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Review

The Emerging Triad in Cancer and Aging: Cellular Senescence, Microbiome, and Tumor Microenvironment

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ABSTRACT: Aging is accompanied by a marked increase in cancer incidence and mortality, yet most studies still consider cellular senescence, the tumor microenvironment, and the microbiome as largely separate axes. Here, we propose an integrative triad framework in aging-related cancers in which cellular senescence, tumor microenvironment (conceptualized here as part of a broader tumor microecology), and the microbiome dynamically interact to shape tumor initiation, evolution, and treatment response. We summarize how senescent cells, via context-dependent senescence-associated secretory phenotypes (SASPs), remodel stromal, immune, and metabolic niches in aging hosts and how gut and intratumoral microbiota both induce and are reshaped by senescence. Focusing on colorectal cancer (CRC), hepatocellular carcinoma (HCC) and pancreatic ductal adenocarcinoma (PDAC), together with pan-cancer transcriptomic and microbiome analyses. We highlight disease and subtype-specific patterns in which senescence signatures, immune contexture, and microbial features co-stratify prognosis and therapeutic outcomes, and integrate pan-cancer transcriptomic and microbiome analyses to illustrate shared and divergent triad configurations across tumor types. Finally, we discuss the therapeutic implications of this triad, including timing-dependent use of senolytics and senomorphics, diet and microbiome-targeted interventions, fecal microbiota transplantation (FMT), and the ecological risks of antibiotics, particularly in multimorbid older patients. We argue that triad-informed biomarkers and trial designs integrating senescence, microenvironment, and microbiome readouts will be important for mechanism-based, age-adapted cancer prevention and therapy in older adults, especially those with CRC, HCC, and PDAC.

Keywords: cellular senescence, tumor microecology, tumor microenvironment, microbiome; aging, related cancer

1. Introduction

The global population is aging rapidly, and cancer incidence rises steeply with age, making malignancy a major health burden in older adults. Epidemiological data consistently show that cancer incidence and mortality escalate from mid-life onwards, and that older patients more often present with advanced disease, multiple comorbidities, treatment-related complications, and poorer functional outcomes than younger individuals [1, 2]. Aging and cancer, however, do not merely coexist in time: they share deeply intertwined biological foundations. Both processes are driven by overlapping upstream causes, including endogenous damage, lifestyle factors, and chronic inflammation, and converge on genomic instability, telomere erosion, epigenetic remodeling, and altered stress responses [3, 4]. Together, these observations support the view that cancer in older individuals arises from an aged biological context rather than in isolation and motivate closer scrutiny of cellular senescence, tumor microenvironment, and the microbiome as key nodes through which aging shapes cancer risk, behavior, and therapeutic response.

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At the cellular level, senescence is classically defined as a state of stable, essentially irreversible cell-cycle arrest triggered by diverse stresses such as DNA damage, telomere dysfunction, oncogenic signaling, and oxidative stress, accompanied by chromatin remodeling, metabolic reprogramming, and a pro-inflammatory senescence-associated secretory phenotypes (SASPs) [5]. In cancer, senescence is a double-edged sword: it acts as a barrier to malignant transformation by preventing the expansion of damaged cells, yet chronic accumulation of senescent cells and their SASPs can remodel surrounding tissues and ultimately promote tumor initiation, progression, and therapy resistance [6, 7]. As illustrated in Figure 1, in this review, we refer to the tumor microenvironment in the classical sense, encompassing malignant, stromal, vascular, and immune components and their soluble mediators. To emphasize the ecosystem-level dynamics that also include microbial communities and host systemic factors, we use the term tumor microecology as an extension of the tumor microenvironment. In other words, tumor microecology builds upon the established tumor microenvironment and immune microenvironment concepts by explicitly incorporating spatially and temporally dynamic interactions among tumor, stromal, immune, and microbial compartments [8]. Throughout the manuscript, we therefore use "tumor microecology" when discussing these integrated ecosystem-level interactions, while retaining "tumor microenvironment" and "immune microenvironment" when referring to more classical or compartment-specific findings from the literature.

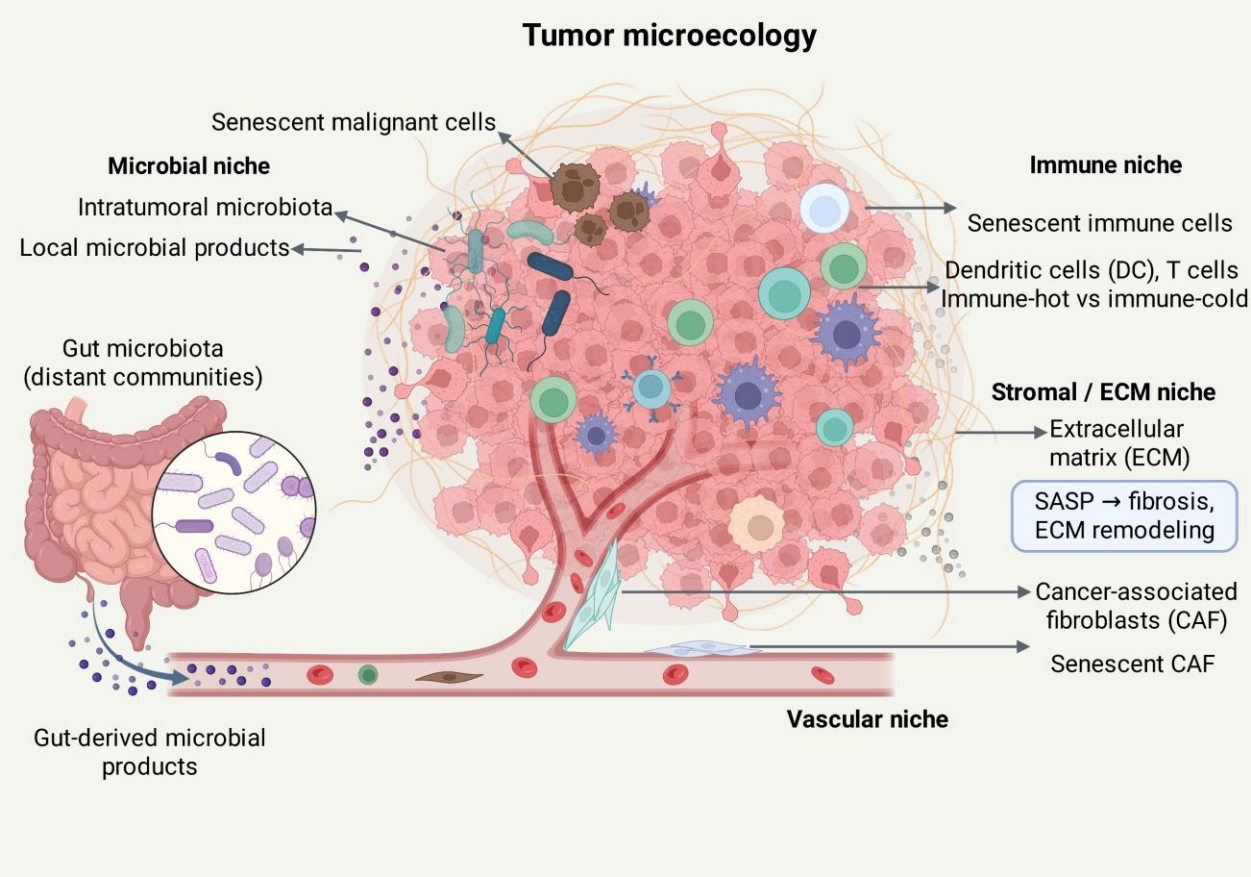

Figure 1. Tumor microecology in aging-related cancers. A tumor mass is embedded within interacting immune, stromal/extracellular matrix, vascular and microbial niches. Immune niches contain dendritic cells, effector T cells and senescent immune cells that shape immune-hot versus immune-cold states. Stromal/ECM niches comprise CAF, senescent and extracellular matrix, with SASP-driven fibrosis and remodeling. The vascular niche provides abnormal vessels and perivascular cells. Local intratumoral microbiota and their products interact with malignant and immune cells, while distant gut microbial communities supply circulating metabolites and microbial products that enter the tumor and further remodel microecology and therapy response.

