healthspan and mitigating age-associated tissue degeneration (Bi & Ji, 2026).

The gastrointestinal tract is particularly susceptible to aging-related changes because it functions as a critical barrier between the host and the external environment. Intestinal aging is associated with structural and functional alterations, including impaired epithelial renewal, reduced intestinal stem cell function, dysregulated immune responses, microbial imbalance, and increased intestinal permeability (Abadías-Granado et al., 2021). These changes compromise gut barrier integrity and facilitate the translocation of microbial products into the circulation, thereby contributing to systemic inflammation and age-related morbidity (Hohman et al. 2022; Rangareddy et al. 2025). Emerging evidence suggests that age-associated intestinal dysfunction not only affects digestive health but also influences metabolic, immune, and neurological processes through the gut-organ axis (Shen et al., 2025).

Recent studies have demonstrated the accumulation of senescent cells within multiple intestinal compartments, including epithelial cells, intestinal stem cells, stromal cells, endothelial cells, and immune cells. The SASP produced by these senescent cells appears to play a pivotal role in intestinal aging by promoting inflammatory signaling, disrupting epithelial barrier function, impairing stem cell maintenance, and altering interactions between host tissues and the gut microbiota (Jang et al., 2024). Furthermore, SASP-mediated communication can propagate senescence to neighboring cells, creating a self-amplifying cycle that exacerbates tissue dysfunction and accelerates intestinal aging. These findings highlight the importance of understanding how senescent cells and their secretory phenotype contribute to the age-related deterioration of intestinal homeostasis (Ortiz-Perez et al., 2025).

Despite the growing recognition of the role of cellular senescence in aging, the specific contribution of SASP to intestinal aging remains incompletely understood. Existing studies have generated important insights into the molecular pathways linking senescence, inflammation, stem cell dysfunction, and barrier impairment; however, the evidence remains fragmented. Therefore, a comprehensive synthesis of current findings is needed to clarify the mechanisms through which SASP drives intestinal aging and to identify potential therapeutic strategies targeting senescent cells and SASP signaling.

This narrative review aims to summarize recent evidence regarding the role of the senescence-associated secretory phenotype in intestinal aging, with a particular focus on its molecular mechanisms, biological consequences, and emerging therapeutic opportunities. The findings of this review provide both theoretical and practical contributions. Theoretically, this review synthesizes fragmented evidence on the role of SASP in intestinal aging by integrating molecular, cellular, and physiological perspectives to develop a comprehensive understanding of how cellular senescence disrupts intestinal homeostasis through chronic inflammation, stem cell dysfunction, barrier impairment, extracellular matrix remodeling, and microbiota dysbiosis. This integrated framework advances the current understanding of intestinal aging mechanisms and provides a foundation for future mechanistic studies and the identification of intestine-specific SASP biomarkers. Practically, this review provides clinicians and researchers with a current synthesis of therapeutic strategies targeting SASP, including senolytics, senomorphics, and microbiota-based interventions, thereby informing the development of targeted interventions to preserve intestinal health and promote healthy aging. Additionally, this review serves as a resource for guiding future research directions by highlighting key knowledge gaps and proposing experimental approaches to validate SASP-targeting strategies in clinical settings.

METHOD

This study employed a narrative review design to synthesize current evidence on the role of the senescence-associated secretory phenotype (SASP) in intestinal aging. This approach was selected to integrate findings from diverse research areas, including molecular biology, cellular physiology, immunology, and geroscience, while providing a framework for synthesizing mechanistic and translational evidence. A literature search was conducted in PubMed using the Boolean string ("senescence-associated secretory phenotype" OR SASP) AND (gut OR intestin* OR gastrointestin*) AND aging in June 2026, yielding 113 publications. Following title and abstract screening, 60 articles were retained. The exclusion of review articles, editorials, conference abstracts, and other non-original publications resulted in 28 original studies, with 26 articles ultimately included for qualitative synthesis after full-text assessment. Inclusion criteria comprised original peer-reviewed studies investigating SASP or cellular senescence in intestinal tissues within the context of aging-related mechanisms. Exclusion criteria included review articles, non-original publications, studies unrelated to intestinal SASP, cancer-focused studies without relevance to aging, and studies with inaccessible full texts. Data were extracted on SASP-related molecular mechanisms, effects on intestinal stem cells, epithelial barrier function, microbiota interactions, and potential therapeutic strategies. The findings were synthesized narratively across thematic categories, including SASP regulation, epithelial regeneration, barrier integrity, microbiota interactions, and senotherapeutic approaches. Due to heterogeneity in study designs and outcome measures, a formal meta-analysis was not performed; instead, a qualitative narrative synthesis was conducted to provide a critical appraisal of the available evidence.

