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Seminars in Cancer Biology 108 (2025) 1–16

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

The interplay between cell death and senescence in cancer

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ARTICLE INFO

Keywords:
Cancer
Cell death
Senescence
Senotherapy

ABSTRACT

Cellular senescence is a state of permanent proliferative arrest that occurs in response to DNA damage-inducing endogenous and exogenous stresses, and is often accompanied by dynamic molecular changes such as a senescence-associated secretory phenotype (SASP). Accumulating evidence indicates that age-associated increases in the upstream and downstream signals of regulated cell death, including apoptosis, necroptosis, pyroptosis, and ferroptosis, are closely related to the induction of cellular senescence and its phenotype. Furthermore, elevated levels of pro-inflammatory SASP factors with aging can be both a cause and consequence of several cell death modes, suggesting the reciprocal effects of cellular senescence and cells undergoing regulated cell death. Here, we review the critical molecular pathways of the regulated cell death forms and describe the crosstalk between aging-related signals and cancer. In addition, we discuss how targeting regulated cell death could be harnessed in therapeutic interventions for cancer.

Abbreviations: Abbreviations that are not standard in this field are defined at their first occurrence in the article and are used consistently throughout the article.

1. Cellular senescence and cell death in cancer

Aging is an inevitable and persistent phenomenon that affects all living organisms. This process is characterized by a gradual deterioration of physiological, tissue, and cellular functions, potentially elevating the likelihood of developing various age-associated pathologies, such as cancer. *In vivo* studies have revealed a strong connection between aging and cellular senescence, as demonstrated in a progeroid mouse model [1]. A growing body of evidence showed that the accumulation of senescent cells leads to aging and associated disorders [2,3], and that the selective removal of these cells can promote longevity and alleviate the onset of aging-related diseases in mice [1,4–8]. Cellular senescence was first discovered by Heyflick and Moorhead [9]. Diploid fibroblasts exit the cell cycle permanently upon reaching the maximum number of cell divisions, referred to as the Heyflick limit. With each cell division, the chromosomal telomeres gradually become shorter. When they reach a critical length; i.e., the Heyflick limit, the DNA damage response (DDR) is triggered, leading to the onset of cellular senescence, which is characterized as replicative senescence [10–12].

The accumulation of replicative senescence contributes to the gradual deterioration of tissue function as an individual ages. However, it also plays a vital role in preventing replicative stress and genomic instability [13]. Since senescent cells exhibit permanent cell cycle arrest and exit [14], cellular senescence is widely regarded as a natural defense mechanism against cancer [15,16]. In addition to replicative senescence, another form of cellular senescence develops independently of telomere shortening. Various DNA damage-inducible stresses, such as genotoxic (e.g., anti-cancer agents targeting replication process), oncogenic (e.g., oncogene-enforced replication with error), and oxidative (e.g., ROS-induced DNA breaks) stresses, trigger premature senescence [17]. Besides stable cell cycle arrest, senescent cells also exhibit another notable characteristic that triggers tissue inflammation and repair. This is a secretory pattern featuring proinflammatory cytokines (e.g., IL-1α, IL-1β, IL-6, IL-8), chemokines (e.g., CCL2, CCL5, CXCL1), growth factors (e.g., HGF, EGF, TGFα), proteases (e.g., matrix metalloproteinase [MMP] 1 and 3), non-protein molecules (e.g., prostaglandin E_2 [PGE_2], ROS, nitric oxide), and cell death ligands/receptors (e.g., tumor necrosis factor [TNF], tumor necrosis factor receptor 1 [TNFR1], Fas), which is referred to as the senescence-associated secretory phenotype (SASP) [18–20]. The underlying mechanism of SASP is the chronic DDR, regulated by the NF-κB, p38, mTOR, and C/EBPβ signaling pathways [20]. SASP factors not only reinforce the senescence phenotype in an

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https://doi.org/10.1016/j.semcancer.2024.11.001
Received 15 August 2024; Received in revised form 10 November 2024; Accepted 12 November 2024
Available online 16 November 2024

autocrine manner but also function as paracrine messengers for surrounding cells, such as stromal, immune, premalignant, and cancer cells [20,21]. The compositions of SASP factors vary, based on the cell type and the context. For example, oncogene-mediated persistent genotoxic stress can establish a more tumorigenic type of SASP than replicative stress [18,22]. In addition, SASP factors, such as TNF, ROS, and IL-6, can trigger apoptosis or lytic cell death in cancer cells, depending on the situation [20,23,24]. Thus, while SASP is beneficial in promoting tissue repair and activating the immune system to eliminate senescent and cancer cells during acute senescence, the persistent presence of proinflammatory SASP factors intensifies the senescent state and contributes to tumorigenesis.