Building on these conceptual advances, over the past decade, several comprehensive reviews have mapped the shared biology of aging and cancer, emphasizing hallmarks of aging, chronic inflammation, and tissue

ecosystem changes as key drivers of tumorigenesis in older adults [9-11]. Within this broader framework, more recent senescence-focused reviews have provided holistic overviews of cellular aging and senescence in cancer, detailing context-dependent tumor-suppressive and tumor-promoting effects, fate determinants, and emerging senotherapeutic strategies [12]. In parallel, an expanding body of work has characterized tumor-resident microbiota across multiple cancer types and linked intratumoral bacterial and fungal communities to immune phenotypes and prognosis, often using pan-cancer atlases and multi-omics analyses [13, 14]. Complementary pan-cancer studies have delineated senescence-related gene programs, molecular subtypes, and immune landscapes across solid tumors, and have developed computational frameworks to quantify cellular senescence at the tissue and immune-cell levels [15, 16].

In contrast to prior reviews that have focused primarily on cellular senescence or on the microbiome in isolation, building on these strands of evidence, we do not treat cellular senescence, the tumor microenvironment, and host-microbiome interactions separately. Instead, we integrate them into a unified "cellular senescence-tumor microecology-microbiome" triad and discuss their bidirectional interactions in aging-related cancers. We place particular emphasis on colorectal cancer (CRC), hepatocellular carcinoma (HCC), and pancreatic ductal adenocarcinoma (PDAC). These are malignancies along the gut-liver-pancreas axis, where senescence programs, microenvironment remodeling, and microbes are tightly linked. We also synthesize pan-cancer senescence subtypes and multi-omics senescence signatures with new atlases of intratumoral microbiota and immune states. We propose that these integrated "triad-informed" molecular and microecologic profiles might guide biomarker development, risk stratification, and trial design for aging-associated cancers. Our aim is to bridge senescence biology, tumor microenvironment, and microbiome science, thereby providing an integrated, triad-based framework for cancer prevention and treatment in older adults.

2. Conceptual Framework of the Cellular Senescence-Tumor Microecology-Microbiome Triad

In this review, we conceptualize cellular senescence, tumor microenvironment, and the microbiome as the vertices of a dynamic triad that shapes cancer in the aging host. Figure 2 summarizes how senescent cells shape the tumor microenvironment and, more broadly, the tumor microecology, in concert with gut and intratumoral microbiota in aging-related cancers. At the first vertex, senescent cells, which arise among malignant cells, cancer-associated fibroblasts, endothelial cells, and immune cells, enter stable proliferative arrest yet remain metabolically active, releasing SASPs rich in cytokines, chemokines, growth factors, and matrix-remodeling enzymes [17, 18]. At the second vertex lies the tumor microecology, encompassing immune and stromal compartments, the extracellular matrix (ECM), vasculature, and local metabolic cues that collectively determine whether tumors are constrained or allowed to progress. Senescent cells can profoundly reprogram this microecology through SASP-driven inflammation, fibrosis, and immune modulation [19]. The third vertex is formed by microbial communities, including gut microbiota and low-biomass intratumoral microbiota that inhabit tumor and immune cells and are tightly linked to immune phenotypes and prognosis across cancer types [20-22]. Together, these components participate in a feedback loop in which senescent cells, via SASPs, alter immune and stromal niches, thereby reshaping microbial ecologies, which in turn feed back on senescence and tumor behavior.

Building on this triad perspective, the proposed triad sits naturally within contemporary theories linking aging to cancer. Hallmarks of aging, such as genomic instability, telomere attrition, mitochondrial dysfunction, altered nutrient sensing, and chronic low-grade inflammation, are tightly intertwined with the emergence and persistence of cellular senescence in multiple tissues [23]. The concept of "inflammaging" further emphasizes that the age-associated accumulation of senescent cells and their SASPs creates a pro-inflammatory milieu that can accelerate malignant transformation and shape tumor evolution [24]. In this situation, senescent cells, tumor microecology, and the microbiome can be viewed as three interdependent and, importantly, therapeutically tractable nodes within the broader aging–cancer network. Zhang et al. have argued that targeting senescence is a promising strategy to modify aging trajectories and age-related diseases, including cancer, highlighting senolytics and senomorphics as emerging interventions [25, 26]. Consequently, our framework focuses specifically on how manipulating senescent cell burden and phenotype, reshaping tumor microecology, and modulating host-microbiome interactions might collectively rewire the aging host-tumor interface.

