**Review**

**Cellular senescence and cancer in the gastrointestinal tract**

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Abbreviations:

CDK, cyclin-dependent kinase; COVID-19, coronavirus disease 2019; CRC, colorectal cancer; CXCR2, C-X-C motif chemokine receptor 2; DYRK1A, dual specificity tyrosine-phosphorylation-regulated kinase 1A; E. coli, Escherichia coli; ERK, extracellular signal-regulated kinase; GI, gastrointestinal tract; GIST, gastrointestinal stromal tumor; GDF15, growth differentiation factor 15; *H. pylori*; *Helicobacter pylori*; IL-6, interleukin 6; IL-8, interleukin-8; ICC, interstitial cells of Cajal; MMP3, metallopeptidase 3; PTEN, phosphatase and tension homolog; PUMA, p53 up-regulated modulator of apoptosis; SASP, senescence-associated secretory phenotype; SENP1, SUMO specific peptidase 1; WHO, world health organization

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**Abstract**

Due to the advancement of medicine in the modern era, higher proportions of the population will continue to age with longer lifespans. Increased lifespan does not always correlate with improved healthspan and hence an increase in aging-related diseases and disorders. These diseases are often attributed to cellular senescence, where cells become disengaged from the cell cycle and instead become inert to cell death, and characterized with a pro-inflammatory secretome. While it is a natural function intended to prevent further DNA damage, the pro-inflammatory senescence associated secretory phenotype (SASP) proteins, create a microenvironment suited for tumor progression. This is most evident in the gastrointestinal (GI) tract, where a combination of bacterial infections, senescent cells, and inflammatory proteins can lead to oncogenesis. As a result, it is important to find potential senescent biomarkers for novel therapies regarding GI diseases and disorders including cancers. However, there may be value in finding therapeutic targets for the microenvironment of the GI to reduce the risk of GI tumor onset. This review summarized the impacts of the cellular senescence on GI aging and cancers to improve our understanding and to enhance future therapy.

**Introduction**

According to the world health organization (WHO), 1.4 billion people globally will be over the age of 60 years old in 2030 [1]. As a result of this, a decent portion of the population will be subject to aging related health conditions: one being problems related to cellular senescence, an irreversible cell cycle arrest and key driver of aging and aging associated diseases, and another being a higher risk of cancer. Incidence of gastrointestinal (GI) diseases including cancers increase with age partially due to the accumulation of senescence cells [2] and will no doubt be more prominent with the rising percentage of older populations in the next 10 years. One therapeutic option in GI cancers may be to regulate cellular senescence, a state of irreversible cell cycle arrest, typically in response to DNA damage. While cellular senescence plays central roles in aging-related diseases/disorders, it can also be used to manage tumors. For instance, given the risk of toxicity from extreme drug dosages in chemotherapies, combining pro-senescence with senolytic therapy may reduce that risk while amplifying cancer destruction [3]. The detailed roles of cellular senescence in GI cancers are not clear, but there is evidence that the senescent fibroblast microenvironment can increase the risk of colon cancers [4]. The relationship between cellular senescence and GI cancers is neither simple nor clearly defined, however, this provides motivation to further develop research efforts into this topic in order to progress therapeutic options for the future aging populations of the world.

The fragility of the elderly often stems from compounded sources of disease, accumulation of senescent cells, and cascading effects caused by those sources. Some infectious diseases become high risk such as the coronavirus disease 2019 (COVID-19), intestinal bacterial overgrowth, and GI ulcers [5, 6]. Many of these diseases can be attributed to senescence in some capacity; for example, COVID-19 overloads the elderly with senescent cells, DNA damage accumulation, and inflammatory cytokines [7, 8]. This could be detrimental in the long term for the elderly as this may lead to the development of other diseases and disorders if left untreated. Elderly individuals are already affected by higher morbidity of common GI disorders such as esophageal reflux, dysphagia, chronic constipation, and gastroparesis [9, 10]. Compounded with the high risk of infectious diseases, GI bleeding, and cancer progressions, mortalities are highly likely in the aging population. As a result, it becomes necessary to understand how components and mechanisms of senescence interact to better understand how they contribute toward disease development.