The initiation and maintenance of senescence involves critical tumor suppressive signaling pathways. DNA damage is a significant trigger of senescence [22], and the p53/p21 [25] and p16 [26] signaling pathways are primarily responsible for this process. p53 is a crucial tumor suppressor that protects genomic integrity by activating transactivation in response to various cellular stress signals. The DDR triggers p53 transactivation, leading to the transcription of its downstream target genes, controlling cell death, cell cycle regulation, and DNA damage repair. Among the p53 targets, p21, a cyclin-dependent kinase (CDK) inhibitor, plays a significant role in blocking the activities of CDK2 and CDK4/6. The inhibition decreases the extent of phosphorylation in retinoblastoma protein (RB) and promotes RB-E2F1 complex formation to suppress E2F1 function, resulting in cell cycle arrest at the G1/S checkpoint [25]. The p16 signaling pathway also epigenetically induces cellular senescence. p16 is a cytostatic factor that inhibits the activities of CDK4 and CDK6, which play crucial roles in regulating the cell cycle. Various stress signaling pathways activate p16 expression to inhibit CDK4/6 activity and prevent S-phase gene transcription via RB-E2F complex formation, leading to cell cycle arrest and senescence [26]. Consequently, the convergence of the p53/p21 and p16 pathways on RB highlights its central role in cellular senescence. Acute stress signals such as DDR mainly activate p53/p21 signaling. In contrast, chronic and oncogenic stresses activate p16 signaling, suggesting that p53/p21 plays a role in inducing senescence at an early phase, and p16 maintains the senescence status [27]. These two pathways can operate independently or cooperatively to induce and sustain senescence in a manner dependent on distinct cellular stresses.

The senescence and cell death signaling pathways are tightly interconnected in the aging process [28,29]. Cells may undergo either cell death or senescence in response to stress, contingent on the magnitude of damage and the specific cellular context [30]. Lethal or irreparable damage triggers cell death, while sublethal or chronic stress induces senescence. Cell death is largely divided into regulated cell death and necrosis. Regulated cell death is a controlled essential mechanism for stress responses, development, and tissue homeostasis. In contrast, necrosis is uncontrolled passive cell death resulting from acute cellular injury that leads to cell swelling and membrane rupture [28]. The regulated cell death pathways include four major forms of cell death: apoptosis [31], necroptosis [32], pyroptosis [33], and ferroptosis [34]. (1) Apoptosis is a regulated and non-lytic form of cell death that involves cell shrinkage and plasma membrane blebbing [35]. It can be triggered by an intrinsic pathway via mitochondrial pro-death proteins or an extrinsic pathway via death receptors [36,37]. Key molecules, especially p53, determine whether cells undergo apoptosis or senescence. SASP factors can induce apoptosis in adjacent damaged or transformed cells [30,38], and at sublethal mitochondrial stress levels, they maintain chronic inflammation and induce senescence. In contrast to apoptosis, necroptosis, pyroptosis, and ferroptosis cause cell membrane rupture and immunogenic reactions [37]. (2) Necroptosis is programmed necrotic cell death that is crucial for pathogen defense and inflammation regulation [32,39]. It occurs when apoptosis is inhibited, leading to cell swelling and membrane rupture, and thus triggering an inflammatory response. SASP factors, including TNF, can activate necroptosis in neighboring cells, promoting an inflammatory environment. Key components include receptor-interacting protein kinase 1 (RIPK1) and RIPK3, which form the necrosome upon death receptor activation. RIPK3 phosphorylates mixed lineage kinase domain-like protein (MLKL), causing membrane disruption and cell lysis. (3) Pyroptosis is inflammation-associated regulated cell death triggered by microbial infections and noninfectious stimuli [33], and occurs in phagocytotic immune cells and epithelial cells under inflammatory conditions [40,41]. This process involves cell swelling, membrane disruption, and the subsequent release of pro-inflammatory contents, playing a crucial role in the immune response [42]. Inflammasomes, including NLR family pyrin domain containing 3 (NLRP3), absent in melanoma 2 (AIM2), and NLR family CARD domain containing 4 (NLRC4), activate caspase-1, which cleaves the pro-inflammatory cytokines IL-1β and IL-18, and gasdermin D (GSDMD) [42]. The cleaved GSDMD forms pores in the plasma membrane, facilitating the release of inflammatory cytokines and damage-associated molecular patterns (DAMPs). The DAMPs recruit and activate immune cells, and SASP attracts immune cells to senescent cell sites. The crosstalk between SASP and pyroptosis activates the immune response, thereby enhancing the inflammatory environment and senescence. (4) Ferroptosis is a regulated cell death process involving iron-dependent lipid peroxidation, characterized by lipid reactive oxygen species (ROS) accumulation and loss of membrane integrity [34]. Excess free iron catalyzes ROS generation, leading to lipid peroxidation and cell death. Glutathione peroxidase 4 (GPX4) suppresses ferroptosis by reducing lipid peroxides, using glutathione (GSH) synthesized with cystine imported by system x_c^- (xCT). Inhibition of xCT depletes GSH, promoting ferroptosis [43]. Senescent cells, with high iron and ROS levels, are more susceptible to ferroptosis due to their increased DNA damage and senescence phenotype.