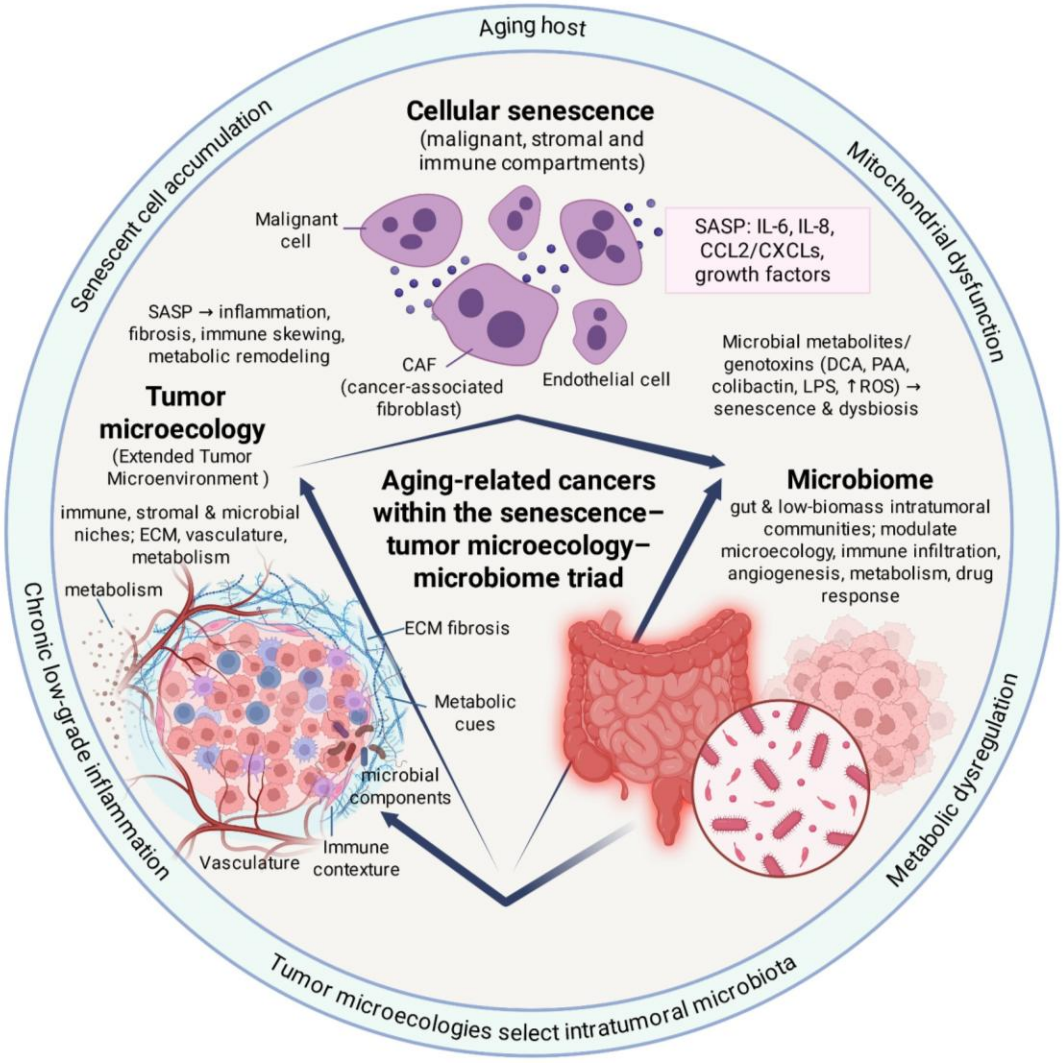

Figure 2. Conceptual framework of the cellular senescence-tumor microecology-microbiome triad in aging-related cancers. Tumor microecology is defined here as an ecosystem-level extension of the classical tumor microenvironment, encompassing malignant, stromal, vascular and immune cells together with local microbial communities, metabolic gradients and extracellular matrix organization. Cellular senescence arises in malignant, stromal and endothelial/immune compartments and, via SASPs, reshapes immune and stromal niches, extracellular matrix structure, vasculature and metabolic cues. Within this remodeled microecology, senescent cells, immune and stromal niches, and vascular networks interact to influence tumor initiation, evolution and treatment response. Gut and low-biomass intratumoral microbiota modulate systemic and local inflammation, angiogenesis, metabolism and drug effects, while tumor microecologies in turn select specific intratumoral microbial communities. The dynamic interactions among senescent cells, tumor microecology and the microbiome collectively shape the behavior of aging-related cancers.

3. Cellular Senescence as a Driver of Tumor Microenvironment Remodeling

3.1. The Double-edged Sword Effect of Cellular Senescence in Cancer

In cancer, cellular senescence exemplifies a prototypical double-edged sword (Fig. 3 provides a comparative schematic). Oncogene-induced senescence was first recognized as a potent barrier to malignant transformation, with classic work showing that activation of oncogenic Ras in primary cells triggers a permanent G1 arrest accompanied by p53/p16 upregulation, thereby preventing clonal expansion of damaged cells [27]. Genetic and histopathological studies in mouse models and human premalignant lesions have since confirmed senescence as an important early tumor-suppressive checkpoint [28]. However, senescent cells remain metabolically active and acquire SASPs, which can fuel chronic inflammation, epithelial-mesenchymal transition

(EMT), and invasion [29]. Krtolica and colleagues' experiments showed that senescent fibroblasts selectively stimulate premalignant and malignant epithelial cells to proliferate and form tumors, directly linking stromal senescence to tumor promotion [30]. More recently, chemotherapy-induced senescent cancer cells have been found to undergo transcriptional reprogramming toward a stem-like state, enhancing tumor-initiating capacity upon escape from arrest and contributing to relapse and drug resistance [31]. Therapy-induced senescence (TIS) also accumulates in non-malignant stromal and immune cells, amplifying SASP-driven toxicity and creating a tumor-supportive milieu [32].

In conclusion, these studies collectively illustrate that senescence of the malignant, stromal, and immune compartments can initially restrain but ultimately remodel the tumor microenvironment in ways that favor chronic inflammation, plasticity, and therapeutic failure. thereby setting the stage for SASP-driven rewiring of the immune microenvironment described in the following section.

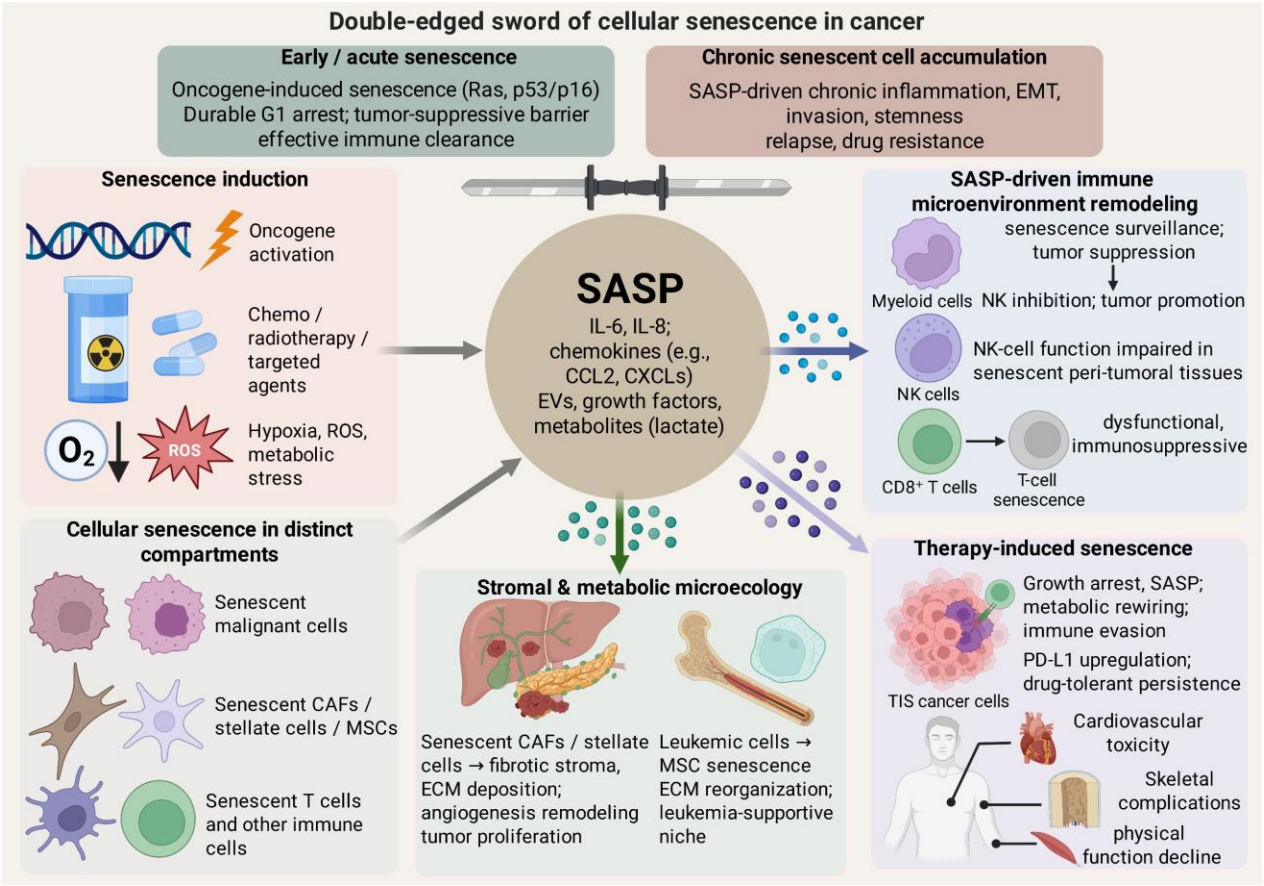

Figure 3. Double-edged roles of cellular senescence in cancer. Diverse stresses, including oncogene activation, cytotoxic therapies and metabolic or oxidative stress, induce senescence in malignant, stromal, endothelial and immune cells. Early acute senescence (e.g. Ras-p53/p16 pathways) enforces durable G1 arrest and enables immune surveillance, acting as a tumor-suppressive barrier. With chronic senescent cell accumulation, a persistent SASP rich in IL-6, IL-8, CCL2/CXCLs, growth factors and metabolites drive inflammation, EMT, invasion and resistance. SASP remodels immune, stromal and metabolic microecology, skewing myeloid and T-cell compartments. Therapy-induced senescence further contributes to PD-L1 – mediated immune evasion and late cardiovascular, skeletal and functional toxicities.

