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Cellular Senescence and Ageing of the Gastrointestinal Tract: Mechanisms, Functional Alterations, and Nutritional Implications—Literature Review

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Abstract

Ageing of the gastrointestinal tract—also termed gastrosenescence—results from the interplay between the accumulation of senescent cells and the structural, functional, and microbiological changes characteristic of old age. Cellular senescence, defined by permanent cell-cycle arrest and an associated secretory phenotype (SASP), plays a dual role: it facilitates the clearance of damaged cells and acute tissue repair, yet, when persistent, it promotes chronic inflammation, fibrosis, and a protumoural microenvironment. The intestinal microbiota and its genotoxic metabolites modulate senescence and SASP, thereby influencing colorectal and hepatic carcinogenesis. Along the digestive tract, age-related changes include loss of taste and dentition, hypochlorhydria, variable gastric emptying, malabsorption—particularly of lactose—and slowed colonic transit, all of which contribute to the anorexia of ageing, protein-energy malnutrition, and sarcopenia. Histologically, an imbalance between proliferation and apoptosis and hormonal alterations predispose to neoplastic development. Optimal management requires a multidisciplinary approach encompassing detection of senescence biomarkers, senolytic and senostatic therapies, microbiota modulators, dietary texture adaptation, specialised supplementation, and correction of micronutrient deficiencies. This integrated strategy may improve quality of life, reduce complications, and optimise prognosis in geriatric patients with gastrointestinal disorders.

Keywords

Cellular Senescence, Gastrointestinal Tract/Ageing, Intestinal Microbiota, Protein-Energy Malnutrition, Gastroenterology

1. Introduction

Human ageing is a multifactorial process characterised by the accumulation of biological, molecular, and cellular changes that interact with genetic, environmental, and lifestyle determinants to drive the functional decline of multiple organ systems [1]. In this context, the gastrointestinal tract—from the oral cavity to the colon and its accessory organs (pancreas, liver, and gallbladder)—is no exception; indeed, its continuous exposure to exogenous substances, the microbiome, and constant cellular turnover renders it particularly susceptible to senescence-related alterations [1] [2].

In old age, beyond the classical structural changes such as loss of muscle mass, mucosal atrophy, and thickening of the lamina propria, a progressive decline in functional reserve and epithelial turnover is observed, leading to a diminished capacity to respond to physical, chemical, and even immunological insults [3]. Simultaneously, the cells that constitute these tissues accumulate oxidative stress and DNA damage, activating the cellular senescence programme—an irreversible cell-cycle arrest that, through the senescence-associated secretory phenotype (SASP), promotes a chronic pro-inflammatory micro-environment [3]-[5].

Gastrosenescence, defined as the convergence of age-related changes with cellular senescence in the digestive tract, directly affects the nutritional status of older patients, their risk of infectious, inflammatory, or neoplastic diseases, and their therapeutic response to pharmacological or nutritional interventions [1] [2] [6]. Consequently, it is essential to deepen our understanding of the molecular mechanisms of senescence, its interaction with the microbiota, the motor and secretory changes along the digestive tract, and the diagnostic and therapeutic strategies that can mitigate its deleterious effects [6].

2. Foundations of Cellular Senescence in the Gastrointestinal Tract

2.1. Definition and Types of Senescence

Cellular senescence is an evolutionary safeguard that limits the proliferation of cells bearing genomic damage or exposed to excessive mitogenic stimuli. It was originally described by Hayflick and Moorhead in fibroblasts maintained in longterm culture, a phenomenon termed replicative senescence [7]. Additional forms include:

- Oncogene-induced senescence (OIS): a response to aberrant activation of oncogenes (e.g., RAS, MYC) that prevents malignant transformation by enforcing cell-cycle arrest [8] [9].
- Therapy-induced senescence (TIS): triggered by genotoxic treatments such as chemotherapy or radiotherapy, which cause DNA damage and activate the same effectors of cell-cycle blockade [10]-[12].

All of these programs converge on the p53/p21^CIP1 and p16^INK4A/Rb axes, although they may differ in the spectrum of secreted inflammatory factors and in the durability of arrest [8]-[11].

2.2. Markers and Detection of Senescent Cells

Identification of senescent cells in gastrointestinal tissues requires a multimodal panel that typically includes:

- Cyclin-dependent kinase inhibitors: elevated p16^INK4A and p21^CIP1 detectable by immunohistochemistry or Western blot [13].
- Senescence-associated *β*-galactosidase (SA-*β*-Gal): lysosomal activity evident at pH 6.0, visualised with the X-Gal substrate as blue cytoplasmic staining and, in murine models, associated with pro-inflammatory states [14]-[16].
- Senescence-associated secretory phenotype (SASP): measurement of cytokines (IL-6, IL-8, CCL2), chemokines, and matrix proteases in fluids or cell cultures by ELISA or protein arrays [17] [18].
- Additional markers: lamin B1 degradation, senescence-associated heterochromatin foci (SAHF), expression of BHLHE40 or sirtuins [19]-[21].