The senescence and cell death pathways play complex and often dual roles in cancer suppression and progression [20]. Cellular senescence serves as a critical barrier to cancer progression by arresting cell proliferation. Key senescence pathways involve the essential tumor suppressors, RB and p53. Oncogene activation leads to persistently enhanced tumor suppressor pathway activity, triggering cellular senescence, in a phenomenon known as oncogene-induced senescence (OIS) [15]. Therefore, OIS exerts intrinsic cellular defense mechanisms aimed at preventing cancer development and limiting tumor progression [44]. Chemotherapy regimens and radiotherapy trigger the onset of cancer cell senescence. This premature senescence is classified as therapy-induced senescence (TIS) [45]. TIS exhibits antitumor effects by halting cell cycle progression; however, the secretion of pro-inflammatory SASP factors from TIS cells can promote tumor progression. While SASP recruits immune cells to clear senescent and malignant cells, chronic SASP secretion creates a pro-tumorigenic microenvironment that fuels tumor growth and invasion, as well as acquired drug resistance, thereby leading to recurring tumorigenesis [20]. Therefore, targeting TIS-mediated adverse effects may increase the efficacy of cancer treatment. Notably, combinatorial treatments with chemotherapeutic drugs and senolytics (drugs that selectively eliminate senescent cells) [46–48] have shown promising anticancer effects [45,49–51]. Drugs that selectively target detrimental SASP factors without inducing cell death, termed senomorphics, are another encouraging senotherapeutical approach [52,53]. Senomorphic drugs aim to mitigate chronic inflammation by retaining the beneficial roles of senescent cells, such as tumor suppression and wound healing. Therefore, the specific elimination of SASP factors by senomorphics and the acute induction of regulated cell death in cancer cells in tumor microenvironments might also hold promise for treatments. The following sections provide an overview of the role of each regulated cell death pathway in cellular senescence and explore the possible implications for anticancer therapies.