3.2. SASPs and Remodeling of the Immune Microenvironment

Extending this double-edged paradigm, SASPs profoundly remodel the tumor–immune interface by reshaping the recruitment, composition, and functional state of immune cells. Senescent cells secrete high levels of IL-6, IL-8, and CCL2, among other mediators, which attract and skew myeloid and lymphoid populations in the tumor microenvironment. In a liver cancer model, Eggert and colleagues showed that chemokines released by oncogene-induced senescent hepatocytes drive CCL2-CCR2-dependent accumulation of myeloid cells: in early stages, these cells support "senescence surveillance" and tumor suppression, but in established hepatocellular carcinoma, they become immunosuppressive, inhibit NK-

cell activity, and accelerate tumor growth [33]. Conversely, therapy-induced senescent cancer cells can also be strongly immunogenic: Marin et al. demonstrated that senescent tumor cells upregulate antigen-processing machinery and alarmins, eliciting robust $CD8^+$ T-cell responses and durable antitumor immunity in mouse models [17]. Yet a persistent senescent cell burden can blunt immunotherapy; Maggiorani et al. showed that senescent cells foster an immunosuppressive, myeloid-rich milieu that restricts intratumoral $CD8^+$ T-cell accumulation and renders PD-L1 blockade ineffective, a defect reversed by senolytic treatment [34]. Furthermore, T cells themselves undergo senescence within tumors, acquiring a distinct dysfunctional state that amplifies local immunosuppression and cooperates with SASP-driven remodeling to promote immune evasion [35].

3.3. SASP-Driven Remodeling of the Stromal and Metabolic Tumor Microenvironment

In parallel with immune rewiring, SASPs are key drivers of stromal and metabolic remodeling in tumors. In pancreatic ductal adenocarcinoma, a distinct subset of senescent myofibroblastic cancer-associated fibroblasts accumulates with disease progression and secretes immunosuppressive and matrix-remodeling mediators that reshape the fibrotic stroma and vascular niche [36]. Another similar study shows that signaling networks in cancer stromal senescent cells coordinate ECM deposition, angiogenesis, and growth factor signaling to establish a malignant microenvironment [37]. At the organ level, senescent pancreatic stellate cells secrete CXCR2-agonist chemokines (CXCLs) that enhance the proliferation and migration of pancreatic cancer cells, supporting a dense, hypoperfused desmoplastic niche [38].In the liver, senescent hepatic stellate cells release extracellular vesicles that stimulate macrophage epidermal growth factor(EGF) production and, in turn, increase hepatoma cell viability, linking fibrotic remodeling with paracrine growth support [39]. In the bone marrow niche, leukemic cells induce mesenchymal stem cell senescence with elevated reactive oxygen species (ROS) and SASPs, altering ECM organization and skewing hematopoiesis toward leukemia suppor [40].

Metabolically, senescent stromal cells adopt a PDK4-dependent hypercatabolic state with enhanced glycolysis and lactate release; lactate boosts NOX1-mediated ROS, which further amplifies SASPs expression, creating a positive feedback loop between metabolic stress and inflammatory secretion [41]. Collectively, these data support a model in which SASPs orchestrates fibrosis, angiogenesis, ECM remodeling, and metabolite gradients in an organ-specific manner, thereby re-stratifying nutrient and oxygen distribution and reinforcing tumor-promoting microenvironment in bone, liver, and pancreas. This multilayered remodeling renders the tumor microenvironment particularly susceptible to therapeutic perturbations, providing an essential backdrop for understanding the impact of therapy-induced senescence.

3.4. TIS and the Reprogramming of Tumor Microenvironment

Against this remodeled microecologic background, TIS has emerged as a common fate of tumor and stromal cells exposed to chemotherapy, radiotherapy, and targeted agents, initially reinforcing tumor control by enforcing durable growth arrest. However, accumulating evidence indicates that persistent TIS cells become a long-term liability for the tumor-bearing host [42]. Classic lineage-tracing experiments by Demaria et al. demonstrated that chemotherapy-induced senescent cells persist systemically in mice and that their clearance reduces inflammation, treatment toxicity, and cancer relapse, implicating TIS as an active driver of post-therapy disease evolution [32].

More recently, Bajtai et al. showed that in breast cancer, TIS represents a transient drug-tolerant state from which cells can re-enter the cell cycle with enhanced aggressiveness and clonal diversity [43]. At the immune interface, Hwang et al. demonstrated that TIS cancer cells upregulate and stabilize PD-L1 via RPN1-dependent glycosylation, creating a “PD-L1 umbrella” that shields residual tumor cells from cytotoxic T cells [44]. Complementarily, Maggiorani et al. showed that senescent cell accumulation after chemo-irradiation induces an immunosuppressive myeloid skewing that compromises immune checkpoint blockade, whereas senolytic clearance restores $CD8^+$ T-cell activity and immunotherapy efficacy [34]. These researches support a dynamic view in which TIS not only reprograms tumor microenvironment toward chronic inflammation and immune escape, but also selects for resistant subclones, providing a mechanistic rationale for “one-two punches” strategies that combine pro-senescent regimens with senolytics or SASP-targeting agents.

Taken together, these observations crystallize a clinical dilemma: transient, therapy-induced senescence can be harnessed to amplify anti-tumor immunity and improve initial tumor control, yet persistent pools of senescent tumor and stromal cells may drive late toxicities, chronic inflammation, and therapeutic resistance. This dual nature implies that the net impact of TIS is highly context and time-dependent and highlights the need for careful consideration of treatment timing, dosing, and patient selection when implementing senescence-modulating strategies. In parallel, several emerging approaches aim to therapeutically remodel the

tumor microenvironment, through rational combinations of immunotherapy, stromal reprogramming, and metabolic or vascular targeting, and early data from such studies further support evaluating TIS-directed and tumor microenvironment interventions in an integrated rather than isolated manner [45-47]. This integrated perspective on TIS and microenvironmental remodeling is particularly relevant in aging-related cancers, where baseline senescent cell burden and comorbidities may magnify both the benefits and risks of such strategies.

From a geriatric oncology perspective, TIS is increasingly recognized as a biological substrate of "accelerated aging" phenotypes in older adults with cancer. Persistent TIS and SASP-driven low-grade inflammation have been linked to higher burdens of cardiovascular toxicity, skeletal complications, fatigue, and physical function decline after chemotherapy, radiotherapy, and targeted agents, particularly in patients with pre-existing frailty or multimorbidity [48, 49]. Cohort and interventional studies in geriatric oncology further indicate that frailty indices, geriatric assessment domains, and candidate senescence biomarkers predict grade $\geqslant$3 toxicities, functional decline, hospitalization, and reduced survival beyond chronological age, as well as tumor factors [50-52]. These observations suggest that TIS should be conceptualized not only as a tumor-intrinsic resistance program but also as a systemic driver of late toxicities that constrain the tolerability and long-term benefits of cancer therapy in older adults, reinforcing the need to embed senescence and microecology-aware strategies within personalized treatment planning for this growing patient population.

4. Interactions Between Cellular Senescence and the Microbiome

4.1. Age-Related Remodeling of the Gut Microbiome and Its Links to Inflammaging

Aging is accompanied by a characteristic remodeling of the gut microbiome, marked by reduced microbial diversity, loss of health-associated core taxa (for example, *Ruminococcaceae* and *Lachnospiraceae*), and expansion of opportunistic or pro-inflammatory species. Some studies report that "unhealthy" aging is typically associated with depletion of short-chain fatty acid (SCFA) producers and enrichment of pathobionts, whereas "healthy" aging maintains a more diverse, SCFA-rich community [53-56]. Large metagenomic analyses show that the aging trajectory of gut microbiota is tightly coupled to metabolic disease, Fu et al. report that deviations in "microbiota age" from chronological age associate with hypertension, diabetes, and obesity in a dose-dependent manner [57]. Extending this, a Nature Medicine cohort demonstrates that a "younger" gut microbial age attenuates cardiovascular risk in metabolically unhealthy older adults, linking microbial configurations directly to hard outcomes [58].

