Trends in Cancer

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Review

Amino acid metabolism at the senescence–cancer interface

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Amino acid (AA) metabolism plays a fundamental role in the regulation of cellular senescence. Through profound AA metabolic reprogramming, senescent stromal cells can sustain tumor progression, metastatic dissemination, and the establishment of an immunoevasive microenvironment. Conversely, alterations in AA availability within the tumor microenvironment can enforce tumor-suppressive senescence in malignant cells. In this review, we discuss how senescence-driven rewiring of AA metabolism shapes tumor–stroma interactions and immune responses. We propose that AA-targeted interventions may represent an effective therapeutic strategy to simultaneously mitigate the detrimental effects of stromal senescence while inducing tumor-suppressive senescence in cancer cells.

Highlights

Senescent cells exhibit diffuse metabolic alterations and selective dependencies on specific amino acids, driven by increased demands for redox homeostasis, protein turnover, and biosynthesis of the senescence-associated secretory phenotype.

Amino acid metabolism rewiring has a dual role in cancer: promoting tumor progression via stromal senescence while counteracting tumor growth through the induction of cancer cell senescence.

Dysregulated amino acid metabolism in senescent cells promotes immune evasion, creating a permissive environment for malignant progression.

Amino acid-driven metabolic changes in stromal senescent cells facilitate pre-metastatic niche formation, supporting the colonization and reawakening of dormant disseminated tumor cells.

Targeting senescent cells' metabolic vulnerabilities offers a promising strategy to enhance cancer therapy and overcome immune suppression.

Amino acid metabolism in cancer and senescence: a double-edged sword

Cellular senescence is a stable cell cycle arrest that arises in response to different stress signals, including genomic damage, oncogenic signaling, oxidative stress, and chemotherapy-induced toxicity. Senescent cells have classically been associated with profound metabolic rewiring, characterized by the accumulation of dysfunctional mitochondria, increased production of **reactive oxygen species (ROS)** (see Glossary), impaired oxidative phosphorylation, alterations in the NAD^+/NADH balance, and a shift toward glycolytic metabolism [1] (Box 1). However, accumulating evidence indicates that these metabolic changes are not merely passive consequences of cellular stress but rather constitute an active and regulated adaptive program that enables the establishment and maintenance of the senescent phenotype and supports the **senescence-associated secretory phenotype (SASP)** [4]. In this context, amino acids (AA) metabolism is increasingly emerging as a critical player in the regulation of cellular senescence (Figure 1 and Box 2). Beyond their canonical role as building blocks for protein synthesis, AA function as key metabolic regulators and signaling molecules that influence multiple aspects of the senescent program. Indeed, specific AA and their metabolites can modulate pathways involved in cell cycle arrest, stress responses, and the regulation of the SASP (Box 2).

Cellular senescence plays a dual role in cancer biology: acting as both a tumor suppressor and a tumor promoter. In early tumorigenesis, senescence serves as a protective mechanism by arresting the proliferation of damaged or transformed cells through pathways such as p53/p21 and p16/Rb. This growth arrest, together with the SASP, helps to prevent malignant transformation and promotes immune-mediated clearance of premalignant cells by recruiting cytotoxic immune cells. However, in later stages of cancer, senescence can become detrimental. Specifically, persistent senescent stromal cells and the proinflammatory SASP can create an immunosuppressive **tumor microenvironment (TME)** that supports tumor progression, invasion, metastasis, therapy resistance, and relapse [15–18]. Indeed, removal of senescent cells, including populations of macrophages and endothelial cells (ECs), significantly decreases tumor burden

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Box 1. Metabolic changes in cellular senescence

Cellular senescence is a state of stable cell cycle arrest induced by different stressful conditions, associated with significant metabolic reprogramming crucial for maintaining bioenergetic, biosynthetic, and redox homeostatic needs. Senescent cells exhibit altered metabolic profiles, including mitochondrial dysfunction with a consequent shift toward glycolysis, as well as changes in lipid and AA metabolism. These alterations are not mere byproducts of senescence but are essential for sustaining SASP, influencing inflammation, tissue remodeling, and immune surveillance.

Despite an increase in mitochondrial mass and mtDNA, senescent cells exhibit mitochondrial dysfunction, reduced mitochondrial membrane potential, and a decreased NAD+/NADH ratio. Furthermore, as a consequence of inefficient ATP production, senescent cells display an increased AMP/ATP ratio, activating the AMP-activated protein kinase (AMPK)/p53 pathway [2]. Altered mitochondrial function also contributes to the accumulation of ROS, which activate the JNK (c-Jun N-terminal Kinase) kinase and the proinflammatory component of the SASP [3]. Another key metabolic change in senescent cells is the shift toward glycolysis, redirecting energy production from mitochondria to the glycolytic pathway. This reprogramming allows senescent cells to meet their energy demands and manage oxidative stress. Intermediates of glycolysis and the TCA cycle support the biosynthesis of nucleotides, AA, and lipids functional to sustain the SASP [4].

Additionally, senescent cells also exhibit significant alterations in lipid metabolism, including changes in the sphingomyelin/ceramide pathway and upregulation of enzymes involved in both fatty acid synthesis and oxidation. In addition, senescent cells accumulate lipid droplets, and polyunsaturated fatty acids (PUFAs) are released from cell membranes, contributing to the SASP. Elevated levels of PUFAs, such as eicosapentaenoic acid and arachidonic acid, are linked to the production of bioactive lipids, including oxylipins such as prostaglandins, which reinforce the proliferative arrest in senescent cells [2].

Cellular senescence is also marked by significant changes in AA metabolism, mainly through the upregulation of specific AA transporters and metabolic enzymes. Glutaminolysis plays a critical role in the survival of senescent cells, and increased GLS1 expression has been observed in this context. In keeping with this, GLS1 inhibition restores mitochondrial function and ameliorates several senescence-associated aging phenotypes [5].

in different mouse models [19] and senescent cancer-associated fibroblasts (CAFs) inhibit immune-responses and predict tumor recurrence in breast cancer [20].

This duality underscores the need for therapeutic strategies that selectively enhance the tumor-suppressive functions of senescence while limiting its pro-tumorigenic effects. Although the contribution of cytokines and other protein components of the SASP has been extensively investigated, little is known about the role of metabolic mediators derived from the senescent stroma in supporting tumor development [21] or how metabolic remodeling within tumor cells can drive proliferation arrest, cellular senescence, and, in certain contexts, restrain tumor progression.

In this review, we discuss how AA metabolism in senescent cells influences tumor evolution through a complex, bidirectional dynamic: on one side, AA provided by senescent stromal cells sustain tumor progression, and on the other side, metabolic dependencies in cancer cells make them vulnerable to AA deprivation, leading to tumor cell cycle arrest and senescence [17].

Metabolic pathways contribute to senescence in cancer

Several mechanisms link AA metabolism to the induction of senescence in cancer cells. **Therapy-induced senescence (TIS)** promotes distinct AA metabolic dependencies in lung cancer cells, including reduced oxidation of glucose and increased reliance on glutamine [22].

In addition, in breast and lung adenocarcinoma cell lines escaping from TIS, glutamine is not used for fueling the tricarboxylic acid (TCA) cycle or maintaining redox homeostasis; rather, it provides an advantage by partially supporting *de novo* nucleotide biosynthesis (mainly adenine) and contributing to the nonessential amino acid (NEAA) pool. Elevated NEAA favors TIS escape by enabling glutamine synthetase expression and subsequent glutamine biosynthesis [23].

Glossary

Auxotrophic: an organism that has lost the ability to synthesize a specific metabolite required for growth and survival, and thus depends on external supplementation.
CpG islands: genomic regions rich in CpG dinucleotides, typically unmethylated and located near gene promoters. They are associated with transcription initiation and play key roles in epigenetic regulation.
Disseminated tumor cells (DTCs): cancer cells detached from a primary tumor that have entered the circulation and subsequently seeded distant organs.
Glutaminolysis: a mitochondrial pathway responsible for the deamination of glutamine by GLS, yielding ammonia and glutamate, which is then converted into α-ketoglutarate, driving the TCA cycle.
Immune tolerance: a state of reduced responsiveness of the immune system to specific antigens, which tumors can exploit to evade immune surveillance.
Mitophagy: the selective degradation of damaged or dysfunctional mitochondria via autophagy to prevent the accumulation of defective organelles.
One-carbon metabolism (OCM): a biochemical pathway that transfers one-carbon units (e.g., methyl, formyl, and methylene groups) for nucleotide synthesis, methylation reactions, and redox balance, supporting cancer cell proliferation and survival.
Osteoclastogenesis: differentiation and maturation of osteoclasts from hematopoietic precursors, central to bone remodeling.
Polyamine: positively charged molecule with two or more amino groups (e.g., putrescine, spermidine, and spermine) involved in DNA stabilization, translation, and cell proliferation. Dysregulation of polyamine metabolism is common in cancer.
Pre-metastatic niche (PMN): a secondary organ environment conditioned by tumor-derived factors that supports the survival and colonization of metastatic tumor cells.
Reactive oxygen species (ROS): highly reactive oxygen derivatives (e.g., superoxide and hydrogen peroxide) generated during metabolism and stress, which can damage DNA and other cellular components if they accumulate.