RESULTS AND DISCUSSION

Senescence-Associated Secretory Phenotype (SASP) in Intestinal Aging

Accumulating evidence indicates that the senescence-associated secretory phenotype (SASP) is a central mediator of intestinal aging by disrupting tissue homeostasis, promoting chronic inflammation, and impairing regenerative capacity (Di Micco et al., 2021; Kumar et al., 2019; Yun et al., 2023). Senescent cells within the intestinal microenvironment secrete a diverse array of pro-inflammatory cytokines, chemokines, growth factors, and proteases that act through autocrine and paracrine mechanisms to propagate senescence and alter neighboring cell function (Basisty et al., 2020; Kumari & Jat, 2021). In particular, SASP contributes to a persistent low-grade inflammatory state (inflammaging) that compromises intestinal barrier integrity and accelerates age-related intestinal dysfunction (Bar et al., 2025). Persistent DNA damage and oxidative stress appear to be important upstream triggers of this process, leading to the accumulation of senescent cells and sustained SASP production within intestinal tissues (Kumar et al., 2019; Bar et al., 2025). Experimental evidence has shown that intestinal stem cells (ISCs) exposed to chronic stress acquire a senescent phenotype accompanied by increased expression of SASP components, including IL-6, IL-8, and VEGF, which ultimately impair epithelial homeostasis and increase susceptibility to intestinal dysfunction (Kumar et al., 2019).

Recent findings further demonstrate that SASP directly interferes with intestinal stem cell differentiation and epithelial regeneration. Yun et al. (2023) identified secreted protein tyrosine kinase 7 (Ptk7) as a novel SASP component released by senescent fibroblasts that disrupts intestinal organoid development. Secreted Ptk7 activated non-canonical Wnt/Ca^{2+} signaling through FZD7 receptors and subsequently induced nuclear translocation of Yes-associated protein (YAP), resulting in defective symmetry breaking, impaired stem cell differentiation, and reduced generation of secretory epithelial lineages. Interestingly, these alterations were reversible, suggesting that SASP primarily modifies the intestinal microenvironment rather than causing irreversible stem cell depletion. These findings highlight a previously underappreciated mechanism whereby senescent stromal cells indirectly impair intestinal regeneration through aberrant intercellular signaling pathways, emphasizing the importance of senescent cell–stem cell interactions during intestinal aging (Di Micco et al., 2021).

Given the detrimental effects of SASP on intestinal homeostasis, targeting SASP has emerged as a promising therapeutic strategy. Two recent studies demonstrated that modulation of SASP can attenuate age-related intestinal dysfunction. Pharmacological inhibition of ADAM19 reduced gut permeability, DNA damage, inflammatory responses, and several SASP-associated factors, supporting its potential role as a novel senomorphic intervention. Likewise, resveratrol suppressed SASP through activation of the SIRT1/NF-κB pathway, resulting in reduced expression of pro-inflammatory cytokines, preservation of intestinal epithelial cells and ISCs, and delayed intestinal aging (Robbins et al., 2021; Liu et al., 2018). Together, these findings suggest that therapeutic approaches aimed at suppressing SASP, rather than eliminating all senescent cells, may represent an effective strategy to preserve intestinal barrier function, maintain stem cell homeostasis, and mitigate age-related intestinal deterioration (Bar et al., 2025).