These compositional shifts correlate with inflammaging and frailty. The NU-AGE randomized trial showed that a 1-year Mediterranean diet in older Europeans increased SCFA-producing taxa, reduced pro-inflammatory species, and improved frailty scores and inflammatory markers, supporting a causal link between diet-driven microbiome changes and systemic inflammation [59]. Longevity cohorts further indicate that long-living adults retain higher abundances of beneficial butyrate producers (*Roseburia, Eubacterium rectale, Faecalibacterium*), which associate positively with physical function and metabolic resilience [60]. Taken together, these observations position the aging gut microbiome as both a marker and a potential driver of inflammaging, providing a natural entry point for investigating how microbial changes intersect with cellular senescence.

4.2. Microbiome-Driven Mechanisms of Cellular Senescence

Accumulating evidence indicates that gut dysbiosis can actively drive cellular senescence through converging inflammatory and metabolic insults. Chronic enrichment of pathobionts increases mucosal permeability and systemic exposure to microbial products, sustaining low-grade inflammation, reactive ROS production, and DNA damage responses that ultimately trigger senescence programs in multiple tissues. A study by Yoshimoto et al. in obese mice showed that dysbiosis elevates the secondary bile acid deoxycholic acid (DCA), which causes DNA damage in hepatic stellate cells, induces a robust SASP, and thereby promotes hepatocellular carcinoma development [61]. Beyond bile acids, microbiota-derived aromatic metabolites directly impose senescence: Saeedi Saravi et al. demonstrated that phenylacetic acid(PAA) and its byproduct phenylacetylglutamine(PAGln) are increased in aged humans and mice, and that colonization with a PAA-producing Clostridium strain drives endothelial senescence via mitochondrial H_2O_2 generation and amplification of SASP signaling, while age-related loss of acetate removes a SIRT1-dependent senomorphic brake [62]. At the immune level, persistent stimulation by commensal bacteria induces *p16*^{INK4a}-positive germinal-center B-cell senescence in Peyer's patches and isolated lymphoid follicles, reducing IgA quantity and diversity and thereby reshaping the gut microbiota towards an aged, dysbiotic configuration [63]. These findings are defined

as a bidirectional feedback loop in which dysbiosis, oxidative stress, and senescence mutually reinforce each other across vascular, stromal, and immune compartments [64]. This conceptual loop provides a mechanistic bridge from age-related gut dysbiosis and metabolic derangements to widespread cellular senescence at barriers and systemic sites. In turn, it raises the question of how senescent mucosal barriers feedback to reprogram the microbiome in aging, which we address in the next section.

4.3. Senescent Mucosal Barriers Reprogram the Gut Microbiome in Aging

Building on these observations, accumulation of senescent cells within the intestinal epithelium and mucosal immune system progressively reshapes gut microbial communities and barrier function in older hosts. At the epithelial interface, chronic infection or sterile stress can drive DNA damage and ROS-mediated senescence; in a recent mouse model of Toxoplasma gondii-associated colitis, colonic senescent cells accumulated with elevated $p16^{INK4a}$/$p21^{CIP1}$ and SASPs, tightly correlating with reduced tight-junction proteins, mucus thinning, and increased serum LPS, while senolytic dasatinib-quercetin restored barrier integrity and dampened inflammation [65]. Complementary work in naturally aged mice shows that age-related defects in epithelial renewal, junctional integrity, and local immune tone are strongly microbiota-dependent: transferring young microbiota or depleting aged microbiota improves barrier function and reduces mucosal stress responses [66]. Together with earlier research, it shows that aging-associated dysbiosis increases permeability, systemic inflammation, and macrophage dysfunction in a feed-forward loop [67]. These data indicate that barrier senescence and microbiome alterations are tightly intertwined rather than independent phenomena.

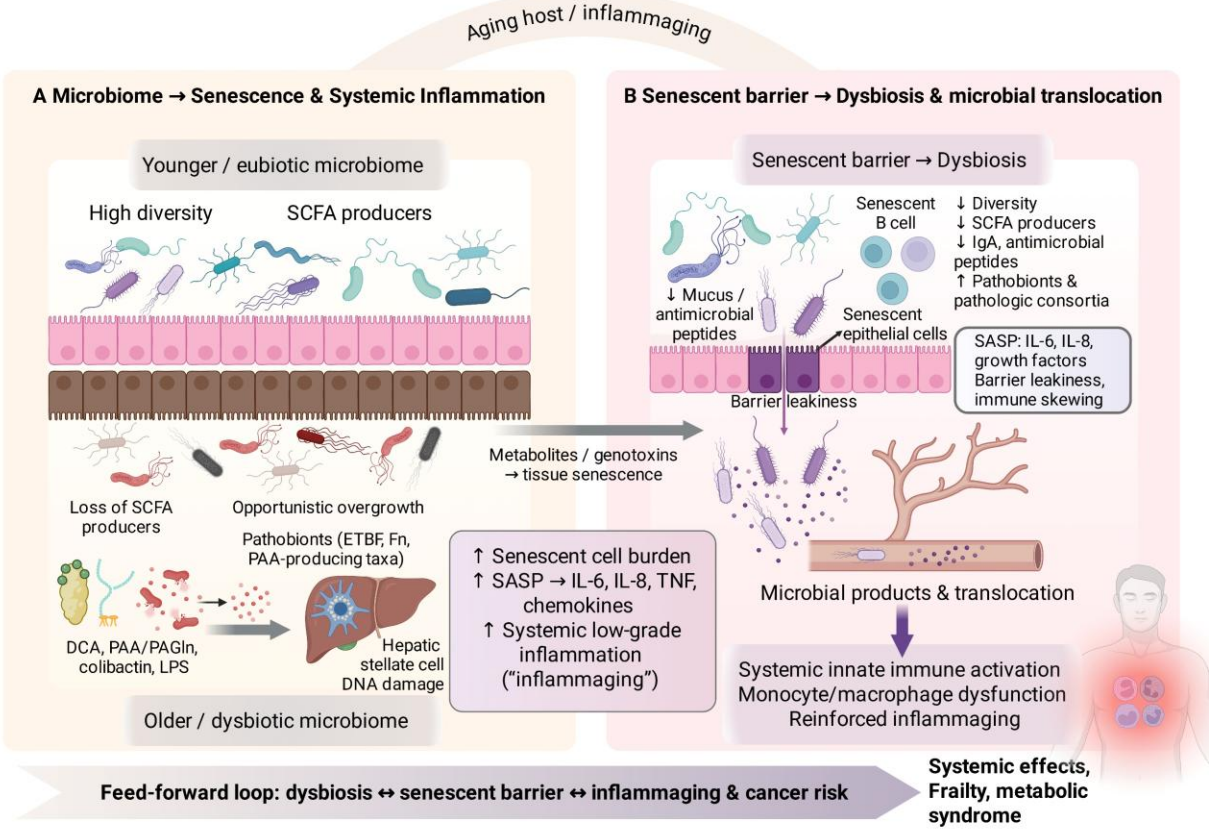

Figure 4. Bidirectional crosstalk between the gut microbiome, cellular senescence and inflammaging. (A) With aging, a younger/eubiotic microbiome characterized by high diversity and SCFA producers shifts toward an older/dysbiotic state with loss of SCFA producers, opportunistic overgrowth and pathobionts (e.g. Enterotoxigenic Bacteroidesfragilis (ETBF), Fusobacterium nucleatum (Fn), PAA-producing taxa). Microbial metabolites and genotoxins (DCA, PAA/PAGln, colibactin, LPS) drive tissue senescence, increased SASP and systemic low-grade inflammation ("inflammaging"). **(B)** Senescent epithelial and B cells within the intestinal barrier secrete SASP, reduce mucus and antimicrobial peptides, disrupt IgA repertoire and cause barrier leakiness, promoting dysbiosis and microbial product/translocation-induced innate immune activation. A feed-forward loop reinforces dysbiosis, inflammaging, frailty and cancer risk.