**Cellular Senescence**

Aging can be defined as the development of the human body from conception to mortality. Throughout this process, humans undergo an eventual decline of cellular function [11]. This decline is often associated with the accumulation of DNA damage and related cellular fates such as senescent cells, which result in the aging of the human body. Cellular senescence causes cells to undergo cell cycle arrest, where the cells in question are no longer able to grow and replicate, but still remain metabolically active so as to affect normal cells both locally and systemically [12]. It is an important defense mechanism against DNA damage, telomere destruction, and other stressors. Without it, DNA damage would rampantly increase tumor proliferation and progression [13]. The senescent pathway involves DNA damage which activates tumor antigens such as tumor suppressor p53 and cyclin-dependent kinase (CDK) inhibitors p16 and p21 which then lead to cell cycle arrest and increased generation of a myriad of cytokines, chemokines, and other inflammatory proteins from senescent cells, also termed as senescence-associated secretory phenotype (SASP). Telomere shortening or telomeric DNA damage can also lead to the activation of p16 and p21[14], and stimuli such as cytokines or oncogene activity can also lead to cell cycle arrest and subsequent senescent phenotypic expression [15].

DNA damage is one of the main contributors to aging as it occurs naturally due to metabolic processes such as oxidative byproducts created by mitochondria [16]. Given this info, it coincides with p53 causing mitochondrial apoptosis [17], mitochondria dysfunction increasing p53 expression in senescent cells [18], and p53 inhibiting mitochondria elongation in cell senescence [19]. Mitochondria elongation is a mechanism that increases cell viability which implies that p53 inherently increases the likelihood of cell apoptosis [20]. This is interesting considering senescence acts opposite to apoptosis, and neither are directly correlated with each other. However, a recent study defined p53’s two downstream proteins, p53 up-regulated modulator of apoptosis (PUMA),a key protein linked to p53-mediated apoptosis),and p21 (one of the genes linked to cellular senescence), as significant contributors to lymphoma prevention. It also showed that DNA repair worked cohesively with p53[21]. The main implication here is that all three processes (cellular senescence, DNA repair, and apoptosis) work together through p53, acting like a liaison.

Hypothetically, it could be that the three processes are dependent on the needs of the cell, as a preference of senescence or apoptosis would fit different situations. This is possible given how different organs varied in response to aging, such as the intestinal cells being more likely to undergo apoptosis, which implies epigenomic alterations to the genome in response to different cell types [22]. This contributes to the necessity of a variety of senescence studies, especially in GI, as the variety of different cells throughout the GI tract will likely lead to a greater variation in senescence expression. p53 is implied to have an epigenetic effect on cells as shown by its positive relationship with a-ketoglutarate, a key substrate to some epigenetic processes [23]. Additionally, a recent study conducted in-vitro studies on the effect of a-ketoglutarate on senescent cells which did not show an effect on p21 expression but did show effect on SASP-related cytokine expression [24]. This suggests p53 may have an epigenetic effect on its downstream SASP expression.

Some SASP, like interleukin-8 (IL-8), are involved in immune cell recruitment, such as neutrophils, to impede malignant cell growth [25, 26]. SASP’s main functions are to promote cell proliferation, tissue repair, and stem cell renewal; all of these suggest that the end goals of SASP is to repair damage and prevent cancer development [27, 28]. Ultimately, this lends to the idea that p53 acts as regulator that tries to prevent any cancer development, even from its own downstream elements.

SASP overexpression can cause tumor progression by creating an inflammatory environment that leads to epithelial-mesenchymal transitions (EMT) which then increases cancer cell invasion [29]. The presence of SASP such as interleukin 6 (IL-6) and IL-8 has also been shown to interact with chemokines and oncogenic proteins to promote cancer growth [30, 31]. As a result, there is value in accounting for SASP when researching oncogenic development of the elderly population [32]. Given that mutations are more likely to occur through aging, it is possible that a mutation in p53 would lead to dysregulation of SASP and subsequent cancer development. This is supported by a study done on zebrafish where a p53 mutation supported such a phenomenon and such mutations are common in human tumors [33]. It could be that most oncogenic development does not stem from SASP expression caused by natural senescent cell build up but rather mutations in senescent regulation.

**Senescence in GI mucosa and muscle:**

The susceptibility of GI cells to the senescence process varies depending on the specific cell types in GI tract, regions of GI tract, and their potential contribution to age-related changes in GI health have not been fully investigated [10]. While cellular senescence seems to be prevalent in GI mucosa [34, 35], interstitial cells of Cajal (ICC), pacemaker and neuromodulator cells of GI motor function, and their progenitor cells decline through aging in the reduced extracellular signal-regulated kinase (ERK) signaling rather than the senescent pathway [34]. Senescence is not only cell-dependent or organ-dependent, as different regions of the colon have shown significant contrasts in p16 expression, suggesting that senescence is also region-dependent [36]. Additionally, given that there is no specific senescence marker [37, 38], there is merit in finding novel senescence markers specific to the GI tract. It would be rash to apply currently used senescence markers to the GI tract. Researching senescent cells in the GI tract is critical for improving our understanding of their roles.