Molecular Mechanisms and Biological Consequences of SASP in the Aging Intestine

The deleterious effects of the senescence-associated secretory phenotype (SASP) on the aging intestine are mediated through multiple interconnected signaling pathways that

collectively disrupt intestinal homeostasis. Persistent activation of the DNA damage response (DDR), oxidative stress, mitochondrial dysfunction, and telomere attrition induce cellular senescence and stimulate the production of SASP through transcription factors such as nuclear factor-κB (NF-κB) and CCAAT/enhancer-binding protein-β (C/EBPβ). The resulting secretion of pro-inflammatory mediators, including IL-1β, IL-6, IL-8, TNF-α, CXCL chemokines, transforming growth factor-β (TGF-β), and matrix metalloproteinases (MMPs), establishes a chronic inflammatory microenvironment known as inflammaging. Importantly, these mediators reinforce senescence in an autocrine manner while inducing paracrine senescence in neighboring cells, thereby amplifying tissue dysfunction throughout the intestinal niche. Persistent activation of NF-κB signaling further sustains SASP production, creating a self-perpetuating inflammatory loop that compromises tissue repair and regenerative capacity (Di Micco et al., 2021; Kumari & Jat, 2021; Basisty et al., 2020). Recent evidence also indicates that age-related dysbiosis and impaired intestinal barrier integrity potentiate SASP-associated inflammation through reciprocal interactions between the gut microbiota and the immune system, thereby accelerating intestinal aging.

One of the most significant biological consequences of SASP is the impairment of intestinal stem cell (ISC) function and epithelial regeneration. Senescent stromal cells alter the intestinal stem cell niche by secreting SASP factors that interfere with key regenerative pathways, including Wnt, YAP, and Hippo signaling. A landmark study by Yun et al. (2023) demonstrated that senescent fibroblasts release soluble protein tyrosine kinase 7 (Ptk7), which activates non-canonical Wnt/Ca^{2+} signaling through the FZD7 receptor and promotes YAP nuclear translocation in ISCs. This signaling cascade disrupts symmetry breaking during organoid development, suppresses stem cell differentiation, and reduces the generation of secretory epithelial cell lineages without permanently eliminating the stem cell population. In parallel, chronic SASP exposure induces oxidative stress, persistent DNA damage, and premature senescence in ISCs, further limiting epithelial renewal and compromising mucosal repair. These findings suggest that SASP not only affects differentiated epithelial cells but also disrupts the regenerative machinery responsible for maintaining intestinal integrity, thereby accelerating functional decline during aging (Ferreira-Gonzales et al., 2025).

Beyond stem cell dysfunction, SASP profoundly alters intestinal barrier function and tissue architecture. Pro-inflammatory cytokines and proteolytic enzymes secreted by senescent cells weaken epithelial tight junctions, degrade extracellular matrix components, and increase intestinal permeability, facilitating the translocation of microbial products and endotoxins into the systemic circulation. This "leaky gut" phenotype promotes immune cell activation and perpetuates chronic inflammation, establishing a vicious cycle between barrier dysfunction, microbial dysbiosis, and SASP amplification (Conway et al., 2024). Matrix metalloproteinases further contribute to extracellular matrix remodeling and stromal dysfunction, whereas TGF-β signaling promotes age-associated fibrosis and tissue remodeling. Collectively, these mechanisms demonstrate that SASP functions as an active driver of intestinal aging by integrating chronic inflammation, stem cell exhaustion, barrier dysfunction, extracellular matrix remodeling, and microbiota alterations into a self-reinforcing pathogenic network. Consequently, targeting the molecular pathways that regulate SASP production or signaling may provide a rational strategy to preserve intestinal homeostasis and promote healthy aging (Yin et al., 2025). The molecular mechanisms and biological consequences of SASP in intestinal

aging are summarized in Figure 1, illustrating how senescence-associated signaling triggers chronic inflammation, intestinal stem cell dysfunction, epithelial barrier disruption, extracellular matrix remodeling, and gut microbiota dysbiosis, ultimately leading to progressive loss of intestinal homeostasis and accelerated intestinal aging.