2. Apoptosis

Apoptosis, the first described type of regulated cell death, plays a

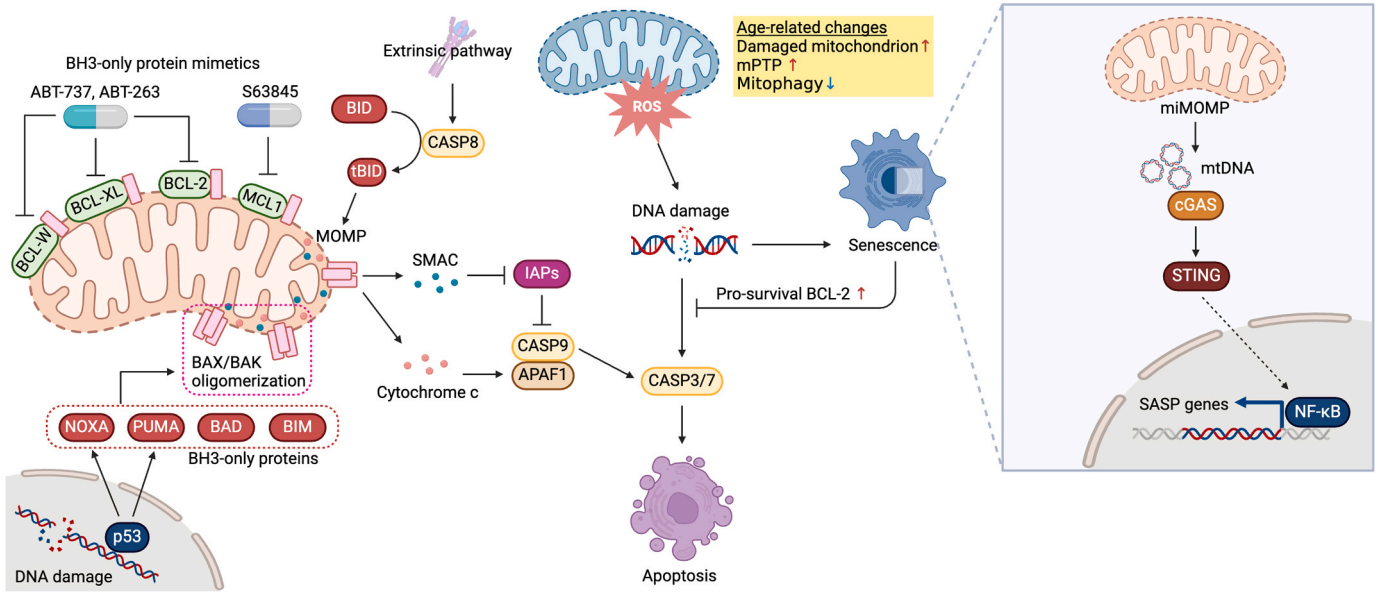

Fig. 1. Intrinsic apoptotic pathway and crosstalk with aging-related changes. Upon apoptotic stimuli to drive the intrinsic pathway, BH3-only proteins bind to the pro-survival BCL-2 proteins to liberate the pro-death BCL-2 family members BAX and BAK. Oligomerization of BAX and BAK causes MOMP, followed by the release of cytochrome c and SMAC, activating CASP9 mediated by an apoptotic protease-activating factor 1 (APAF1). CASP3/7 proteolytically activated by CASP9 cleaves numerous substrates to execute apoptosis. Age-related changes, such as increases in damaged mitochondria, may promote cellular senescence and SASP through the cGAS-STING pathway. The BH3 mimetics ABT-737 and ABT-263 and the MCL1 inhibitor S63845 are increasingly used as senolytic agents. CASP, caspase; SMAC, a second mitochondria-derived activator of caspase; IAPs, inhibitors of apoptosis.

fundamental role in tissue homeostasis by eliminating unwanted cells, including preneoplastic cells. In the process of apoptosis, the cells undergo shrinkage, organelle and DNA fragmentation, and plasma membrane blebbing without releasing cellular contents. Phagocytic cells, such as macrophages, engulf apoptotic cells before they rupture. Thus, apoptosis has been considered a form of immunologically silent cell death, compared to necrosis. However, delayed or impaired clearance of apoptotic cells compromises their membrane integrity, eventually leading to secondary necrosis and subsequent inflammatory and immune responses [54]. In addition, apoptotic extracellular vesicles or exosomes may also be involved in the pathogenesis of various inflammatory diseases, including cancer [54]. The biochemical and morphological changes during apoptosis are mediated by cysteine–aspartate protease (caspase)-dependent cleavage of numerous substrates. Two major pathways induce apoptosis: The extrinsic pathway is initiated through death receptors localized on the plasma membrane, whereas the intrinsic pathway refers to mitochondrial apoptotic signaling without involving death receptors.

2.1. Intrinsic apoptosis and senescence

Intrinsic apoptosis can be triggered by unfavorable extracellular or intracellular conditions, including growth factor deprivation, DNA damage, endoplasmic reticulum (ER) stress, or oxidative stress. The common and critical event of the intrinsic pathway is mitochondrial outer membrane permeabilization (MOMP) induced by the activation of pro-apoptotic BCL-2 family members, BCL-2-associated X protein (BAX) and BCL-2 antagonist/killer 1 (BAK, gene symbol: *BAK1*), which results in the cytosolic release of pro-apoptotic factors, such as cytochrome c, and then leads to the sequential activation of the initiator caspase (caspase-9) followed by the executioner caspases (caspase-3 and caspase-7). The formation of BAX/BAK oligomeric pores in the mitochondrial outer membrane is blocked by direct interactions with pro-survival BCL-2 family proteins, such as BCL-2, BCL-XL (gene symbol: *BCL2L1*), BCL-W (gene symbol: *BCL2L2*), and myeloid cell leukemia 1 (MCL1). Meanwhile, these interactions are antagonized by pro-apoptotic BH3-only BCL-2 proteins, including BCL-2 associated agonist of cell death (BAD), BCL-2 interacting mediator of cell death (BIM, gene symbol: *BCL2L11*), BH3-interacting domain death agonist (BID), NOXA (gene symbol: *PMAIP1*), and PUMA (gene symbol: *BBC3*). Upon perturbation of cellular homeostasis, BAD and BIM are post-translationally activated, and NOXA and PUMA are transcriptionally induced by p53. MOMP is also promoted by a truncated form of BID (tBID) produced by caspase-8 (Fig. 1).