These findings support a bidirectional "senescence-microbiome-barrier" circuit. Senescent epithelial and immune cells weaken physical and immunological barriers, including reduced IgA, antimicrobial peptides, and tight junctions, enabling greater translocation of microbial products and selection of pro-inflammatory taxa; in turn, dysbiotic microbiota and their metabolites reinforce cellular senescence and inflammaging. Notably, lifelong microbiome rejuvenation strategies can partially normalize barrier function and inflammatory tone in aged animals [68], implying that interrupting this positive feedback may lower the chronic pro-tumorigenic "background noise" that predisposes elderly individuals to cancer. Figure 4 depicts the bidirectional crosstalk between the gut microbiome, cellular senescence and inflammaging, providing a mechanistic backdrop for the triad framework we apply to specific aging-related cancers in subsequent sections.

5. Integrated Evidence in Age-Related Tumors

5.1. Cellular Senescence and the Microbiome: Key Forces in Shaping the Microecology of Age-Related Tumors

Among many solid tumors that exhibit age dependence, we focus on CRC, HCC, and PDAC as prototypical models in which cellular senescence, tumor microecology and the microbiome are tightly intertwined. Table 1 summarizes key clinical, microecologic, and microbiome-related features of CRC, HCC, and PDAC within this triad framework. CRC incidence rises steeply with age and is strongly shaped by diet and gut microbial composition; recent work in murine and human CRC shows that age-diet interactions remodel intratumoral gene expression, gut microbiome signatures, and cytokine-defined tumor microecology, directly linking geriatric physiology to microbiome-driven tumor biology [69]. A large integrative atlas of colon cancer further demonstrates that specific intratumoral bacterial consortia co-segregate with immune phenotypes and prognosis, providing a concrete example of microbiome-tumor microecology co-structuring in an age-associated malignancy [70]. HCC typically arises on a background of metabolic liver disease and chronic inflammation; senescence-related gene signatures in HCC stratify prognosis and immune infiltration, highlighting a central role of senescence programs in shaping the hepatic niche [71].

Table1. Key features of the senescence-microecology-microbiome triad in CRC, HCC, and PDAC.

Cancer type	Triad component	Key feature	Model /study type	Reference
CRC	Senescence	Epithelial-stromal senescence	Mouse & human CRC; tissue markers	[128]
CRC	Microecology	Age-diet immune remodeling	Aging/dietary mouse models; immune profiling	[69]
CRC	Microbiome	Pathobiont-rich dysbiosis	Human cohorts; microbiome profiling	[129]
CRC	Integrated/Clinical	Triad-informed geriatric therapy	Conceptual integration; geriatric cohorts	[84]
HCC	Senescence	Stellate cell senescence	Obesity-linked HCC mice; human senescence signatures	[61]
HCC	Microecology	Immunosuppressive niche	Cirrhotic/HCC tissues; multi-omics & immune profiling	[130]
HCC	Microbiome	Gut-liver axis dysbiosis	NAFLD/NASH & HCC cohorts; gut microbiome & gut – liver axis models	[131]
HCC	Integrated / Clinical	Triad-guided HCC therapy	Conceptual & translational HCC triad work	[61]
PDAC	Senescence	Senescent cancer-associated fibroblasts(CAF) barrier	Mouse/human PDAC CAF senescence & immunotherapy experiments	[73]
PDAC	Microecology	Desmoplastic immune exclusion	Preclinical PDAC & tissues; fibrotic, immune-excluded tumor microecology	[132]
PDAC	Microbiome	Intratumoral gemcitabine-metabolizing bacteria	Mouse/huma intratumoral microbiome & gemcitabine-metabolism assays	[133]
PDAC	Integrated / Clinical	Triad-based PDAC strategies	Conceptual & translational triad-based PDAC strategies	[134, 135]

Seminal mechanistic work showed that the microbiota-derived metabolite deoxycholic acid, elevated in obesity, induces senescence and a pro-tumorigenic SASP in hepatic stellate cells, thereby promoting HCC development [61]. PDAC, another strongly age-biased cancer, displays an extremely fibrotic, immunosuppressed microenvironment in which both senescent stromal cells and microbes play key roles: intratumoral, cell-associated bacteria correlate with specific cancer cell programs and immune states [72]. while a defined subset of senescent cancer-associated fibroblasts in PDAC restricts $CD8^+$ T-cell activation and limits the response to immunotherapy [73]. Together, these three tumor types provide rich, mechanistically grounded examples of the senescence-tumor microecology-microbiome triad, which justify their selection as focal cancers in this review.

Beyond these tumor-intrinsic and microecologic features, the broader geriatric context further modifies how the triad is expressed and how it can be therapeutically targeted. In real-world practice, older adults with CRC, HCC and PDAC frequently present with multimorbidity, polypharmacy and pre-existing frailty, all of which shape the senescence-tumor microecology-microbiome triad and the window of therapeutic opportunity. Geriatric oncology cohorts consistently show that polypharmacy, potentially inappropriate medications, and major drug-drug interactions are highly prevalent and independently associated with worse treatment tolerance, unplanned hospitalizations, and mortality in older patients with cancer [74, 75]. Beyond clinical outcomes, geriatric medicine studies link polypharmacy and high anticholinergic burden to reduced gut and oral microbiome diversity and enrichment of pathobionts, providing a mechanistic bridge between medication load, microbiome disruption, and pro-senescent, pro-inflammatory milieus in aging hosts [76, 77]. These data argue that medication optimization and formal geriatric assessment should be integrated into triad-informed strategies, because baseline senescence burden and concomitant drug exposures may critically determine who benefits or is harmed by senescence-targeted therapies, immunotherapy, or microbiome modulation.

5.2. Evidence of Triad Interplay in CRC

In CRC, integrative multi-omics analyses are beginning to reveal a tight coupling between senescence programs, immune infiltration, and gut microbial composition [78-80]. Dai and colleagues identified two senescence-related molecular subtypes of CRC based on 91 senescence-related genes and constructed an eight-gene SRG signature; these subtypes differed not only in prognosis and tumor immune cell infiltration but also in the abundance of several gut bacterial taxa, directly linking senescence states to both the tumor microecology and microbiota [81]. Wu et al. defined “aging-high” and “aging-low” CRC clusters from gut microbiota profiles and transcriptomic data, showing that aging-high tumors in older patients display enrichment of pro-inflammatory and immunosuppressive pathways and distinct microbial signatures, suggesting that age-related dysbiosis imprints a senescence-like, immunologically “cold” phenotype [82, 83]. Mechanistic studies implicate specific CRC-associated bacteria as inducers of DNA damage and senescence in colonic epithelium. Okumura et al. showed that 12 faecal bacterial taxa are enriched in CRC patients, and that two Porphyromonas species accelerate tumorigenesis in $Apc^{A14/+}$ mice via butyrate secretion; disruption of bacterial butyrate-synthesis genes abolishes this effect, and butyrate exposure induces a senescence-like phenotype in colon epithelial cells [84].