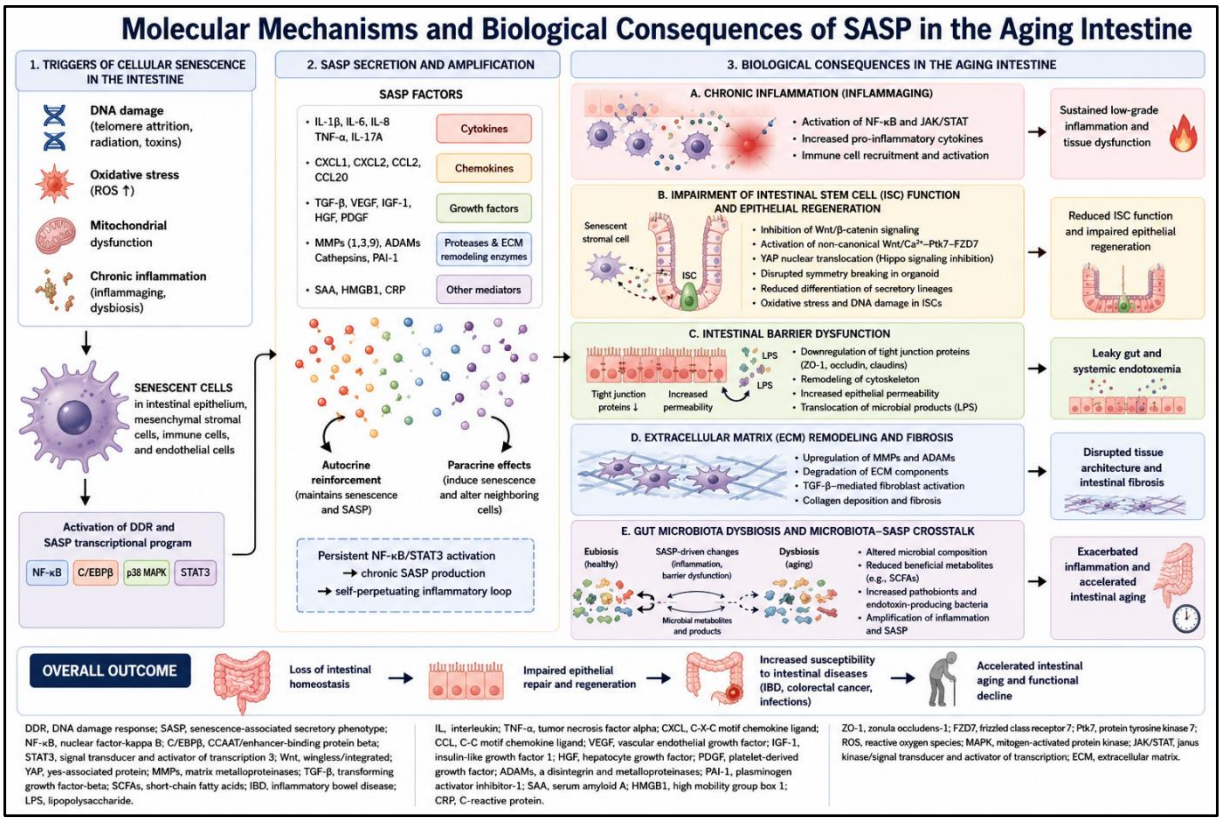

Figure 1. Senescence-associated secretory phenotype (SASP) drives intestinal aging through multifaceted molecular mechanisms and biological consequences
Source: Sourced from a variety of primary sources and a literature review on SASP and gut aging

Cellular senescence in intestinal epithelial cells, stromal cells, immune cells, and endothelial cells is triggered by DNA damage, oxidative stress, mitochondrial dysfunction, and chronic inflammation. Senescent cells secrete SASP factors, including cytokines, chemokines, growth factors, and proteases, through activation of transcription factors such as NF-κB, C/EBPβ, p38 MAPK, and STAT3. SASP exerts both autocrine and paracrine effects, reinforcing cellular senescence and establishing a self-perpetuating inflammatory loop. Consequently, SASP promotes chronic inflammation (inflammaging), impairs intestinal stem cell (ISC) function and epithelial regeneration through dysregulation of Wnt/YAP signaling, disrupts intestinal barrier integrity, induces extracellular matrix remodeling and fibrosis, and contributes to gut microbiota dysbiosis. Collectively, these interconnected mechanisms result in loss of intestinal homeostasis, impaired tissue regeneration, increased susceptibility to intestinal diseases, and accelerated intestinal aging.