Mitochondrial dysfunction and cellular senescence are part of the natural progression of the aging process and are thought to be interrelated [55,56]. A decreased mitochondrial membrane potential [57] and a lower NAD^+/NADH ratio [58], which indicate mitochondrial dysfunction, are typically associated with the increased production of ROS. DNA damage secondary to the accumulation of ROS is one of the leading causes of cellular senescence-inducing stress and tumorigenesis. The accumulation of damaged mitochondria due to decreased mitophagy, a selective form of autophagy for mitochondrial degradation, is observed in senescent cells, where the compromised mitochondrial function may be partially compensated by the increased mitochondrial mass [55,59,60]. Furthermore, impaired mitophagy in *C. elegans* leads to the progressive accumulation of damaged mitochondria during aging [61]. Thus, mitochondrial dysfunction can be a cause and a consequence of cellular senescence (Fig. 1), which establishes feedback loops that lead to and sustain the senescent phenotype, such as excessive ROS production and mitochondrial dysfunction-associated SASP [55,58]. Notably, a recent study showed that the cytoplasmic hydride transfer complex (HTC), composed of malic enzyme 1 (ME1), malate dehydrogenase 1 (MDH1), and pyruvate carboxylase (PC), can compensate for mitochondrial dysfunction by catalyzing NAD^+ regeneration and NADPH production [62]. This NAD metabolic reprogramming supports cell survival by reducing oxidative stress and promotes tumor formation by bypassing cellular senescence.

The mitochondrial permeability transition pore (mPTP) is a Ca^{2+}-dependent, non-selective channel formed in the inner mitochondrial membrane under oxidative stress conditions. Prolonged mPTP opening caused by higher oxidant levels, such as in ischemia/reperfusion, leads to further ROS release and generally activates the intrinsic apoptotic pathway. Natural aging also accelerates the opening probability of the

mPTP [63], and mPTP-mediated cell death is involved in the pathogenesis of aging-related diseases: ischemic heart and brain disease, degenerative diseases of the brain and skeletal muscle, and cancers [64,65]. However, it is unclear to what extent the mPTP opening contributes to cellular senescence and ROS production in senescent cells.

MOMP can occur in a limited subset of mitochondria without resulting in cell death. This minority MOMP (miMOMP) enables non-lethal caspase activation and leads to DNA damage, which in turn promotes genomic instability and oncogenic transformation [66]. Senescent cells with high viability may readily tolerate sublethal mitochondrial apoptotic signaling. Of note, miMOMP with mitochondrial DNA (mtDNA) release was observed during senescence induced by X-ray irradiation or replication stress [38]. The cytosolic mtDNA, in turn, drove SASP by activating the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway (Fig. 1). Pharmacological inhibition of BAX by BAI1 suppressed miMOMP and SASP in senescent cells and improved health span in aged mice [38]. Thus, a senomorphic approach targeting miMOMP may provide human health benefits, including cancer prevention, by counteracting age-associated sterile inflammation.