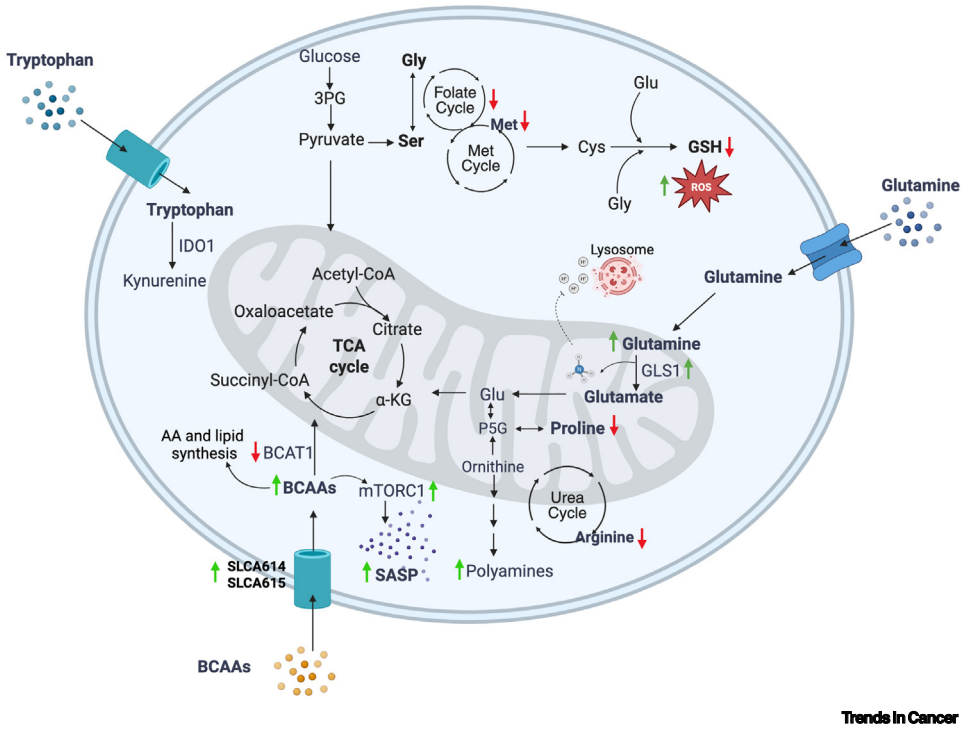


Figure 1. Schematic representation of the major alterations linked to AA metabolism in senescent cells. Tryptophan is generally catabolized through IDO1 to kynurenine. Tryptophan depletion promotes immune evasion. Glucose metabolism feeds into glycolysis, where glucose is converted to 3-phosphoglycerate, pyruvate and subsequently acetyl-CoA, sustaining flux toward serine biosynthesis or through the TCA cycle. The TCA cycle intermediates (citrate, α-KG, succinyl-CoA, and oxaloacetate) support both energy production and biosynthetic processes. Perturbations in OCM metabolism are highlighted by decreased serine and glycine availability and dysregulation of the folate cycle, which in turn affects the methionine cycle. Reduced methionine levels lead to diminished cysteine synthesis, resulting in decreased GSH production. The reduction in GSH compromises antioxidant capacity and contributes to the accumulation of ROS. Glutamine metabolism is another pathway profoundly altered during senescence. Senescent cells exhibit increased expression of GLS1, and the ammonia generated by this reaction is exploited to balance the acidic intracellular environment generated by damaged lysosomes. Despite increased glutamine availability, downstream pathways show selective alterations: proline synthesis from glutamate via P5C is reduced, contributing to the typical mitochondrial dysfunction of senescent cells. Arginine metabolism is downregulated, as indicated by reduced arginine levels and altered flux through the urea cycle. This shift favors the diversion of ornithine toward polyamine synthesis, which is upregulated and may contribute to tumor progression. BCAA metabolism is markedly altered. The upregulation of BCAA transporters (SLC6A14, SLC6A15) is accompanied by reduced expression of BCAT1, leading to intracellular accumulation of BCAAs, which in turn activates mTORC1 signaling. Enhanced mTORC1 activity promotes anabolic processes and is associated with increased production of SASP factors. (Red arrows indicate downregulation, whereas green arrows indicate upregulation of metabolites, enzymes, or pathways). BCAAs: branched-chain amino acids; BCAT1: branched-chain aminotransferase 1; Cys: cysteine; Gly: glycine; Glu: glutamate;GLS1: glutaminase 1; GSH: glutathione; IDO1: indoleamine 2,3-dioxygenase 1; α-KG: α-ketoglutarate; mTORC1: mammalian target of rapamycin complex 1; P5C: pyrroline-5-carboxylate; 3PG: 3-phosphoglycerate; ROS: reactive oxygen species; SASP: senescence-associated secretory phenotype; SLC6A14: solute carrier family 6 member 14; SLC6A15: solute carrier family 6 member 15; TCA: tricarboxylic acid. Figure created using BioRender (https://biorender.com/).

Redox balance: the dynamic equilibrium between oxidizing and reducing reactions within a cell is essential for metabolic homeostasis and the prevention of oxidative damage.
Senescence-associated secretory phenotype (SASP): a proinflammatory and tissue-remodeling secretome produced by senescent cells, containing cytokines, immune modulators, growth factors, and proteases that influence the surrounding microenvironment.
Senolytic: a compound that selectively eliminates senescent cells by targeting their survival pathways.
Senomorphic: a compound that modulates or suppresses the deleterious effects of the SASP or other senescent cell functions without eliminating the cells.
Therapy-induced senescence (TIS): cellular senescence triggered in tumor or normal cells by anticancer treatments, often accompanied by SASP. Generally, it decreases treatment response and increases relapse in cancer.
Tumor microenvironment (TME): the heterogeneous milieu composed of cellular and acellular components surrounding tumor cells, which deeply affects tumor initiation, progression, immune evasion, and therapeutic response.

Deregulation of AA metabolism can also promote cellular senescence by altering gene expression programs. In this context, recent studies investigating the implications of **one-carbon metabolism (OCM)** in aging have highlighted that folate and methionine cycles regulate DNA and histone methylation, linking AA status to epigenetic drift and the induction of cellular senescence [10]. Specifically, methionine metabolism controls the pool of methyl donors that shape the epigenetic and transcriptional landscapes associated with the senescent state in liver cancer

Box 2. Fueling aging: AA as metabolic and signaling hubs in senescence

Alterations in AA metabolism vary depending on the biological context and experimental model [6]. In human lung fibroblasts, human embryonic kidney, and bronchial epithelial cell lines, the upregulation of BCAA transporters (i.e., SLC6A14 and SLC6A15), together with the downregulation of the catabolic enzyme BCAT1, results in accumulated BCAAs. These AA are exploited by senescent cells to fuel NEAA (providing nitrogen) and lipid (providing carbon skeletons) biosynthesis, finally supporting the anabolic demands required for the maintenance of SASP. In addition, elevated BCAA levels also activate the mTORC1 complex, a key driver of SASP gene expression [6] by regulating the translation of mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2) and IL1A (Interleukin-1 Alpha), which increases the mRNA levels of SASP factors, and by directly enhancing the translation of those mRNAs [7,8]. Glutamine metabolism is also rewired during senescence. Human senescent fibroblasts increase the expression of kidney-type GLS, which catalyzes the conversion of glutamine into glutamate, generating free ammonia as a byproduct. This ammonia contributes to buffering the acidic intracellular environment resulting from lysosomal membrane damage, thereby helping maintain cytosolic pH homeostasis and supporting cell survival [9]. In addition, glutaminolysis can partially restore mitochondrial dysfunction in human myofibroblasts derived from patients with progeria syndrome, as well as in mouse models of accelerated aging [5].