***H. pylori*, senescence, and cancer:**

*Helicobacter pylori* (*H. pylori*) is a type of bacteria that infect human stomachs and *H*. *pylori* infection remains the major cause for gastric cancer, which involves multiple steps including gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer development [39, 40]. *H. pylori* increases the inflammatory environment via mucosal lesions and nitric oxidation and DNA damage [41]. Based on the fact that DNA damage directly correlates with accumulation of senescent cells, this suggests *H. pylori* infection may be a key trigger of cellular senescence in the GI tract.

*H. pylori* infection-induced atrophic gastritis have been linked to Wnt/β-catenin signaling activation [42-44]. Given that aberrant Wnt/β-catenin activation can induce gastric ICC decline with age, the presence of the bacteria may also damage ICC in the stomach. In fact, there is already evidence that ICC are reduced in the presence of *H. pylori* [45]. Given that there is evidence of Wnt signaling being correlated with the oncogenesis of gastrointestinal stromal tumor (GIST), a most common human sarcoma occurring in GI muscle layer [46], *H. pylori* presence could lead to higher risks of GIST development [47]. Injuries to the stomach, such as through gastritis, can cause metaplasia of corpus chief cells, gastric gland cells that release pepsinogen, and loss of parietal cells that are responsible to secrete gastric acid to digest food. While these changes are designed for wound healing, much like senescent cells, their presence could be precancerous [48]. Additionally, the pro-inflammatory nature of *H. pylori*-related lesions and nitric oxide may work in tandem with the SASP of the senescent cells to create a highly oncogenic environment [49, 50]. Inflammation and SASP increases immune cell recruitment (includes polymorphonuclear cells like eosinophils and lymphocytes) which correlate with increased metaplasia in the stomach and contribute to the oncogenic progression[51, 52]. This all suggests that senescence cascades with the microenvironment of the GI tract to influence the onset of multiple GI aging disorders, especially cancer.

**Senescence in GI cancers and GIST:**

The relationship between cellular senescence and cancer is defined by contradiction. One study found that senescent cells in advanced tumors reduce immune surveillance via SASP, yet cellular senescence was also shown to help tumor-suppressive mechanisms in hepatic carcinoma [53]. Given senescent cells’ paradoxical roles in tumorigenesis, there is merit in using specific senescent biomarkers to mitigate tumor progression. For instance, the overexpression of the tumor suppressors can induce senescence in tumor cells and prevent tumor cell proliferation [54]. Another example is that the inactivation of genes such as phosphatase and tension homolog (PTEN) or MYC can cause cellular senescence. PTEN specifically causes p53 activation which leads to senescent cell cycle arrest [55]. Given the previous information, it would be reasonable to assume that GIST would have similar relations to senescence. However, there is no evidence that GIST can be treated with either reinduction of senescence. Given that GIST is believed to develop from ICC, which do not display senescent phenotypes, there is still a possibility that a different mechanism is critical for GIST [34, 56].

Instead of cellular senescence, cellular quiescence has more relevant to GIST. Cellular quiescence is a reversible dormancy state of a cell that often leads to a permanent state of senescence [57]. Cellular quiescence is one reason why total remission of GIST does not occur often, which is why quiescent proteins are considered as therapeutic targets. One possible example is combining imatinib, a tyrosine kinase inhibitor of KIT receptor and the mainstay of treatment for GIST, with the quiescent therapeutic target, DREAM complex [58], to induce complete cell death. Often, imatinib causes apoptosis in GIST but also leaves quiescent cells in its wake. As a result, GIST recurrence is highly probable despite imatinib treatment [58]. However, the DREAM complex can be targeted to prevent quiescence via knockdown [59]. It is interesting to note that the protein that causes DREAM complex formation, dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A), is found to have an inverse relationship with both cyclin D1 and p21 [60]. Often times, the presence of quiescent cells leads to the formation of imatinib-resistant GIST [61]. Furthermore, a recent study showed that imatinib-resistant GIST have been found to be highly affected by cyclin D1 targeting via proteasome inhibitor, often leading to cell cycle arrest as well as expression of p53 and p21 [62]. Additionally, an elevated p21 (as well as p53) expression is associated with poor prognosis of GIST [63], and p53 has been found to be a significant biomarker for GIST progression and proliferation [64, 65]. While these are senescence biomarkers, this is not a clear connection between senescence and GIST.