Independently, genomic analyses have identified a characteristic mutational signature of the genotoxin colibactin in human CRC, providing strong evidence that colibactin-producing *E. coli* contribute causally to tumorigenesis by inducing DNA damage in colonic cells [85]. Downstream of this damage, colibactin-triggered SASPs have been shown to foster epithelial-mesenchymal transition, cancer stem-cell emergence and chemoresistance, further integrating microbial genotoxicity with senescence-driven remodeling of the CRC microecology [86]. Together, these data illustrate a CRC-specific triad in which senescence signatures, immune-stromal context, and gut microbiota co-evolve, particularly in aging hosts. thereby providing one of the clearest examples of how the senescence-tumor microecology-microbiome framework plays out in a single cancer type.

5.3. HCC and PDAC: A Nexus of metabolism-microbiome-senescence

Beyond the colon, HCC provides a prototypical example of a tumor driven by the convergence of metabolic stress, gut dysbiosis, and senescence. In obesity/non-alcoholic fatty liver disease(NAFLD) models, a high-fat diet promotes intestinal overgrowth of gram-positive bacteria, and production of lipoteichoic acid and deoxycholic acid, which translocate to the liver and enhance SASP phenotype in hepatic stellate cells; this COX2–PGE_2 program suppresses antitumor immunity and accelerates HCC development [87-89]. Recent clinical and translational studies further show that HCC is accompanied by stage-dependent gut dysbiosis and a characteristic intratumoral microbiota, linking bile-acid perturbation, chronic inflammation, and senescence-prone hepatic niches to tumor progression [90, 91].

On the other hand, PDAC illustrates a related yet anatomically distinct "metabolism-microbiome-senescence" circuitry. PDAC harbors a highly enriched intratumoral microbiome; depletion of these bacteria protects against tumor development, whereas transfer of microbiota from tumor-bearing hosts restores oncogenesis via innate and adaptive immune suppression [92]. In patients, higher intra-tumoral microbial diversity associates with more favorable immune infiltration and improved survival, underscoring the co-evolution of the microbiome-tumor microecology [93]. Importantly, single-cell and functional work has identified a subset of senescent cancer-associated fibroblasts in PDAC that accumulate with disease progression, remodel the extracellular matrix, and orchestrate macrophage-mediated immunosuppression [36]. In conclusion, these data support a model in which metabolic derangements and microbial products foster tissue-specific senescent cell populations, which in turn sculpt liver and pancreatic tumor microecologies that are permissive to carcinogenesis, highlighting HCC and PDAC as complementary exemplars of the triad in metabolically stressed, microbiome-sensitive organs.

5.4. A Pan-Cancer Analysis of the senescence-immune-microbiome Triad

While CRC, HCC, and PDAC illustrate organ-specific realizations of the triad, High-dimensional pan-cancer analyses now provide a systems-level view of how cellular senescence states intersect with tumor immunity and intratumoral microbes. Using >9,700 tumors from 33 cancer types, Chen and colleagues defined five cellular senescence subgroups based on related gene signatures and showed that these subgroups ("C1–C5") differ markedly in inflammatory and metabolic pathways, immune infiltration, prognosis, and the composition of intratumoral microbiota at phylum and genus levels [94]. The "C1 inflamm-aging" subgroup, for example, exhibits strong IL-6/JAK/STAT3 activation, dense leukocyte infiltrates, high PD-L1 expression and enrichment of specific bacterial taxa, whereas "C4 immunologically quiet" tumors are microbially and immunologically depleted, highlighting a structured senescence–immune–microbiome axis at the pan-cancer level.

An independent pan-cancer study of >10,000 TCGA tumors quantified a cellular senescence score and demonstrated that cancers segregate into "protective" and "risky" senescence groups with distinct immune cell compositions and divergent associations with response to chemo- and immunotherapy [95]. Complementing these transcriptomic landscapes, Liu et al. profiled 16S rDNA from 783 tumors across seven cancer types and showed that intratumoral communities share core genera (for example, *Pseudomonas, Streptococcus, Prevotella*) but display cancer-specific diversity and co-abundance networks, reinforcing the concept of tumor-type-specific microbial ecologies [20]. Together, these pan-cancer datasets outline a macro-scale "triad" in which senescence-defined tumor states, immune contexture and intratumoral microbiota are co-stratified, providing a quantitative scaffold for mechanistic and therapeutic studies of the senescence-tumor microecology-microbiome interplay, and linking the disease-specific examples in CRC, HCC, and PDAC to a broader, system-wide landscape of aging-related cancer biology.

6. Therapeutic Implications of the Senescence-Microecology-Microbiome Triad

6.1. Targeting Senescent Cells: Balancing Senolysis and Immunity

Targeting cellular senescence in oncology spans two complementary strategies: senolytics, which selectively eliminate senescent cells, and senomorphics, which attenuate the SASPs without reversing cell-cycle arrest. Preclinical "one-two punch" regimens, in which cytotoxic or CDK4/6-inhibitor therapy first induces TIS and is followed by senolysis, show that clearing residual senescent tumor cells can delay relapse and reduce metastasis [96]. Similarly, in head and neck cancer, cisplatin-induced senescent cells can escape growth arrest, whereas subsequent treatment with navitoclax efficiently triggers BAX-dependent apoptosis and prolongs tumor control, illustrating the potential of timed senolysis after standard chemotherapy [97]. However, TIS is not purely detrimental. Senescent tumor cells can be highly immunogenic: Marin et al. showed that senescent cancer cells elicit robust, $CD8^+$ T cell-mediated antitumor immunity superior to classical immunogenic cell death, suggesting that transient senescence could be exploited as an in situ vaccine or to prime checkpoint blockade [17]. Consistently, senescent cancer cell-based vaccines induce strong cytotoxic T cell responses and synergize with radiotherapy and PD-1 inhibition in murine models [98]. Yet persistent senescent cells can also drive an immunosuppressive, checkpoint-rich tumor microecology and resistance to immune checkpoint inhibitors, highlighting the need to couple senescence induction with timely clearance or SASP modulation [34]. Thus, clinical translation of senescence-targeted strategies requires a careful balance between harnessing short-lived, pro-immunogenic TIS and avoiding the long-term accumulation of deleterious senescent cell pools.

Senomorphics provide a complementary approach by damping harmful SASP signaling. For example, mTOR inhibition with rapamycin suppresses IL-1α-dependent

SASPs and reduces the protumorigenic activity of senescent cells in vivo, without reversing growth arrest [99, 100]. Such adaptive strategies are central to safely exploiting the double-edged nature of senescence within the senescence-tumor microecology-microbiome triad. In older patients, this balance becomes even more delicate, given their higher baseline senescence burden and vulnerability to both toxicity and immune dysfunction.

6.2. Microbiome-Targeted Interventions in Older Cancer Patients

In parallel with direct manipulation of senescent cells, a growing body of work suggests that modulating the gut-tumor microecology through diet and microbiome-directed interventions may be particularly relevant for older cancer patients, whose baseline microbiota often already shows features of dysbiosis [101]. In advanced melanoma, a prospective study demonstrated that patients with high habitual dietary fiber intake had significantly better responses and progression-free survival with immune checkpoint blockade, whereas concurrent use of over-the-counter probiotics was associated with reduced microbial diversity and poorer outcomes [102]. Building on this, several early-phase trials show that fecal microbiota transplantation (FMT) from immunotherapy responders can reprogram the gut ecosystem and restore sensitivity to anti-PD-1 in a subset of patients with refractory melanoma and other solid tumors, accompanied by increased cytotoxic T-cell activity in blood and tumor tissue [103, 104]. More recently, a multicenter trial in refractory, unresectable, or metastatic solid tumors showed that FMT from carefully screened donors improved anti-PD-1 efficacy in gastrointestinal and other cancers, further supporting FMT as a feasible adjunct to immunotherapy [105].