Alterations in OCM also influence the balance between senescence and longevity through metabolic and epigenetic regulatory mechanisms [10]. Notably, mitochondrial/cytosolic OCM is downregulated in the early phases of senescence in human lung fibroblasts, resulting in reduced purine and thymidylate synthesis and decreased serine-to-glycine conversion [11,12]. Consistently, serine and glycine availability influence aging across different model organisms: the lifespan-extending effect depends on an intact methionine cycle, indicating that glycine (and serine) regulates aging primarily by modulating OCM and the epigenetic regulation of gene expression.

Cysteine metabolism and glutathione (GSH) homeostasis represent key regulators of cellular **redox balance** and senescence, with an aging-associated decrease in GSH synthesis contributing to increased oxidative stress. Multiomics profiling in aged muscle stem cells identified GSH metabolism as one of the most profoundly altered pathways [13]. In parallel, proline metabolism also modulates mitochondrial function and senescence. In senescent MSCs, proline supplementation enhances mitochondrial respiration and promotes **mitophagy** via AMPKα activation and Parkin upregulation, independently of proline dehydrogenase 1 (PRODH1) activity, ultimately reducing senescence-associated markers and alleviating key features of cellular aging [14].

Overall, AA emerge as central nodes in the integration of metabolism and cellular senescence, offering potential therapeutic opportunities to modulate cellular aging and its pathological consequences, including tumorigenesis.

cells. Consistently, inhibition of methionine adenosyltransferase 2A (MAT2A) or methionine deprivation induces senescence in hepatocellular carcinoma (HCC) cells, leading to DNA hypomethylation, particularly at **CpG islands** in the promoters of genes encoding cyclin-dependent kinase inhibitors [24].

Arginine metabolism also contributes to the induction of cellular senescence in tumor cells. Unlike normal hepatocytes, HCC cells suppress the expression of all major urea cycle enzymes, rendering them **auxotrophic** for exogenous arginine. Short-term arginine deprivation activates the general control nonderepressible 2 (GCN2) kinase, with a consequent translation of p21 mRNA and inhibition of general protein synthesis, leading to a reversible quiescent state that allows tumor cell survival under nutrient stress. Conversely, inhibiting GCN2 upon long-term arginine deprivation promotes a senescent phenotype because of defective autophagy and the consequent accumulation of toxic waste [25].

Collectively, these findings show that AA metabolism rewiring contributes to tumor cell senescence and may act as a barrier to tumor progression.

Senescent cell-driven metabolic modulation of stromal cells

In the TME, senescent stromal cells, including fibroblasts, ECs, and adipocytes, profoundly influence the proliferative fate of tumor cells through cytokine components of their SASP [17,18]. In prostate cancer, senescent CAFs influence tumor progression through the secretion of paracrine factors that include AA-related metabolites. Decreased levels of arginine, resulting from enhanced

polyamine biosynthesis in fibroblasts, activate the GCN2 kinase, leading to a senescent stromal phenotype that participates in creating a pro-tumorigenic microenvironment. Indeed, dermal fibroblasts from transgenic mice overexpressing ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis, produce SASP factors that increase the invasiveness of stem-like epidermal tumorspheres as well as the polarization of M2-like macrophages [26]. Senescent adipocytes represent another critical component influencing the metabolic landscape of the TME. Multiple myeloma cells alter adipocyte gene expression and cytokine secretory profiles, inducing a senescent-like phenotype. Consequently, senescent adipocytes promote therapy resistance, highlighting a bidirectional crosstalk that results in increased aggressiveness [27]. In addition, the senescence of ECs is characterized by modifications in glucose and AA metabolism [28–30], suggesting that these alterations foster tumor outgrowth. Although the specific contribution of AA-derived metabolites from senescent ECs to cancer progression has not yet been clearly defined, senescent ECs disrupt vascular integrity and increase permeability, thereby creating conditions that facilitate tumor progression and metastasis [31]. ECs in liver metastases of uveal melanoma patients show significant senescence promoted by the upregulation of Krüppel-like factor 4 (KLF4) [32]. Moreover, EC senescence induced by treatment with Sunitinib can enhance vascular permeability and promote myeloid cell recruitment, ultimately contributing to **pre-metastatic niche (PMN)** formation in a mouse model [33].

Collectively, these findings suggest that senescent stromal cells actively reshape the metabolic and signaling landscape of the TME, thereby promoting tumor progression through complex bidirectional interactions, which may, in part, be driven by AA metabolic reprogramming.

Senescent cell-driven metabolic modulation of the tumor immune microenvironment

The immune compartment within the TME actively participates in tumor progression, as immune cells can either recognize and eliminate transformed cells or, under certain conditions, be co-opted to support tumor growth and immune evasion [34]. In this context, cellular senescence exerts spatially and temporally distinct effects. Senescent cells can promote immune surveillance by activating natural killer (NK) cells through natural killer group 2, member D (NKG2D) ligands. This immunogenic phenotype has been observed across different cellular contexts, including both stromal cells (e.g., fibroblasts) and tumor cells undergoing senescence. However, when senescent cells persist, they can experience phenotypic remodeling and contribute to an immunosuppressive microenvironment through SASP components, including chemokine-mediated recruitment of regulatory T cells (Tregs) and increased expression of immune checkpoint molecules such as programmed death-ligand 1 (PD-L1), ultimately favoring immune evasion. Notably, TIS in either stromal or malignant compartments can similarly boost antitumor immunity or, conversely, create an immunosuppressive niche that favors disease progression [35].

SASP protein components play a key role in regulating tumor progression and immune interactions [36–38]; however, less attention has been given to the metabolic side of this crosstalk. Indeed, immune cells are auxotrophic for most AA, making exogenous sources of these metabolites essential regulators of their functions [39]. Depletion or accumulation of specific AA can influence immune cell activation, proliferation, or differentiation. They can act as ‘checkpoints’ to provide an additional layer of control that complements classical immunological signals such as cytokines and receptor-mediated pathways [40,41].

Arginine metabolism

Arginine is a key regulator of T lymphocyte function [40] and Arginase I (Arg1) is a central regulator of immunomodulation. Arg1 expression in myeloid-derived suppressor cells (MDSCs) and dendritic cells (DCs) influences T-cell function, antigen presentation, and tolerance through the

metabolic control of L-arginine availability [40,41] (Figure 2). In murine models, Arg1 also competes with inducible nitric oxide synthase (iNOS) for L-arginine, thereby modulating nitric oxide outputs that affect macrophage and MDSC effector functions [40]. Furthermore, Arg1 can be induced by interleukin-4 (IL-4), IL-10, prostaglandin E2, and tumor-derived factors, promoting the development of tolerogenic DCs with diminished immune-stimulatory capacity [42]. In humans, Arg1 is abundantly expressed in polymorphonuclear MDSCs (PMN-MDSCs) [40]. Upon activation, human PMN-MDSCs release Arg1 extracellularly, producing rapid