No single marker is fully specific; hence a combined approach is mandatory [3] [13] [15] [19].

2.3. Physiological Role and Double-Edged Nature of the SASP

The SASP modulates the tissue microenvironment through the release of more than 40 soluble factors whose effects are context-dependent:

Protective effects

- Recruitment of immune cells (macrophages, lymphocytes) that eliminate damaged or precancerous cells (senescence surveillance) [18].
- Promotion of early wound healing via factors such as PDGF-AA, fostering appropriate extracellular-matrix remodelling [17].

Detrimental effects

- Chronic maintenance of local inflammation that drives fibrosis, delayed repair, and creation of a pro-tumoural niche [22].
- Paracrine stimulation of neighbouring non-senescent cells, accelerating progression of malignant lesions [23].

The balance between SASP duration and immune clearance capacity determines whether senescence becomes an ally or an enemy of gastrointestinal homeostasis

[17] [23].

3. Influence of the Microbiota on Gastrointestinal Senescence

The intestinal microbiota plays a pivotal role in modulating senescence and the SASP through several mechanisms:

- Production of bacterial genotoxins (e.g., colibactin) that induce DNA double-strand breaks and can trigger OIS in epithelial cells [24] [25].
- Conversion of primary to secondary bile acids (deoxycholate, lithocholate); at high concentrations these cause oxidative stress and NF-κB activation, amplifying pro-inflammatory cytokine secretion [24] [25].
- Age-associated dysbiosis, which decreases microbial diversity and favours pro-inflammatory species [24]-[26].

These host-microbiome interactions create a vicious circle: epithelial senescence alters the mucus layer and mucosal environment, changing bacterial niches, whereas bacteria in turn potentiate the SASP and tissue damage [23] [26].

4. Structural and Functional Changes of the Gastrointestinal Tract with Age

4.1. Oral Cavity

With advancing age, the oral cavity undergoes:

- Diminished taste and smell: up to 74 % of older adults report taste alterations and 22 % olfactory loss, which lowers palatability and provokes anorexia [1].
- Tooth loss and xerostomia: associated with polypharmacy (ACEIs, statins, PPIs), these conditions hamper mastication and the initial digestion of starches, limiting the intake of proteins, water-soluble vitamins, and essential fatty acids [27].

These changes translate into marked deterioration of nutritional status with systemic repercussions.

4.2. Oesophagus

Age-related changes in oesophageal innervation entail:

- Altered motility: reduced amplitude of peristaltic waves and decreased lower oesophageal sphincter tone, prolonging reflux episodes without changing their frequency [28] [29].
- Increased dysphagia: prevalence 13% - 59%, depending on neurological or surgical disease; this increases the risk of malnutrition five-fold [30].

Diagnosis and management require clinical-instrumental tools (manometry, pH-metry) and adaptation of diet texture according to international Dysphagia Diet Standardisation Initiative (IDDSI) standards [30] [31].

4.3. Stomach

Data on gastric emptying in the elderly are heterogeneous:

- *In vivo* scintigraphic studies show emptying comparable to young adults, with no significant differences by sex or BMI [32].

- Other studies report mild slowing, accentuated by high-fat meals and sedentary behaviour; oral lipase improves lipid evacuation [28] [33].

More consistent is hypochlorhydria secondary to parietal-cell atrophy (≈40% reduction in acid and pepsin secretion), predisposing to:

- Chronic atrophic gastritis and Helicobacter pylori infection [34] [35].
- Intrinsic-factor deficiency → cobalamin malabsorption in up to 38% of elderly patients with atrophy [36] [37].

These findings explain the increase in dyspepsia, anorexia, and megaloblastic anaemia in older adults.

4.4. Small Intestine

Although mucosal architecture (villi, crypts) changes little with age in humans, barrier function and local immunity do deteriorate:

- Loss of epithelial integrity and dysregulation of secretory mediators facilitate small-intestinal bacterial overgrowth and subsequent malabsorption [28] [32].
- Lactase deficiency in 70% - 90% leads to osmotic diarrhoea, distension, and calcium and protein deficits; low-lactose or fermented products are recommended [38].

Adaptive capacity during fasting or stress is also diminished, favouring rapid loss of body mass during acute hospitalisation [33].