The expression of pro-survival BCL-2 family proteins (e.g., BCL-2, BCL-XL, BCL-W, MCL-1, A1/BFL-1) is transcriptionally regulated by the NF-κB, JAK/STAT, and RB/E2F signaling pathways [67]. Therefore, these pathways can be activated by several SASP factors, such as IL-1β, IL-6, and EGF. Upregulation of the pro-survival BCL-2 family proteins in senescent cells underlies the resistance to apoptosis induced via intrinsic pathways. Pharmacological inhibition of those pro-survival proteins enables the proapoptotic BCL-2 family members to permeabilize the mitochondrial membrane and prolong mPTP opening, activating the intrinsic apoptosis pathway (Fig. 1). Indeed, ABT-737 and ABT-263 (navitoclax), specific inhibitors of BCL-2, BCL-XL, and BCL-W, can eliminate senescent cells *in vitro* and *in vivo*. These senolytic drugs improve the regeneration capacity of skin, blood, and muscle by rejuvenating aged tissue stem cells [46,47]. ABT-737 also enhanced liver regeneration after hepatectomy by eliminating senescent cells characterized by increased p21, but not p16 [68]. Considering the role of SASP in promoting tissue regeneration, the selective elimination of specific senescent cells among heterogeneous populations arising in injured tissues may improve the efficacy of senolytic drugs for tissue regeneration. A recent study identified populations of senescent macrophages in naturally aged lungs and lung tumors that are molecularly similar [69]. Significantly, the removal of senescent macrophages by ABT-737 promoted cancer immunosurveillance and reduced tumor burden in the KRAS-driven lung cancer model. ABT-263 can induce apoptosis in chemotherapy-induced senescent tumor cells and delay tumor relapse [70]. However, ABT-263 may have relatively low specificity and sensitivity for senescent cells, similar to its limitations as an anticancer agent [55]. Notably, a recent single-cell transcriptomics approach revealed that senescent cells are highly heterogeneous, although MCL1 can be a common target to eliminate senescent tumor cells [48]. In mouse models of breast and prostate cancers, S63845, a potent MCL1 inhibitor [71], enhanced the efficacy of therapy as a promising senolytic drug [48,70]. Several compounds have been identified as a new class of senolytic drugs with targets beyond the pro-survival BCL-2 family proteins. The molecular chaperone HSP90 supports cancer cell survival, proliferation, and metastasis by activating and stabilizing a wide range of oncogenic client proteins. Accordingly, it is regarded as an attractive drug target. Notably, a screen for senotherapeutic agents focused on autophagy regulators revealed that HSP90 inhibitors (geldanamycin and its synthetic derivatives: 17-AAG and 17-DMAG) have senolytic activity, based on blocking the client AKT-mediated anti-apoptotic signaling [72]. A more recent study identified ARV825, a degrader of bromodomain and extra-terminal domain (BET) family proteins including BRD4, which provoked apoptosis-driven senolysis by targeting non-homologous end joining (NHEJ) and autophagy in senescent cells, inhibiting obesity-associated liver cancer development, and improving the efficacy of chemotherapy in a mouse xenograft model [73]. However, given the positive aspects of cellular senescence as a tumor suppressor mechanism, the effects of the timing and duration of treatments with these senolytic drugs on cancer development and progression in each tissue should be investigated thoroughly.

In the tumor microenvironment, non-malignant senescent cells, including cancer-associated fibroblasts (CAFs), are induced by various cellular stresses that cause DNA damage or ROS production, such as anticancer treatments, inflammation, and hypoxic conditions, which promote cancer progression and chemoresistance. For instance, the systemic pro-inflammatory state can induce SASP in CAFs with p16 expression, which may confer resistance to intrinsic apoptosis through JAK/STAT3 signaling in tumor cells [74]. Indeed, in a mouse model, the JAK/STAT3 inhibitor WP1066 demonstrated efficacy in preventing peritoneal tumor formation promoted by senescent CAFs. A recent study identified a senescent myofibroblastic CAF population that is positive for neural cell adhesion molecule (NCAM) and p16 in breast cancer, which inhibits natural killer (NK) cell cytotoxicity through extracellular matrix (ECM) deposition and promotes tumor growth [75]. Significantly, ABT-737 treatment could specifically deplete the senescent myofibroblastic CAFs and inhibit breast cancer progression. In another related study, senescent myofibroblastic CAFs in pancreatic ductal adenocarcinoma (PDAC) mediated immune cell dysfunction, including macrophages, dendritic cells, and effector T cells, resulting in the promotion of tumor progression [76]. Although the mechanisms may vary from tissue to tissue, senescent CAFs can exert immunosuppressive and tumor-promoting effects in various cancers. It is notable that the senolysis by ABT-263 in mouse PDAC can delay tumorigenesis and prevent fibrosis [76]. Thus, targeting the intrinsic pathways in certain senescent CAFs could be a rational approach to limit tumor growth.

Since the senescence-like growth arrest of mouse and human fibroblasts is prevented by hypoxic conditions [77,78], oxidative stress is thought to play a critical role in senescent cell accumulation associated with aging. Interestingly, naked mole-rats (NMRs), the longest-lived rodent with resistance to various age-related diseases, including cancer, have a natural senolytic mechanism by which H_2O_2 production, derived from unique serotonin metabolism dependent on the $p16^{INK4a}$-RB pathway, causes progressive cell death of NMR fibroblasts that underwent senescence stress [79]. The inherent susceptibility of NMR fibroblasts to H_2O_2-induced cell death also contributes to this mechanism. Notably, NMR fibroblasts are resistant to γ-irradiation (IR)-induced apoptosis and cellular senescence commitment [80]. Furthermore, the cytoprotective effects due to increased nuclear factor erythroid 2-related factor 2 (NRF2) signaling [81] and abundant high-molecular-mass hyaluronic acid [82,83] contribute to cancer resistance in NMRs. In addition, NMR's social and subterranean lifestyle generates a hypoxic niche in which NMRs have acquired the ability to avoid anoxic injury by using fructose-driven glycolysis [84]. Given that fructose metabolism has been associated with cancer growth in humans [85,86], a specific mechanism in the NMR under hypoxic conditions may abolish the effects of fructolysis that favor tumorigenesis. On balance, these anti-aging mechanisms that evolved in NMRs provide new perspectives for cancer treatment.