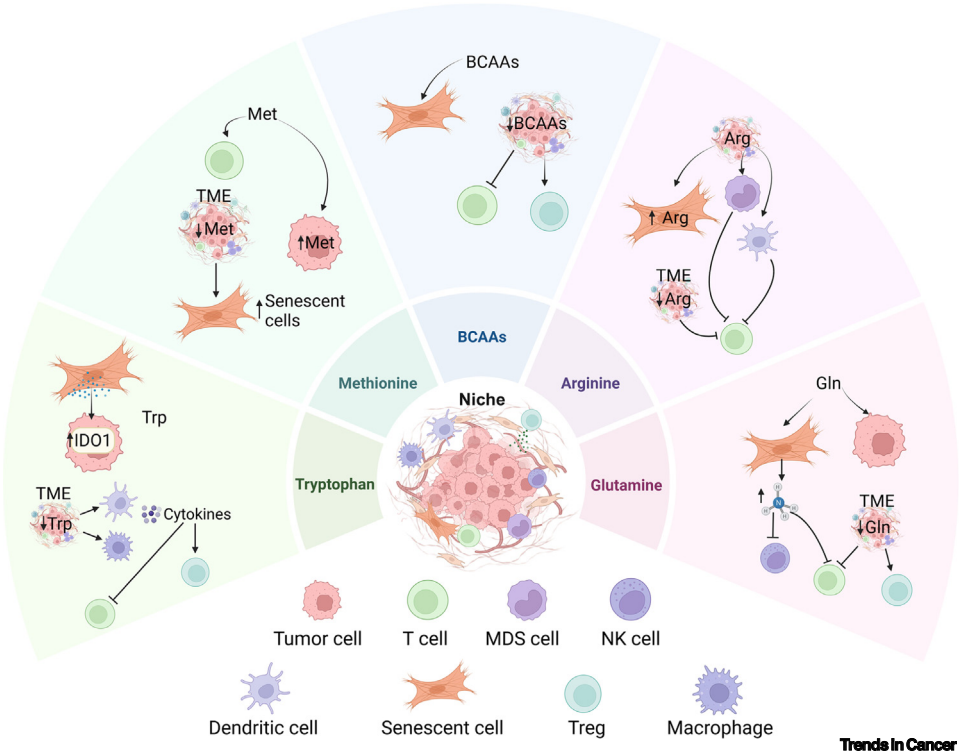


Figure 2. AA-driven metabolic reprogramming and immune modulation within the TME. Schematic representation of the central role of AA metabolism in orchestrating cellular crosstalk within the tumor niche. Tumor cells, stromal cells, and immune populations dynamically compete for and reshape the availability of key AA, thereby influencing tumor growth, immune surveillance, and immune escape. BCAAs are exploited by immune cells to support the increased biosynthetic demands associated with immune cell activation. BCAAs exert a key immunomodulatory role by regulating mTORC1 activation, which in turn controls the differentiation into effector subsets. The presence of senescent cells in the TME could create metabolic competition for BCAAs, leading to an immunosuppressive environment. T-cell functionality is strongly influenced by the presence of arginine in the TME. MDS cells and DCs enzymatically degrade arginine via Arg1, resulting in local arginine depletion and impairing T-cell activation. In addition, senescent cells also contribute to this arginine reduction, impairing T-cell function. Glutamine serves as a major carbon and nitrogen source for rapidly proliferating tumor cells and stromal components. Excessive glutamine consumption in the TME alters metabolic fluxes and restricts its availability for immune cells, thereby impairing the expansion of Th1 and Th17 cells, while promoting the development of Tregs. In this context, senescent cells contribute to creating an immunosuppressive environment that consumes high amounts of glutamine and releases ammonia, which inhibits NK and T-cell activity. Methionine plays a crucial role in the TME: tumor cells are highly dependent on methionine metabolism for proliferation, and methionine availability boosts T-cell-mediated immune responses. This methionine depletion from the TME is strictly linked to senescence induction. Tryptophan catabolism leads to profound immunosuppressive effects. IDO1 is induced during inflammation in macrophages and DCs and by SASP-associated cytokines in tumor cells. The activation of IDO1 leads to extracellular tryptophan depletion and consequent immune tolerance, enhancing Treg recruitment and inhibiting effector T-cell proliferation. BCAAs: branched-chain amino acids; IDO1: indoleamine 2,3-dioxygenase 1; Gln: Glutamine; MDS: myeloid-derived suppressor; Met: methionine; NK: natural killer; TME: tumor microenvironment; Treg: T regulatory; Trp: tryptophan. Figure created using BioRender (https://biorender.com/).

consumption of environmental L-arginine, thus impairing T-cell activation [40]. Senescent macrophages in the TME could also contribute to arginine depletion and consequent T-cell mediated immunity impairment. In an immunocompetent animal model of H-Ras-expressing glioblastoma, it has been demonstrated that, to promote successful tumor initiation, cancer cells induce macrophage senescence along with upregulation of Arg1 in these cells. The consequent arginine depletion causes a downregulation of CD3ζ, limiting the assembly of TCR (T Cell Receptor) and impairing antigen response [43]. In colorectal cancer (CRC), comparison of tumor tissues from younger and older patients reveals that aged hosts exhibit increased infiltration of tumor-associated macrophages (TAMs) with pro-tumor activity. Upon stimulation with tumor-conditioned medium, 'aged' TAMs promote CRC cell growth more effectively and show greater Arg1 induction, whereas 'young' bone marrow-derived macrophages exhibit a larger increase in iNOS expression [44]. Because Arg1 is linked to an immunosuppressive, pro-tumorigenic phenotype, whereas iNOS is associated with antitumor activity, the divergent responses of 'young' and 'aged' macrophages to tumor stimulation underscore cellular senescence as a central mediator of arginine-dependent immune regulation in the TME.

Tryptophan metabolism

Tryptophan is an essential AA in immune cells, catabolized by the enzyme Indoleamine 2,3-dioxygenase (IDO1) to kynurenine [45]. IDO1 activity is strongly induced during inflammation in macrophages, DCs, and fibroblasts [46]. Similarly, SASP-associated cytokines can induce IDO1 in tumor cells. In CRC, IDO1 overexpression increases kynurenine release; kynurenine inhibits the IGFBP5 (Insulin-like Growth Factor Binding Protein 5)–p53 signaling pathway, thereby suppressing cellular senescence and promoting 5-fluorouracil (5-FU) resistance [47]. In lung adenocarcinoma, tumor cells increase IDO1 expression and enzymatic activity upon stimulation with the inflammatory cytokine IL-1β [48]. Once upregulated, IDO1 depletes extracellular tryptophan, thereby promoting long-term **immune tolerance**. Enzymatic activation of IDO1 then leads to increased production of kynurenine, which binds the aryl hydrocarbon receptor (AhR), a transcription factor involved in Treg differentiation, promoting this tolerogenic state [49]. In parallel, tryptophan depletion activates the GCN2 signaling pathway in IDO1-expressing DCs and macrophages, skewing them toward anti-inflammatory cytokine production, promoting Treg recruitment, and inhibiting effector T-cell proliferation [49]. Activated GCN2 phosphorylates eIF2α (Eukaryotic Initiation Factor 2 alpha), which enhances the translation of stress-responsive transcripts such as ATF4 (Activating Transcription Factor 4). In T cells, this integrated stress response (ISR) induces cell cycle arrest and reduces proliferation, while promoting metabolic reprogramming characterized by suppression of mammalian target of rapamycin complex 1 (mTORC1) activity, reduced glycolysis, and adaptation to AA deprivation, ultimately favoring anergy or differentiation toward a regulatory phenotype [49,50]. Together, these findings support a model in which senescence-associated inflammatory signaling directly induces IDO1-mediated immunosuppression, providing a mechanistic bridge between cellular senescence and tumor immune escape (Figure 2).

Branched-chain amino acid catabolism

Branched-chain AA (BCAA) catabolism supports the increased biosynthetic demands associated with immune cell activation. T-cell activation depends on mTORC1-driven metabolic reprogramming. BCAAs, and in particular leucine, display this 'immunomodulatory' role by regulating mTORC1 activity: robust mTORC1 activation promotes glucose and AA uptake and drives effector T-cell differentiation, whereas reduced mTORC1 activity favors Treg or memory T-cell formation [51]. In mice, loss of the essential AA transporter SLC7A5 (Solute Carrier Family 7 Member 5) disrupts leucine uptake and mTORC1 activation, which promotes proliferation and differentiation of T helper 1 (Th1), Th17, and cytotoxic T cells [52]. Furthermore, isoleucine appears important for

sustaining Treg proliferation after lineage commitment in healthy mouse models [52,53]. Once inside T cells, BCAAs are transaminated into their corresponding α-keto acids by the cytosolic and mitochondrial forms of branched-chain AA transaminase (BCAT) (BCATc-cytosolic and BCATm-mitochondrial). Their activities can reduce free leucine levels, causing a decrease in mTORC1, ultimately supporting a model in which BCATc and BCATm act as negative regulators of T-cell activation by fine-tuning leucine-dependent nutrient signaling [51]. By contrast, senescence programs are associated with increased expression of AA transporters [e.g., solute carrier family 6 member 14 (SLC6A14)/SLC6A15] and reduced BCAA catabolism, resulting in intracellular BCAA accumulation. Elevated intracellular BCAA levels can activate mTORC1 signaling, which contributes to the establishment and maintenance of SASP [6]. These observations suggest a potential integrative model: in tumors enriched for senescent cells, these cells act as a BCAA metabolic 'sink', competing with antitumor immune cells for the same nutrient pool, while simultaneously amplifying SASP-dependent signaling that remodels immune composition and function in the TME (Figure 2). However, this senescent–immune competition for BCAAs remains to be fully elucidated.