Therapeutic Strategies Targeting SASP to Prevent Intestinal Aging

The senescence-associated secretory phenotype (SASP) has emerged as a central driver of intestinal aging, and therapeutic strategies aimed at modulating this pathogenic network are broadly categorized into two complementary approaches: senolytics, which selectively eliminate senescent cells, and senomorphics, which suppress the production or activity of pro-inflammatory SASP factors without killing the cells themselves (Dong et al., 2024). Senolytics such as dasatinib plus quercetin (D+Q) and navitoclax (ABT-263) have demonstrated efficacy in clearing senescent cells and ameliorating age-related pathologies in preclinical models, though concerns regarding off-target toxicity, such as thrombocytopenia with navitoclax and potential interference with beneficial senescence in tissue repair warrant careful optimization of dosing regimens, including intermittent administration (Bogdanova et al., 2024). In contrast, senomorphics offer a potentially more refined strategy by targeting specific signaling pathways that drive SASP expression, including NF-κB, JAK/STAT, and mTOR signaling, thereby dampening the chronic inflammatory milieu while preserving the tumor-suppressive and tissue-repair functions of senescent cells. For instance, the JAK1/2 inhibitor ruxolitinib has been shown to reduce pro-inflammatory SASP factors and frailty in aged mice, providing proof-of-concept that pharmacological SASP modulation is feasible and therapeutically relevant (Yang et al., 2024).

Several pharmacological agents with senomorphic properties have demonstrated specific promise in preserving intestinal homeostasis and barrier function. Metformin, a well-established anti-diabetic drug with an unparalleled long-term safety record, engages multiple aging hallmarks through AMPK activation, mTORC1 inhibition, and restoration of autophagic flux, while also reducing systemic inflammaging and SASP expression . Importantly, metformin has been shown to restore gut dysbiosis in aging by improving bacterial taxonomy and metabolic functions, indirectly mitigating the vicious cycle between microbial imbalance, barrier dysfunction, and SASP amplification (Aedh et al., 2026). More recently, inhibition of the metalloprotease ADAM19 has been identified as a novel senomorphic strategy to ameliorate gut permeability and senescence markers. In a Drosophila model of radiation-induced intestinal damage, knockdown of meltrin β (the Drosophila ortholog of ADAM19) reduced gut permeability, DNA damage, and senescence-associated β-galactosidase expression. Pharmacological inhibition of ADAM19 using batimastat (BB-94) similarly reduced intestinal permeability and pro-inflammatory SASP factors in doxorubicin-treated mice, while human primary fibroblasts with ADAM19 knockdown exhibited decreased expression of specific SASP factors, suggesting that this strategy may directly target the SASP-mediated barrier dysfunction that characterizes the aging intestine (Bar et al., 2025).

Beyond pharmacological interventions, emerging evidence highlights the potential of microbiome-targeted and natural product-based strategies to modulate SASP and promote healthy intestinal aging. The gut microbiome undergoes substantial changes with aging, and dysbiosis has been causally linked to the accumulation of senescent cells and the amplification of inflammaging (Sharma, 2022). Beneficial microbial metabolites, such as short-chain fatty acids (SCFAs), support intestinal barrier integrity and reduce inflammation, potentially mitigating senescence onset, whereas pathogenic bacteria introduce factors that accelerate senescence via NF-κB and p53-p21 pathways (Abavisani et al., 2025). Phytochemicals, including phenolic compounds and terpenes with antioxidant and anti-inflammatory activities,

have demonstrated senotherapeutic potential by acting upon senescence-linked cellular pathways, and their interactions with gut microbiota may offer a coordinated strategy to target the interconnected processes of cellular senescence, barrier dysfunction, and microbial dysbiosis (Costa et al., 2025). Collectively, these therapeutic approaches whether through senolytic clearance, senomorphic SASP modulation, or microbiome restoration represent a rational and multi-pronged strategy to disrupt the self-reinforcing pathogenic network of intestinal aging and preserve gastrointestinal homeostasis in the elderly.

CONCLUSION

The available evidence indicates that the senescence-associated secretory phenotype (SASP) is a central driver of intestinal aging through its ability to sustain chronic inflammation, impair intestinal stem cell function, disrupt epithelial barrier integrity, remodel the extracellular matrix, and promote gut microbiota dysbiosis. These interconnected biological processes establish a self-reinforcing pathogenic network that progressively compromises intestinal homeostasis and regenerative capacity. Consequently, therapeutic strategies targeting SASP, including senolytic and senomorphic agents, as well as microbiota-based interventions, represent promising approaches for delaying intestinal aging and improving gastrointestinal health. Nevertheless, most current evidence is derived from experimental studies, and the heterogeneity of SASP composition across different cell types and aging contexts remains a major challenge. Future research should focus on identifying intestine-specific SASP biomarkers, elucidating the interactions between SASP and the gut microbiota, and validating targeted senotherapeutic strategies in clinical settings to facilitate their translation into interventions for healthy aging.

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