2.2. Extrinsic apoptosis and senescence

Extrinsic apoptosis is triggered by cytoplasmic membrane-localized death receptors (DRs), such as Fas (also known as CD95), TNF-related apoptosis-inducing ligand (TRAIL)-receptors (TRAIL-R1/2), and TNFR1, upon the engagement of their cognate ligands: Fas ligand (FasL), TRAIL, and TNF, respectively. The cytoplasmic tails of Fas and TRAIL-R1/2 can mediate the assembly of a death-inducing signaling complex (DISC), in which the adaptor protein Fas-associated via death domain (FADD) recruits and induces the transactivation of caspase-8, an initiator caspase of the extrinsic apoptosis pathway. Meanwhile, TNFR1 activated by TNF rapidly assembles a signaling platform called complex

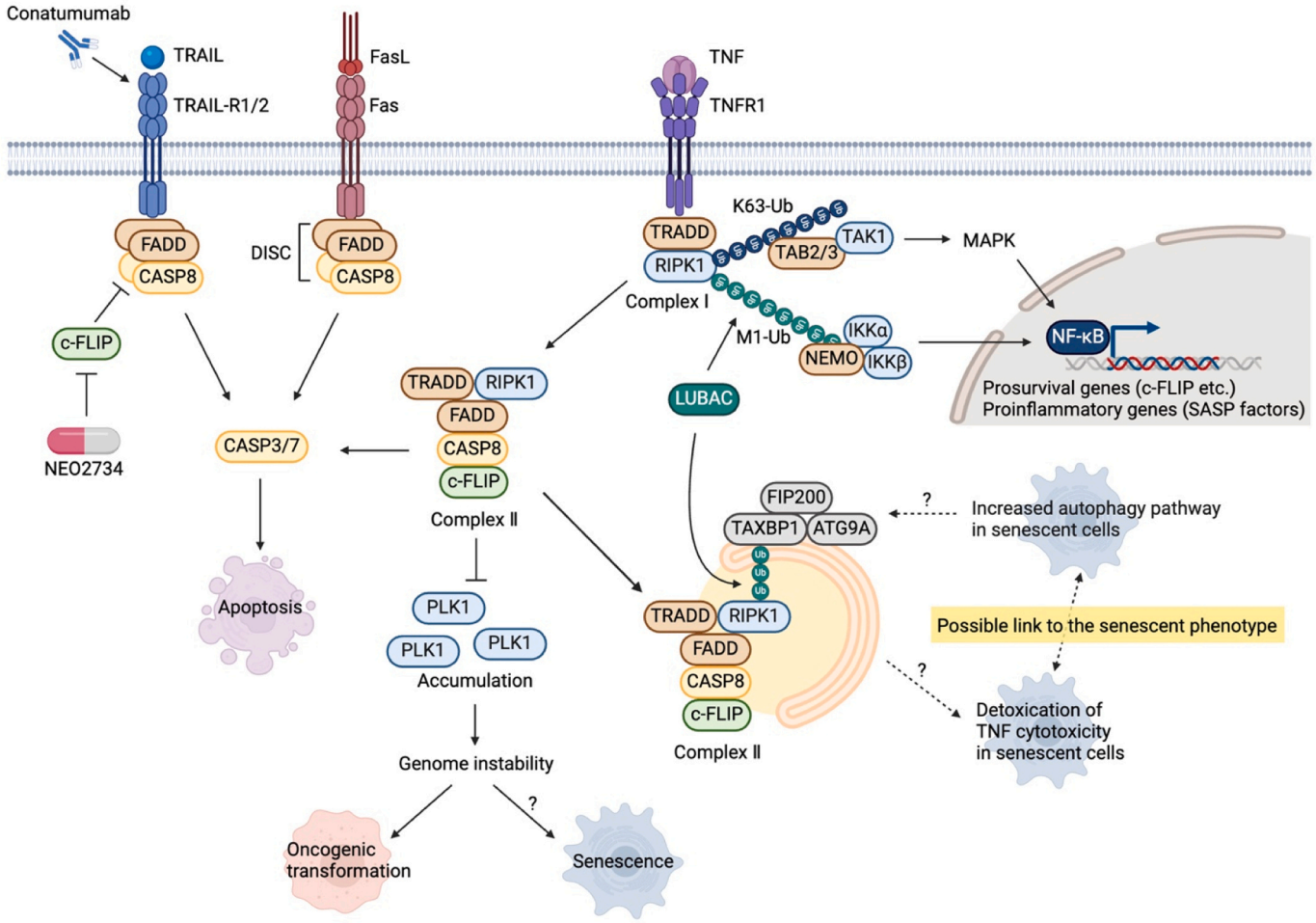

Fig. 2. Extrinsic apoptotic pathway and crosstalk with aging-related changes. The binding of FasL and TRAIL to their cognate death receptors, Fas and TRAILR, respectively, induces the assembly of a DISC to transactivate CASP8. Activated CASP8 can directly cleave and activate CASP3/7. TNF binding to TNFR1 causes the assembly of complex I, leading to the activation of NF-κB and MAPK signaling, which induces the expression of pro-survival and pro-inflammatory genes. A secondary cytosolic complex II provides the platform to activate CASP8. C-FLIP can suppress caspase-8 activation in DISC and complex II. The p300/CBP and BET inhibitor NEO2734 would be available for the senolytic approach by suppressing c-FLIP expression. CASP8-mediated cleavage of PLK1 in the mitotic phase contributes to the maintenance of genome stability, and its disruption may be associated with cellular senescence and oncogenic transformation. ATG9A-dependent unconventional lysosomal degradation of complex II detoxifies TNF cytotoxicity, which may be linked to the senescent phenotype. M1-Ub, Met1-linked linear ubiquitin chains; K63-Ub, Lys63-linked ubiquitin chains; TAB, TAK1-binding protein; TAK1, transforming growth factor (TGF)-β activated kinase 1; IKK, IκB kinase; NEMO, NF-κB essential modulator.

I, which activates the MAPK and NF-κB signaling pathways. Following the transient formation of membrane-bound complex I, the cytosolic complex II, providing the platform for caspase-8 activation, can be assembled under conditions of reduced pro-survival signaling. Complex II contains FADD and caspase-8, with (complex IIb) or without (complex IIa) RIPK1. Cellular FLICE-like inhibitory protein (c-FLIP), a catalytically inactive caspase-8-like molecule, can counteract caspase-8 activation in complex II and DISC (Fig. 2).