Additional metabolic pathways

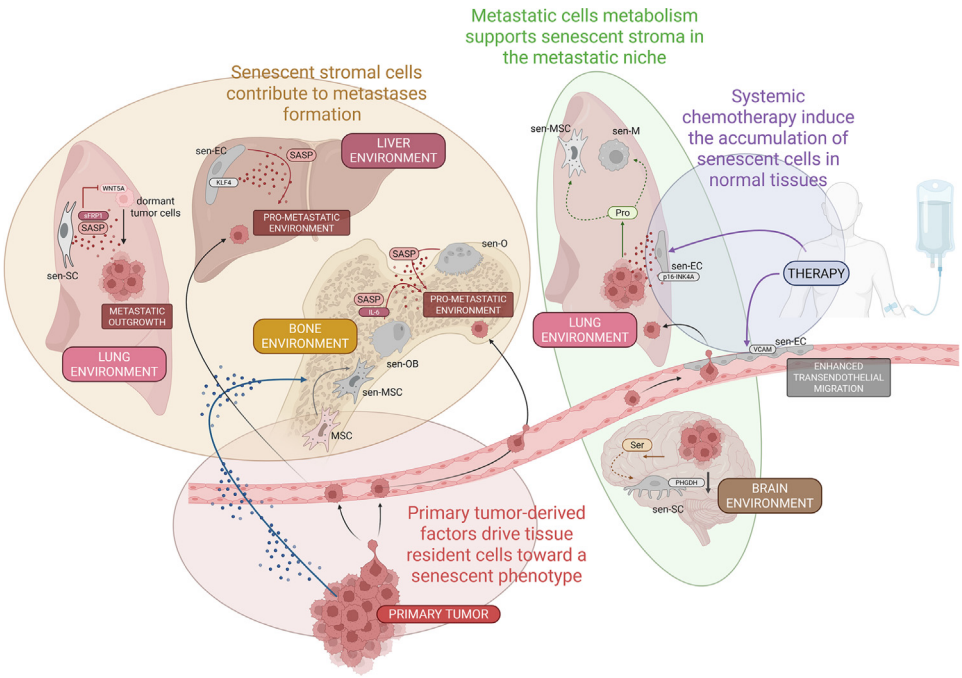
Senescent cells are highly dependent on **glutaminolysis**, resulting in the production of large amounts of ammonia [9]. Ammonia can promote tumor immune escape by inhibiting both NK and T-cell cytotoxic activity [54]. In this context, ammonia derived from senescent stroma could support cancer progression by primarily sustaining immune evasion (Figure 2).

Cancer cells also rely on enhanced methionine uptake for survival, and methionine deprivation has been associated with cellular senescence in liver cancer [24] (Figure 2). This balance in methionine may shape immune cell functions. However, the role of methionine in immunity remains somewhat controversial. While methionine availability can enhance T-cell-mediated immune response in HCC cells, increased methionine levels or S-adenosylmethionine-derived methionine metabolism have also been associated with immune evasion [24]. Together, these observations highlight a scenario where senescent cell-driven rewiring of AA metabolism profoundly impacts the tumor immune microenvironment (Figure 2), establishing a nutrient-restrictive niche that fuels immune evasion.

Senescent cell-driven AA reprogramming in the TME: a metastatic accelerator?

The establishment of a permissive 'fertile soil' supporting disseminated cancer cells is a critical prerequisite for metastatic progression. Despite substantial advances in understanding the genetic and microenvironmental drivers of metastasis, including oncogenic alterations, vascular dynamics, and stromal interactions [55], the contribution of tissue-intrinsic metabolic landscapes to metastatic competence remains relatively less explored. In particular, the capacity of **disseminated tumor cells (DTCs)** to successfully engraft and expand in distant organs is strongly influenced by the local availability of nutrients. Studies mainly conducted in models of breast cancer metastasizing to the lung have demonstrated that AA represent critical determinants of this process, acting both as metabolic substrates [56] or signaling molecules [57]. In brain metastases, scarcity of specific AAs can impose metabolic constraints that limit DTC survival and proliferation across cancers of different origins (i.e., breast cancer and melanoma) [58]. Conversely, in lung metastases, the enrichment of specific nutrients can support cellular adaptation and promote early metastatic colonization [57]. The metabolic state of tissue-resident cells, such as the alveolar type II cells in the lung and astrocytes in the brain, critically shapes AA availability within the metastatic niche [59,60], thereby either promoting or constraining metastatic outgrowth.

In addition to classical determinants of PMN formation [61], cellular senescence has recently emerged as a pivotal contributor to organ metastatic priming (Figure 3). In uveal melanoma,



Trends in Cancer

Figure 3. Senescence-driven mechanisms promoting metastatic progression across organ-specific niches. A schematic overview illustrating the different, nonmutually exclusive mechanisms through which senescent cells (gray) promote metastasis at distinct stages of the metastatic cascade. Red circle: primary tumor (PT)-derived factors induce senescence in tissue-resident stromal cells at distant sites, establishing PMNs prior to tumor cell arrival. In breast cancer, PT-derived signals drive bone MSCs toward a senescent state characterized by enhanced pro-osteoclastogenic activity. Orange circle: sen-SCs actively contribute to the formation of PMNs in distant organs. In melanoma, sen-SCs in the lung promote the reawakening of dormant metastatic cells by inhibiting WNT5A signaling through the secretion of the WNT antagonist sFRP1. In uveal melanoma, sen-ECs overexpressing KLF4 promote a pro-metastatic microenvironment and enhance tumor cell dissemination from the PT via the secretion of a C-X-C motif chemokine ligand 12 (CXCL12)-enriched SASP. In the bone microenvironment, sen-OBs support breast cancer metastatic cell engraftment and outgrowth through an IL-6-rich SASP, whereas sen-Os drive osteolytic bone metastases via SASP-mediated mechanisms. Green circle: metabolic crosstalk between metastatic cancer cells and senescent stromal cells sustains metastatic growth. Local enrichment of specific AAs promotes the emergence or maintenance of stromal senescence, amplifying metastatic progression. In the lung, metastatic breast cancer cells increase Pro secretion, potentially supporting the metabolic demands of senescent MSCs or sen-Ms, which display reduced Pro biosynthesis. In the brain, metastatic cells exhibit enhanced Ser synthesis and secretion, which may sustain sen-SCs characterized by reduced expression of the Ser biosynthetic enzyme PHGDH. Purple circle: systemic chemotherapy induces senescence in normal tissues, leading to the accumulation of senescent cells that enhance metastatic seeding and progression. In breast cancer, Sunitinib treatment induces a senescence-like phenotype in ECs, resulting in increased VCAM1 expression that promotes tumor cell recruitment and adhesion and facilitates transmigration by loosening endothelial junctions. Similarly, Palbociclib treatment drives lung ECs toward a p16-INK4A-high senescent phenotype, further contributing to a pro-metastatic microenvironment. Dashed arrows: hypothetical interactions. IL-6: interleukin-6; KLF4: Krüppel-like factor 4; MSC: mesenchymal stem cell; PHGDH: phosphoglycerate dehydrogenase; p16-INK4A: cyclin-dependent kinase inhibitor 2A; Pro: Proline; sen-EC: senescent endothelial cell; SASP: senescence-associated secretory phenotype; sen-M: senescent macrophage; sen-O: senescent osteocyte; sen-OB: senescent osteoblast; sen-SC: senescent stromal cell; Ser: serines; sFRP1: secreted frizzled-related protein 1; VCAM1: vascular cell adhesion molecule 1; WNT: Wingless-Type MMTV Integration Site Family; WNT5A: Wingless-Type MMTV Integration Site Family, Member 5A . Figure created using BioRender (https://biorender.com/).