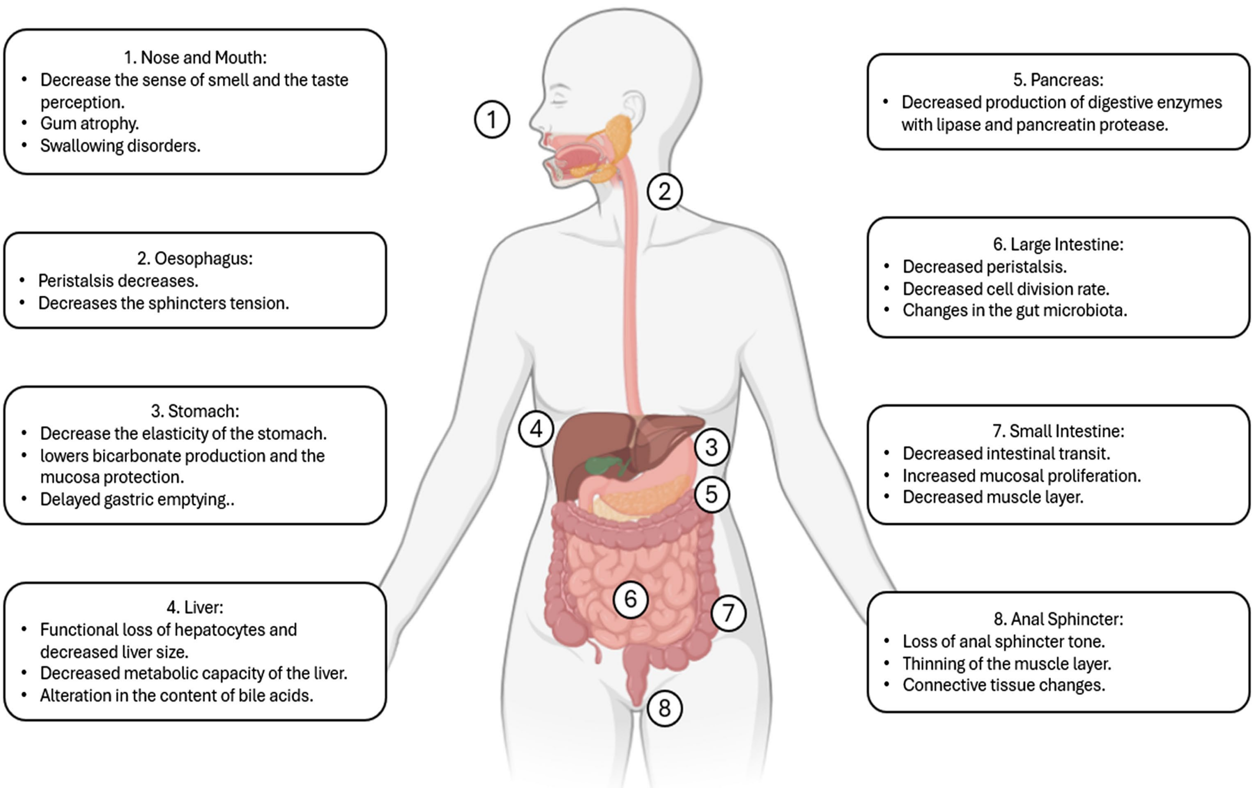

Figure 1. Changes in the aging of the gastrointestinal tract. Source: Prepared with BIORENDER resources.

4.5. Colon

Colonic transit slows because of:

- Degeneration of colonic neurons—particularly cholinergic cells in the myenteric plexus—with reduced acetylcholine release and nitric-oxide-synthase expression [28] [29] [32] [33].
- Up-regulation of mucosal opioid receptors, which exacerbate constipation and can be counteracted with oral μ-opioid antagonists [32] [39].

Consequently, chronic functional constipation affects more than 50% of institutionalised older adults (**Figure 1**), negatively impacting quality of life and leading to complications such as faecal impaction and rectal prolapse [39].

5. Histological and Proliferative Changes in the Gastrointestinal Mucosa

5.1. Proliferation and Apoptosis

In aged animal models, epithelial proliferation is increased while apoptosis is reduced in the stomach, small intestine, and colon, suggesting an imbalance in tissue renewal and a heightened risk of accumulating genomically damaged cells [11] [12] [17] [28].

5.2. Hormonal Regulation and Gastric Mucosa

With advancing age, the gastric response to gastrin diminishes, accompanied by a higher somatostatin-to-gastrin ratio in the antrum, leading to mucosal atrophy. Likewise, expression of gastrin receptors on parietal cells declines, impairing acid and intrinsic-factor secretion [28] [32] [33].