At the same time, antibiotic-induced ecological disruption can undermine these benefits. A large population-based cohort of >12,000 patients receiving immune checkpoint blockade(ICB) found that systemic antibiotic exposure in the 12 months before treatment initiation was independently associated with worse overall survival, consistent with a detrimental impact of microbiome depletion on antitumor immunity [106]. A meta-analysis across cancer types confirmed that peritherapy antibiotics significantly reduce ICB efficacy [107]. Beyond oncology, work in progeroid and naturally aged mice shows that FMT or "young microbiota" transfer can extend healthspan and modulate systemic inflammation [108], suggesting that microbiome rejuvenation strategies might be leveraged not only to enhance tumor immunity but also to improve resilience and treatment tolerance in elderly cancer patients—provided that interventions are carefully timed and individualized to avoid blunting beneficial immune responses. Taken together, these data argue for viewing diet, antibiotics, probiotics, and FMT as ecologic levers within the triad, rather than as isolated adjuncts to systemic therapy.

6.3. Triad-Informed Biomarkers and Patient Stratification

Building on the aging–tumor microecology-microbiome triad, an obvious next step is to move from single-axis markers to composite, "triad-informed" classifications [109]. Recent pan-cancer work has already shown that senescence-related gene expression can define discrete cellular senescence subgroups with distinct prognoses, immune phenotypes, and intratumoral microbiota, and can be inferred by a machine-learning model that predicts immunotherapy response [94]. At the immune level, the ISENICS framework quantifies senescent immune cells across 23 cancers and demonstrates that high immune senescence scores associate with immune-cold tumor microecology and poorer checkpoint inhibitor responses [110].In parallel, pan-cancer profiling of intratumoral microbiota reveals recurrent microbial genera and diversity patterns that covary with tumor type and microecology features [20]. Pan-cancer analysis reveals intratumoral microbial diversity across multiple cancers using amplicon technology [111]. Across multiple tumor types and regions, gut metagenomic signatures and functional pathways further stratify responders versus non-responders to immune checkpoint inhibitors [112]. Multi-kingdom microbiome models extend this concept by integrating bacteria, fungi, archaea, and viruses to define microbiome-based ICI response subtypes [113].

Collectively, these studies support a triad-informed strategy in which senescence signatures, microbiome (gut and intratumoral) profiles, and tumor microecology are combined into composite risk scores and trial stratification schemas, particularly valuable for older patients with high senescence burden and microbiome dysbiosis. In practice, this suggests future clinical trials that prospectively incorporate senescence indices, geriatric assessment, and microbiome profiling into enrollment and treatment decisions, allowing the triad framework to move from a conceptual model to a basis for precision, age-adapted oncology.

7. Future Directions and Challenges

7.1. Methodological and Causal-Inference Challenges in Triad Research

Disentangling causation from correlation in the senescence-tumor microecology-microbiome triad

remains a major challenge. Most current evidence comes from cross-sectional multi-omics datasets in which senescence signatures, immune states, and microbial reads are co-measured but not temporally resolved. As a result, many of the links highlighted in this review should still be regarded as hypothesis-generating associations rather than established causal relationships. As Liu and colleagues emphasize for the intratumoral microbiota, rigorous inference will require integrated designs that combine spatially resolved sequencing, mechanistic animal models, and validation in human cohorts [114]. Bibliometric mapping of gut microbiota-senescence research similarly highlights a scarcity of longitudinal and intervention studies capable of supporting causal claims [115]. In parallel, the lack of standardized approaches to measuring and reporting senescence further limits comparability across studies: the newly proposed MICSE ("Minimal Information on Cellular Senescence Experimentation in vivo") guidelines and related recommendations from the SenNet consortium stress the need to use combinations of validated markers, report tissue and context-specific assay conditions, and provide transparent documentation of experimental design and data processing when quantifying senescent cells in vivo [116, 117].

Technical artefacts further complicate the interpretation of the cancer microbiome component of the triad. Re-analyses of TCGA-derived cancer microbiome data and other pan-cancer cohorts have demonstrated that low-biomass microbial signals are highly susceptible to contamination, misclassification, and batch effects, and that inappropriate preprocessing can generate spurious cancer type-specific signatures [118, 119]. More general guidelines for low microbial-biomass microbiome studies recommend rigorous sampling and reagent controls, the inclusion of negative and environmental blanks, batch-aware experimental design, and explicit reporting and benchmarking of decontamination pipelines [120, 121].Taken together, these methodological and causal-inference challenges mean that future progress will depend on triad-aware study protocols that prospectively integrate senescence, microecology, and microbiome readouts using standardized, contamination-conscious workflows. Future work at the interface of cellular senescence and tumor microecology will therefore need to integrate these emerging standards for senescence experimentation with best practices for low-biomass microbiome profiling to generate robust, causally informative datasets.

7.2. Clinical Translation in Older Adults: Multimorbidity, Senotherapies, and Microbiome Interventions

Against this methodological backdrop, translating the senescence-tumor microecology-microbiome triad into practice is particularly complex in older cancer patients, who frequently present with multimorbidity and polypharmacy. Large geriatric oncology analyses emphasize that common comorbidities substantially constrain treatment choices and increase toxicity risk, yet are rarely incorporated into trial designs or biomarker strategies [122]. Polypharmacy itself reshapes host microbial and metabolic states: in multidrug-treated older adults, the number and class of medications correlate with reduced gut microbial diversity and broad shifts in metagenomic species and metabolic pathways [77, 123]. These data imply that senescence burden and microbiome composition in older patients are heavily drug-modified, complicating both risk prediction and intervention. Consequently, any triad-informed strategy must account for background comorbidity and medication landscapes rather than assuming a "healthy" aging baseline.

Early human trials of senolytics illustrate parallel ethical and safety uncertainties. Idiopathic pulmonary fibrosis (IPF) is an archetypal senescence-associated disease. IPF open-label and randomized studies of dasatinib plus quercetin suggest feasibility and modest functional benefit, but also highlight off-target toxicities and the need for careful dosing and monitoring in frail older adults [124, 125] Likewise, systematic reviews and meta-analyses of FMT to augment immunotherapy report encouraging signals but are limited by small sample sizes, heterogeneous protocols and very short follow-up, underscoring unresolved questions about long-term safety, donor selection and pathogen transmission in immunocompromised, comorbid hosts [126, 127]. From a triad perspective, these experiences with senotherapies and microbiome interventions caution against assuming that strategies beneficial in younger or fitter populations will translate directly to geriatric oncology. Together, these considerations argue that senolytics and microbiome-directed therapies in elderly cancer populations must be embedded within geriatric assessment frameworks, with long-term pharmaco-vigilance and explicit evaluation of quality-of-life and functional outcomes, so that benefits to tumor control are weighed against risks to overall healthspan and independence.

8. Conclusion

Taken together, the studies synthesized in this review support a conceptual view in which cellular senescence, the tumor microecology, and the microbiome form a functional triad that may collectively shape the initiation, evolution, and treatment responsiveness of aging-related cancers. However, most available data are cross-sectional

or correlative, and robust causal inference for this triad remains limited, underscoring the need for longitudinal cohorts and interventional studies that jointly profile senescence, microecologic remodeling, and microbial dynamics in humans. Viewed through this triad lens, senescence signatures, ecosystem-level features of the tumor microenvironment, gut and intratumoral microbiota emerge as complementary, and potentially actionable, dimensions for biomarker development and risk stratification. Future work should prioritize triad-informed molecular classifications and clinical trial designs that prospectively integrate senescence indices, geriatric assessment, and microbiome profiling, particularly in older adults with high senescence burden and microbiome dysbiosis. Ultimately, translating this framework into practice will require not only refining causal maps between triad components and clinical outcomes, but also rigorously balancing tumor control, toxicity, and functional independence to achieve truly mechanism-based, age-adapted cancer prevention and therapy.

Author contributions

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The authors declare no competing interests.

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