senescent ECs that overexpress KLF4 are enriched in liver metastases and actively promote cell migration through the SASP, which contributes to the formation of a pro-metastatic microenvironment [32]. In the bone microenvironment, senescent osteoblasts participate in creating a 'hospitable niche' for metastasizing breast cancer cells. Indeed, these osteoblasts, characterized by a SASP enriched in IL-6, exhibit impaired mineralization capacity and promote **osteoclastogenesis**, thereby facilitating metastatic breast cancer cell engraftment and outgrowth in

bone [62]. In addition, osteocytes can develop premature senescence and a distinctive SASP that favors bone destruction, triggering lytic bone metastases from breast cancer [63]. This process can be exacerbated by the influence of the primary tumor even before the arrival of metastatic cells at distant tissues (Figure 3). Primary breast tumors can systemically modify bone marrow mesenchymal stem cells (MSCs), driving them toward a senescent phenotype characterized by ROS accumulation, increased inflammatory signaling, and enhanced pro-osteoclastogenic activity. These alterations might contribute to PMN establishment by fostering a pro-metastatic and pro-resorptive bone [64]. In *in vivo* models of breast cancer, systemic chemotherapy can further amplify these effects by inducing normal tissue damage and accumulation of senescent fibroblasts, which in turn facilitate the outgrowth of DTCs at distant sites and promote metastatic disease in mouse models [65]. In metastatic breast cancer, Sunitinib treatment induces a senescence-like phenotype in ECs, leading to increased inflammatory chemokine secretion and vascular cell adhesion molecule 1 (VCAM1) expression, ultimately creating a PMN that enhances distant metastasis [33]. Similarly, pretreatment with the CDK4/6 (Cyclin-Dependent Kinase 4/6) inhibitor Palbociclib in breast cancer triggers cellular senescence in healthy lung tissue and ECs, promoting a favorable environment that increases the ability of drug-resistant cancer cells to form metastases in the lungs. Palbociclib-enhanced lung colonization can be partially mitigated by the removal of host senescent cells expressing cyclin-dependent kinase inhibitor 2A (p16INK4A) [66].

The presence of senescent stromal cells may also enhance metastatic outgrowth by facilitating the reawakening of dormant metastatic cells seeded at secondary sites (Figure 3). In melanoma, senescent fibroblasts in the lungs increase their secretion of the WNT (Wingless-Type MMTV Integration Site Family) antagonist, secreted frizzled-related protein 1 (sFRP1), which inhibits WNT5A (Wingless-Type MMTV Integration Site Family, Member 5A) in dormant melanoma cells, thus inducing metastatic outgrowth [67].

In addition to these mechanisms, alterations in AA metabolism in senescent resident cells may further facilitate DTC seeding and metastatic outgrowth (Figure 3). However, no studies have demonstrated this hypothesis. In parallel, alterations in nutrient availability within metastatic lesions may further promote the emergence or maintenance of senescent stromal cells, thereby amplifying metastatic progression. For instance, detached metastatic cells can increase proline secretion in 3D colon cancer models [68]. This metabolite may support the metabolic needs of senescent MSCs, which are characterized by reduced proline biosynthesis from glutamate via pyrroline-5-carboxylate (P5C) [14], similar to what has been demonstrated for macrophages in the same metabolic context [68]. Likewise, metastatic cells in specific organs, such as the brain, exhibit enhanced serine synthesis and secretion [58]. This metabolic rewiring may provide an exogenous source of serine to senescent stromal cells, which typically display decreased intracellular serine levels and reduced expression of the serine-biosynthetic enzyme phosphoglycerate dehydrogenase (PHGDH), as shown in senescent vascular ECs [69]. Collectively, these nutrient exchanges suggest a model in which metastatic cells sculpt a metabolic microenvironment that not only supports their own growth but also fosters stromal senescence, further reinforcing a PMN.

Although several aspects remain unresolved, emerging evidence points to a dual contribution of AA metabolism in senescent stromal cells to metastatic colonization: metabolic alterations may sustain the induction of a senescent phenotype within the stromal compartment of the PMN, while simultaneously increasing nutrient availability for incoming metastatic cancer cells.

From metabolic rewiring to targeted therapy: exploiting senescent cell vulnerabilities

Alterations in the metabolism of specific AA, such as glutamine, serine, methionine, and BCAAs, are distinctive characteristics of cellular senescence, providing interesting therapeutic

opportunities for cancer. In contrast to stromal cells, senescence in cancer cells can be tumor-suppressive. In this context, AA availability emerges as a key factor that can be targeted to suppress cancer cell growth. Inhibition of glutaminolysis in aged mice specifically eradicates senescent cells in different tissues and improves age-associated organ dysfunction [9]. Blocking glutaminase 1 (GLS1) significantly improves mitochondrial function in senescent MSCs and ameliorates aging hallmarks in a mouse model of accelerated aging [5] (Box 2). Moreover, GLS1 inhibition alleviates senescence phenotypes and reduces SASP markers in senescent Wharton's jelly-derived MSCs [70]. Furthermore, targeting glutaminolysis in stromal and cancer senescent cells could be effective in the reactivation of the immune response by restoring NK cell and T-cell activity [54].

Glutamine is also a key player in tumor metabolism. In esophageal squamous cell carcinoma (ESCC) cells, increased expression of RNA binding motif protein 4 (RBM4) contributes to bypassing doxorubicin-induced senescence. However, this adaptive strategy renders ESCC cells dependent on glutamine metabolism, increasing their sensitivity to the GLS inhibitor CB-839 [71]. In HCC cells, the nuclear translocation of β-catenin enhances glutaminolysis and ammonia excretion through SLC4A11; loss of SLC4A11 promotes senescence and sensitizes β-catenin-mutant cells to targeting approaches against senescent cancer cells [72]. Several GLS inhibitors have been developed to target glutamine metabolism in tumors. Among them, the selective GLS1 inhibitor Telaglenastat represents the most clinically advanced compound and has been evaluated in multiple clinical trials, often in combination with other anticancer therapies [73]. Therefore, targeting glutaminolysis may provide therapeutic advantages by simultaneously suppressing the pro-tumoral function of senescent stromal cells and limiting the growth of glutamine-addicted cancer cells.

Additionally, senescent immune cells exhibit increased IDO1 activity, which leads to the depletion of L-tryptophan and the build-up of immunosuppressive metabolites, further weakening antitumor immune responses [74,75]. Consistently, IDO1 inhibitors such as Navoximod, Epacadostat, Linrodostat, and Indoximod are being explored as immunomodulatory therapies, both alone and in combination with other antitumor strategies [76]. In CRC cells, IDO1-driven tryptophan catabolism promotes escape from 5-FU-induced senescence and chemoresistance, and both phenotypes are reversed upon restoration of tryptophan availability [47]. Overall, this scenario highlights how targeting IDO1 could represent a valid strategy to increase tryptophan availability; therefore, exerting a dual therapeutic effect by mitigating immunosenescence, simultaneously restraining tumor progression, and improving responsiveness to anticancer therapies.

Different types of senescent stromal cells have been reported to produce lower levels of asparagine due to reduced expression of asparagine synthetase (ASNS) [77]. Consequently, these cells become increasingly dependent on extracellular asparagine to sustain protein synthesis and cellular homeostasis. In this context, L-asparaginase (L-ASNase) combined with autophagy inhibitors effectively eradicated senescent stromal cells by synergistically restricting asparagine availability. Indeed, this strategy simultaneously blocked both extracellular asparagine supply and intracellular recycling mechanisms, thereby exposing a metabolic vulnerability of senescent cells [77]. Several malignancies rely on exogenous asparagine for their growth. For this reason, L-ASNase is widely used in the treatment of acute lymphoblastic leukemia and has also shown activity in other ASNS-low tumors [78]. Based on these observations, it can be hypothesized that in such therapeutic settings, L-ASNase may exert a dual effect by inhibiting tumor cell proliferation and metastasis (as already demonstrated for breast cancer metastasis in a mouse model) [79] through systemic depletion of asparagine, while also contributing to the removal of senescent stromal cells within the TME.

Moreover, recent evidence underlines the importance of targeting AA metabolism in combination with **senomorphic** and **senolytic** strategies to selectively eliminate SASP and senescent cells. Although most senolytics and senomorphics act on pro-survival or anti-inflammatory pathways, targeting AA metabolism could potentially remove senescent cells by exploiting their metabolic vulnerabilities. Inhibiting methionine metabolism through MAT2A blockage results in DNA damage and cell cycle arrest in HCC. A combination of MAT2A and the senolytics glycogen synthase kinase 3 (GSK3) inhibitors effectively decreases liver cancer growth [24]. Moreover, inhibition of GCN2 in arginine-deprived senescent HCC cells renders them vulnerable to senolytic compounds. Consistently, preclinical models confirm that a combination of arginine deprivation, GCN2 inhibition, and senolytic agents effectively promotes HCC regression [25]. Moreover, in therapy-induced senescent melanoma cells, GLS1 inhibition promotes cancer cell death *in vitro* and *in vivo*. This senolytic approach is also effective in inhibiting Vemurafenib-resistant melanoma cells.