5.3. Carcinogenesis

The accumulation of mutations in tumour-suppressor genes (e.g., *APC*, *TP53*) and oncogenes, together with a chronic microenvironment dominated by the SASP, accounts for the marked rise in gastric and colorectal cancer from the sixth to seventh decade of life [17] [18]. The SASP, by recruiting immature myeloid cells and suppressing antitumour immunity, fosters neoplastic progression by establishing a protumoural niche [6] [8] [10] [13].

6. Nutritional and Clinical Impact of Gastrointestinal Ageing

The convergence of cellular senescence, motor dysfunction, and malabsorption results in:

- **Anorexia of ageing:** early satiety due to gastroparesis and delayed gastric emptying limits the energy and protein intake required to maintain muscle mass [40] [41].
- **Protein-energy malnutrition and sarcopenia:** prevalent in 38.6% of older adults in Colombia and linked to an increased risk of falls and protein-energy malnutrition-related mortality of up to 44.8% in individuals over 80 years, Ac-

cording to the SABE survey of the Ministry of Health and Social Protection [42].

- **Systemic complications:** greater susceptibility to infections, delayed wound healing, poor drug tolerance, and impaired immune responses [32] [42].

These findings underscore the need for diagnostic strategies such as anaemia screening, motor and absorption function tests, and continuous nutritional monitoring in the geriatric population.

7. Therapeutic Strategies and Nutritional Management

7.1. Senolytics and SASP Modulation

- Senolytics: Agents such as BCL-2 inhibitors or dasatinib with quercetin, which eliminate senescent cells, have been shown to improve hepatic fibrosis and intestinal function in murine models, evidencing a study scenario for human models [43] [44].
- Senostatics: JAK/STAT inhibitors (e.g., ruxolitinib) or CXCR2 antagonists that reprogramme the SASP toward an antitumour profile, thereby enhancing the response to chemotherapy in colorectal cancer [45] [46].
- Among the adverse effects of these pharmacological groups are cytopenias, myelosuppression, pleural effusion, pulmonary hypertension, QT interval prolongation, as well as gastrointestinal and dermatological symptoms. Therefore, each patient must be individually assessed, and the risk-benefit ratio carefully weighed [43]-[46].

7.2. Specialised Nutritional Intervention

- Oral or enteral supplementation with FODMAP-free (fermentable oligosaccharides disaccharides monosaccharides and polyols) oligomeric formulas in severe gastroparesis, administered in 4 - 6 daily portions, enhances tolerance and minimises steatorrhoea [42].
- Micronutrient correction: Sublingual or chewable preparations of vitamin B_{12}, calcium, and iron to avoid pharmacobezoar formation and improve absorption [36] [37] [41].

7.3. Microbiota Management

- Probiotics and prebiotics to restore microbial diversity, reduce genotoxin production, and modulate local inflammation [25].
- Selective antibiotics for small-intestinal bacterial overgrowth, using short cycles and rotating classes to prevent resistance [26].
- A 12-week double-blind intervention with inulin-oligofructose in 200 prefrail older adults increased microbiota richness and Shannon diversity index, restoring bacterial diversity and improving frailty parameters [47].

8. Limitations and Future Directions

Current evidence is limited by the near-absence of longitudinal human studies that serially quantify validated senescence biomarkers and relate them to clinically meaningful gastrointestinal outcomes. Most data come from cross-sectional tissue analyses or very short pilot trials; for instance, the first human senolytic study (intermittent dasatinib + quercetin) assessed biomarker clearance over just 11 days and collected no digestive or functional follow-up [44].

Future directions should include multi-centre prospective cohorts with 3 - 5-year follow-up that integrate tissue, circulating, and imaging markers of senescence with comprehensive geriatric and gastrointestinal phenotyping. Harmonised protocols for specimen collection, assay calibration, and data sharing will be crucial.

9. Conclusion

Gastrosenescence poses an increasing challenge in contemporary clinical practice, as it integrally affects motility, absorption, and the immunological barrier of the digestive tract. The accumulation of senescent cells and a persistent SASP create a chronic inflammatory microenvironment that heightens the risk of malnutrition, infectious morbidity, and neoplasia. A multidisciplinary approach is required, incorporating early diagnostic tools (senescence biomarkers, motility studies), targeted therapies (senolytics/senostatics), personalised nutritional interventions, and microbiota modulators. Only through such an integrated strategy can quality of life be improved, healthcare burdens reduced, and the prognosis of older adults with gastrointestinal disorders optimised.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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