 Luckily, there is at least evidence for manipulating senescent cells to prevent a tumor progressive environment in the GI tract. A recent study showed that cellular senescence and *H. pylori*’s cooperative relationship is dependent on C-X-C motif chemokine receptor 2 (CXCR2) signaling [66]. *H. pylori* upregulates CXCR2 which then has positive feedback on p53 which then increases cellular senescence. It is possible that CXCR2 can be pharmaceutically manipulated to decrease senescence caused by *H.pylori* and thus reduce the inflammatory cascade caused by the bacterial infection; subsequently, reducing the likelihood of cancer progression [66, 67].

In a similar vein, the CXCR4 signaling pathway is involved in tumor invasion and metastasis for colorectal cancers (CRC) [68], the third leading estimated cause of cancer death [69]. However, the pathway is most important for showcasing the relationship between senescent tumor cells and immune cell impairment. Senescent tumor cells induce CXCR4 loss in T cells which lead to impaired leukocyte migration, inhibiting CD8+ T cell infiltration [70]. This suggests senescence is integral to colorectal cancer development due to the weakened immune system allowing further tumor cell invasion. Additional links between CRC and senescence include: the presence of a high number of senescent cells in the stroma of colorectal tumors and the relationship between SASP with colorectal growth [4, 71]. Senescent fibroblasts in colonic stroma can enhance adenoma and CRC formation via a paracrine-mediated process that involves growth differentiation factor 15 (GDF15) [4]. Escherichia coli (*E. coli*) is a bacteria that can cause colorectal cancer via SASP protein secretion. This bacterial infection can upregulate miR-20a-5p in colonic mucosa which negatively regulates SUMO specific peptidase 1 (SENP1, a negative regulator of p53) which leads to increased SASP and thus colorectal cancer growth [71]. These colorectal cancer studies show that CXCR4, GDF15, and miR-20a-5p are all potential biomarkers that could be targeted to reduce the oncogenic effect of senescent cells on the colon.

**Senotherapeutics and Clinical Trials:**

 Besides senescence manipulation, the destruction of senescent cells may provide optimal therapies. Senolytics are drugs that eliminate senescent cells through apoptosis and senostatics are drugs that inhibits senescence cells’ function [72]. There are already several clinical trials that show the impact of senotherapies, that involve senolytics and senostatics, can have on diseases. Senotherapies have been shown to decrease senescent cells in people with diabetic kidney disease [73]. Circulating levels of α-Klotho, an anti-aging protein that can alleviate aging processes, was reported to be restored through oral senolytics [74]. There is even a clinical trial that shows senolytic drugs can decrease the effects of diabetes in obese patients[75]. A study done on premalignant pancreatic intraepithelial neoplasia lesions shows how senolytic therapies can reduce the progression of inflammatory lesions into cancer via senescent cell removal [76]. Given that these pancreatic lesions show a similar relationship with senescence as another study done on H. pylori-induced atrophic gastritis [66], there is reason to believe a similar effect would occur on pre-cancerous gastritis when using senolytics. When accounting the potential of these drugs, senotherapies could be used to prevent the tumor progressive microenvironment of an elderly GI tract. Unfortunately, there is a scarcity of current senolytic clinical trials regarding the GI tract. However, with a recent study showing that senotherapies can improve intestinal inflammation and overall health in older mice and another study that shows the anti-aging potential destroying senescent cells can bring [77, 78], there may be potential for more variation in senotherapy clinical trials involving the GI in the future.

**Conclusion:**

All in all, there is evidence that suggests senescence is highly correlated to the onset of GI diseases and disorders including cancers. Whether through the disruption of tumor suppression genes in the pathway or the combination of factors resulting from SASP and the GI’s microenvironment, targeting senescence can influence the development of tumors. As a result, further experimentation with GI cancers and cellular senescence is pertinent as it would expand on the relationship between aging and tumor development. This relationship can then be used to create novel senolytic therapies that would help reduce the risk of GI oncogenesis in the aging population.

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**Figures**



**Figure 1**. Cellular senescence and cancer development. Cellular senescence is a stress response pathway that elicits an irreversible and permanent cell cycle arrest and releases inflammatory cytokines termed as the senescence-associated secretory phenotype (SASP) which typically recruits immune cells, such as neutrophils, to respond to malignant tumor cells.

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**Figure 2.** The effect of *H. pylori* and senescent cells on the mucosa of the stomach. *H. pylori* produces oxidative stress on gastric mucosa which leads to the creation of more senescent cells due to DNA damage. This, in turn, leads to oversecretion of SASP which creates a highly inflammatory microenvironment in the GI. While SASP usually is tumor suppressive due to an immune response, the combination of gastritis and inflammatory factors is tumor promotive. This increases the chances of gastrointestinal oncogenesis.