Current anticancer therapies often target not only malignant cells but also multiple stromal components of the TME, including fibroblasts, adipocytes, and ECs, which can undergo TIS, thus contributing to tumor progression and resistance [38]. Despite their distinct biological characteristics, cancer cells and senescent stromal cells share notable metabolic similarities, highlighting common vulnerabilities that can be therapeutically exploited. In this context, simultaneously targeting both proliferating tumor cells and pro-tumorigenic senescent stromal populations may provide a significant therapeutic advantage. Moreover, interventions aimed at modulating the altered AA metabolism of senescent cells may not only suppress their pro-tumorigenic secretory phenotype but also contribute to the restoration of antitumor immunity. Collectively, these observations support the development of combinatorial strategies integrating metabolic inhibitors, senolytic agents, and immune-based therapies to improve cancer treatment outcomes.

Concluding remarks and future perspectives

AA metabolism has emerged as a central hub at the cellular senescence and cancer progression interface. Senescent stromal cells undergo marked metabolic changes that sustain the SASP, promote immunosuppressive TMEs, and contribute to the formation of PMNs. Together, these alterations create metabolic conditions that support tumor growth while weakening antitumor immune responses.

The metabolic dependencies of senescent cells also represent therapeutic opportunities. Targeting specific AA pathways may selectively eliminate senescent cells, improve the sensitivity of cancer cells to therapy, and enhance antitumor immunity. Future studies should define how AA metabolism changes over time during senescence, use single-cell approaches to capture metabolic heterogeneity within senescent populations, and systematically test combination strategies that integrate AA pathway inhibitors with senolytic or senomorphic agents and immunotherapies (see Outstanding Questions). Successful clinical translation will require the identification of robust biomarkers to stratify patients and careful evaluation of potential toxicities in normal tissues with high metabolic activity. Given the accumulation of senescent stromal cells in aged tissues and TMEs, targeting AA metabolic dependencies offers the opportunity to simultaneously blunt the deleterious effects of senescent stromal cells while enforcing growth arrest and immune sensitivity in malignant cells, opening new avenues for integrated anticancer strategies.

Outstanding questions

Can the selective targeting of amino acid metabolism (e.g., glutamine, serine, methionine, or arginine pathways) eliminate senescent cells without altering systemic physiology or compromising the metabolic fitness of healthy tissues?

Could combining amino acid-targeted therapies with senolytic or senomorphic agents improve the selectivity and efficacy of cancer treatments?

Can senescence-driven nutrient restriction modulate the efficacy of immunotherapy?

What combination, timing, and dosing strategy can best integrate metabolic inhibitors with senolytic and immune-based therapies?

Does the metabolic composition of different tissues influence the efficacy of therapeutic strategies targeting cellular senescence?

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Declaration of interests

The authors declare no competing interests.

References

1. Miwa, S. *et al.* (2022) Mitochondrial dysfunction in cell senescence and aging. *J. Clin. Invest.* 132, e158447
2. Wiley, C.D. and Campisi, J. (2021) The metabolic roots of senescence: mechanisms and opportunities for intervention. *Nat. Metab.* 3, 1290–1301
3. Vizioli, M.G. *et al.* (2020) Mitochondria-to-nucleus retrograde signaling drives formation of cytoplasmic chromatin and inflammation in senescence. *Genes Dev.* 34, 428–445
4. Kim, Y. *et al.* (2024) Metabolic remodeling in cancer and senescence and its therapeutic implications. *Trends Endocrinol. Metab.* 35, 732–744
5. Choudhury, D. *et al.* (2022) Inhibition of glutaminolysis restores mitochondrial function in senescent stem cells. *Cell Rep.* 41, 111744
6. Liang, Y. *et al.* (2024) Branched-chain amino acid accumulation fuels the senescence-associated secretory phenotype. *Adv. Sci. (Weinh)* 11, e2303489
7. Herranz, N. *et al.* (2015) mTOR regulates MAPKAPK2 translation to control the senescence-associated secretory phenotype. *Nat. Cell Biol.* 17, 1205–1217
8. Laberge, R.-M. *et al.* (2015) MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. *Nat. Cell Biol.* 17, 1049–1061
9. Johmura, Y. *et al.* (2021) Senolysis by glutaminolysis inhibition ameliorates various age-associated disorders. *Science* 371, 265–270
10. Bou Ghanem, A. *et al.* (2023) Exploring the complexities of 1C metabolism: implications in aging and neurodegenerative diseases. *Front. Aging Neurosci.* 15, 1322419
11. Kim, J.Y. *et al.* (2023) Time-resolved proteomic analyses of senescence highlight metabolic rewiring of mitochondria. *Life Sci. Alliance* 6, e202302127
12. Majumder, A. *et al.* (2024) The pivotal role of one-carbon metabolism in neoplastic progression during the aging process. *Biomolecules* 14, 1387
13. Benjamin, D.I. *et al.* (2023) Multiomics reveals glutathione metabolism as a driver of bimodality during stem cell aging. *Cell Metab.* 35, 472–486.e6
14. Choudhury, D. *et al.* (2024) Proline restores mitochondrial function and reverses aging hallmarks in senescent cells. *Cell Rep.* 43, 113738
15. Reimann, M. *et al.* (2024) Cellular senescence: neither irreversible nor reversible. *J. Exp. Med.* 221, e20232136
16. Lam, Y. *et al.* (2025) Cellular senescence in cancer: unveiling dual roles, tumor microenvironment dynamics and therapeutic innovations (Review). *Oncol. Lett.* 30, 592
17. Zhang, F. *et al.* (2024) Cellular senescence and metabolic reprogramming: unraveling the intricate crosstalk in the immunosuppressive tumor microenvironment. *Cancer Commun. (Lond.)* 44, 929–966
18. Zhang, Y. *et al.* (2025) Signaling networks in cancer stromal senescent cells establish malignant microenvironment. *Proc. Natl. Acad. Sci. U. S. A.* 122, e2412818122
19. Haston, S. *et al.* (2023) Clearance of senescent macrophages ameliorates tumorigenesis in KRAS-driven lung cancer. *Cancer Cell* 41, 1242–1260.e6
20. Ye, J. *et al.* (2024) Senescent CAFs mediate immunosuppression and drive breast cancer progression. *Cancer Discov.* 14, 1302–1323
21. Ye, M. *et al.* (2023) Senescent stromal cells in the tumor microenvironment: victims or accomplices? *Cancers (Basel)* 15, 1927
22. Llop-Hernández, À. *et al.* (2022) Nutritional niches of cancer therapy-induced senescent cells. *Nutrients* 14, 3636
23. Pacifico, F. *et al.* (2021) Glutamine promotes escape from therapy-induced senescence in tumor cells. *Aging (Albany NY)* 13, 20962–20991
24. Li, F. *et al.* (2024) Blocking methionine catabolism induces senescence and confers vulnerability to GSK3 inhibition in liver cancer. *Nat. Can.* 5, 131–146
25. Missiaen, R. *et al.* (2022) GCN2 inhibition sensitizes arginine-deprived hepatocellular carcinoma cells to senolytic treatment. *Cell Metab.* 34, 1151–1167.e7
26. Alexander, E.T. *et al.* (2025) Elevated polyamine metabolism activates fibroblasts via GCN2 activation and generates senescent fibroblasts to promote tumor formation and progression. *Mol. Carcinog.* 64, 1872–1884
27. Fairfield, H. *et al.* (2021) Myeloma-modified adipocytes exhibit metabolic dysfunction and a senescence-associated secretory phenotype. *Cancer Res.* 81, 634–647
28. Le, N.-T. (2023) Metabolic regulation of endothelial senescence. *Front. Cardiovasc. Med.* 10, 1232681
29. Suda, M. *et al.* (2025) Endothelial senescent-cell-specific clearance alleviates metabolic dysfunction in obese mice. *Cell Metab.* 37, 2455–2465.e6
30. Reynolds, L.E. *et al.* (2024) Effects of senescence on the tumour microenvironment and response to therapy. *FEBS J.* 291, 2306–2319
31. Jiang, B. *et al.* (2024) Targeting senescent cells to reshape the tumor microenvironment and improve anticancer efficacy. *Semin. Cancer Biol.* 101, 58–73
32. Ma, L. *et al.* (2024) Senescent endothelial cells promote liver metastasis of uveal melanoma in single-cell resolution. *J. Transl. Med.* 22, 605
33. Wang, D. *et al.* (2020) Sunitinib facilitates metastatic breast cancer spreading by inducing endothelial cell senescence. *Breast Cancer Res.* 22, 103
34. Ye, Z. *et al.* (2024) Immunocytes interact directly with cancer cells in the tumor microenvironment: one coin with two sides and future perspectives. *Front. Immunol.* 15, 1388176
35. Liu, Y. *et al.* (2024) Therapy-induced cellular senescence: potentiating tumor elimination or driving cancer resistance and recurrence? *Cells* 13, 1281
36. Chen, H.-A. *et al.* (2023) Senescence rewires microenvironment sensing to facilitate antitumor immunity. *Cancer Discov.* 13, 432–453
37. Chibaya, L. *et al.* (2022) Senescence and the tumor-immune landscape: implications for cancer immunotherapy. *Semin. Cancer Biol.* 86, 827–845
38. Colucci, M. *et al.* (2025) Senescence in cancer. *Cancer Cell* 43, 1204–1226
39. Yang, L. *et al.* (2023) Amino acid metabolism in immune cells: essential regulators of the effector functions, and promising opportunities to enhance cancer immunotherapy. *J. Hematol. Oncol.* 16, 59
40. Canè, S. *et al.* (2025) The roles of arginases and arginine in immunity. *Nat. Rev. Immunol.* 25, 266–284
41. Zheng, Y. *et al.* (2023) Amino acid metabolism reprogramming: shedding new light on T cell anti-tumor immunity. *J. Exp. Clin. Cancer Res.* 42, 291
42. Martí I Líndez, A.-A. and Reith, W. (2021) Arginine-dependent immune responses. *Cell. Mol. Life Sci.* 78, 5303–5324
43. Wada, H. *et al.* (2023) Tumor cell-induced macrophage senescence plays a pivotal role in tumor initiation followed by stable growth in immunocompetent condition. *J. Immunother. Cancer* 11, e006677
44. Li, Y. *et al.* (2022) Age-related macrophage alterations are associated with carcinogenesis of colorectal cancer. *Carcinogenesis* 43, 1039–1049
45. Fiore, A. and Murray, P.J. (2021) Tryptophan and indole metabolism in immune regulation. *Curr. Opin. Immunol.* 70, 7–14
46. Meireson, A. *et al.* (2020) IDO expression in cancer: different compartment, different functionality? *Front. Immunol.* 11, 531491
47. Li, Y. *et al.* (2024) IDO1-mediated kynurenine production inhibits IGFBP5 signaling to promote 5-fluorouracil-induced senescence escape and chemoresistance in colorectal cancer. *Am. J. Cancer Res.* 14, 4551–4566
48. Nawas, A.F. *et al.* (2023) IL-1β mediates the induction of immune checkpoint regulators IDO1 and PD-L1 in lung adenocarcinoma cells. *Cell Commun. Signal* 21, 331

49. Peyraud, F. *et al.* (2022) Targeting tryptophan catabolism in cancer immunotherapy era: challenges and perspectives. *Front. Immunol.* 13, 807271
50. Mukherjee, D. *et al.* (2020) Regulation of cellular immunity by activating transcription factor 4. *Immunol. Lett.* 228, 24–34
51. Wetzel, T.J. *et al.* (2023) The emerging role of the branched chain aminotransferases, BCATc and BCATm, for anti-tumor T-cell immunity. *Immunometabolism (Cobham)* 5, e00014
52. Yahsi, B. and Gunaydin, G. (2022) Immunometabolism – the role of branched-chain amino acids. *Front. Immunol.* 13, 886822
53. Ikeda, K. *et al.* (2017) Slc3a2 mediates branched-chain amino-acid-dependent maintenance of regulatory T cells. *Cell Rep.* 21, 1824–1838
54. Domagala, J. *et al.* (2025) Ammonia suppresses the antitumor activity of natural killer cells and T cells by decreasing mature perforin. *Cancer Res.* 85, 2448–2467
55. Pranzini, E. *et al.* (2025) Adapt and shape: metabolic features within the metastatic niche. *Trends Endocrinol. Metab.* 36, 205–218
56. Rinaldi, G. *et al.* (2021) *In vivo* evidence for serine biosynthesis-defined sensitivity of lung metastasis, but not of primary breast tumors, to mTORC1 inhibition. *Mol. Cell* 81, 386–397.e7
57. Doglioni, G. *et al.* (2025) Aspartate signalling drives lung metastasis via alternative translation. *Nature* 638, 244–250
58. Ngo, B. *et al.* (2020) Limited environmental serine and glycine confer brain metastasis sensitivity to PHGDH inhibition. *Cancer Discov.* 10, 1352–1373
59. Liu, X.Z. *et al.* (2026) Targeting the lipid metabolism proteins FASN and GPAM in alveolar type II cells decreases lung metastasis. *Cancer Discov*. https://doi.org/10.1158/2159-8290.CD-25-0191
60. Zou, Y. *et al.* (2019) Polyunsaturated fatty acids from astrocytes activate PPARγ signaling in cancer cells to promote brain metastasis. *Cancer Discov.* 9, 1720–1735
61. Wang, Y. *et al.* (2024) Pre-metastatic niche: formation, characteristics and therapeutic implication. *Signal Transduct. Target. Ther.* 9, 236
62. Luo, X. *et al.* (2016) Stromal-initiated changes in the bone promote metastatic niche development. *Cell Rep.* 14, 82–92
63. Kaur, J. *et al.* (2024) Single-cell transcriptomic analysis identifies senescent osteocytes that trigger bone destruction in breast cancer metastasis. *Cancer Res.* 84, 3936–3952
64. Borzone, F.R. *et al.* (2023) Senescent mesenchymal stem/stromal cells in pre-metastatic bone marrow of untreated advanced breast cancer patients. *Oncol. Res.* 31, 361–374
65. Perkins, D.W. *et al.* (2024) Therapy-induced normal tissue damage promotes breast cancer metastasis. *iScience* 27, 108503
66. Gallanis, G.T. *et al.* (2023) Stromal senescence following treatment with the CDK4/6 inhibitor palbociclib alters the lung metastatic niche and increases metastasis of drug-resistant mammary cancer cells. *Cancers (Basel)* 15, 1908
67. Fane, M.E. *et al.* (2022) Stromal changes in the aged lung induce an emergence from melanoma dormancy. *Nature* 606, 396–405
68. Pilley, S.E. *et al.* (2023) Loss of attachment promotes proline accumulation and excretion in cancer cells. *Sci. Adv.* 9, eadh2023
69. Wu, Y. *et al.* (2023) Phosphoglycerate dehydrogenase activates PKM2 to phosphorylate histone H3T11 and attenuate cellular senescence. *Nat. Commun.* 14, 1323
70. Lee, E.J. *et al.* (2024) Glutaminase-1 inhibition alleviates senescence of Wharton's jelly-derived mesenchymal stem cells via senolysis. *Stem Cells Transl. Med.* 13, 873–885
71. Chen, L. *et al.* (2023) RBM4 dictates ESCC cell fate switch from cellular senescence to glutamine-addiction survival through inhibiting LKB1-AMPK-axis. *Signal Transduct. Target. Ther.* 8, 159
72. Wang, Y. *et al.* (2024) β-catenin activation reprograms ammonia metabolism to promote senescence resistance in hepatocellular carcinoma. *Cancer Res.* 84, 1643–1658
73. Li, Z. *et al.* (2026) Overview of glutamine metabolism in stromal components of the tumor microenvironment and potential anti-tumor therapies. *Genes Dis.* 13, 101834
74. Gao, D. *et al.* (2025) Senescent immune cells in the tumor microenvironment: emerging insights into cancer immunotherapy resistance. *Front. Immunol.* 16, 1656733
75. Sas, K. *et al.* (2018) Mitochondria, oxidative stress and the kynurenine system, with a focus on ageing and neuroprotection. *Molecules* 23, 191
76. Le Naour, J. *et al.* (2020) Trial watch: IDO inhibitors in cancer therapy. *Oncoimmunology* 9, 1777625
77. Huang, Z. *et al.* (2025) Asparaginase and autophagy inhibitors effectively remove senescent cells by synergistically limiting asparagine supply. *Aging Cell* 24, e70203
78. Chiu, M. *et al.* (2019) Asparagine synthetase in cancer: beyond acute lymphoblastic leukemia. *Front. Oncol.* 9, 1480
79. Knott, S.R.V. *et al.* (2018) Asparagine bioavailability governs metastasis in a model of breast cancer. *Nature* 554, 378–381