Beyond its role as a pro-apoptotic protein, caspase-8 is reportedly essential for maintaining chromosomal stability, which highlights its tumor-suppressive function [87]. Mechanistically, in the process of physiological mitosis, a complex IIb-like platform composed of RIPK1/FADD/caspase-8/c-FLIP is assembled, which inhibits the accumulation of active Polo-like kinase 1 (PLK1) by caspase-8-mediated cleavage and therefore contributes to faithful chromosome segregation [88] (Fig. 2). Indeed, cells lacking RIPK1 or caspase-8 exhibited chromosome alignment defects [88], suggesting that the limited activation of pro-death complexes during mitosis prevents cellular senescence.

The kinase activity of RIPK1 is required for caspase-8 activation in complex IIb and RIPK3 activation in the necrosome to induce apoptosis and necroptosis (see next section). Conversely, the scaffold function of RIPK1 plays a vital role in limiting these cell death modes, allowing an escape from the early postnatal lethality mediated by caspase-8 and RIPK3 [89–91]. Notably, T cell-specific RIPK1-deficient mice develop chronic inflammatory diseases with aging, leading to premature death [92,93]. Mechanistically, a recent study revealed that RIPK1 deficiency induces premature senescence in T cells with SASP, associated with basal activations of mTORC1 and caspase-3/7. Meanwhile, the pharmacological inhibition of caspase-8 or mTORC1 can inhibit T cell senescence, SASP, and caspase-3/7 activation. Thus, the apoptotic pathway in the RIPK1–caspase-8 axis may offer new therapeutic strategies to regulate T cell senescence and age-related diseases, including cancer.

Apoptosis evasion is one of the fundamental features of senescent cells. Interestingly, a genome-wide CRISPR knockout approach revealed that TNF cytotoxicity is prevented by autophagy-related protein 9 A (ATG9A)-dependent, but LC3-independent, unconventional lysosomal degradation of complex II [94]. The autophagy adaptor Tax1-binding protein 1 (TAX1BP1) recruits the autophagy-initiation machinery, including FIP200, to complex II through M1-ubiquitinated RIPK1 by linear ubiquitin chain assembly complex (LUBAC) (Fig. 2). ATG9A deletion indeed leads to embryonic lethality due to uncontrolled

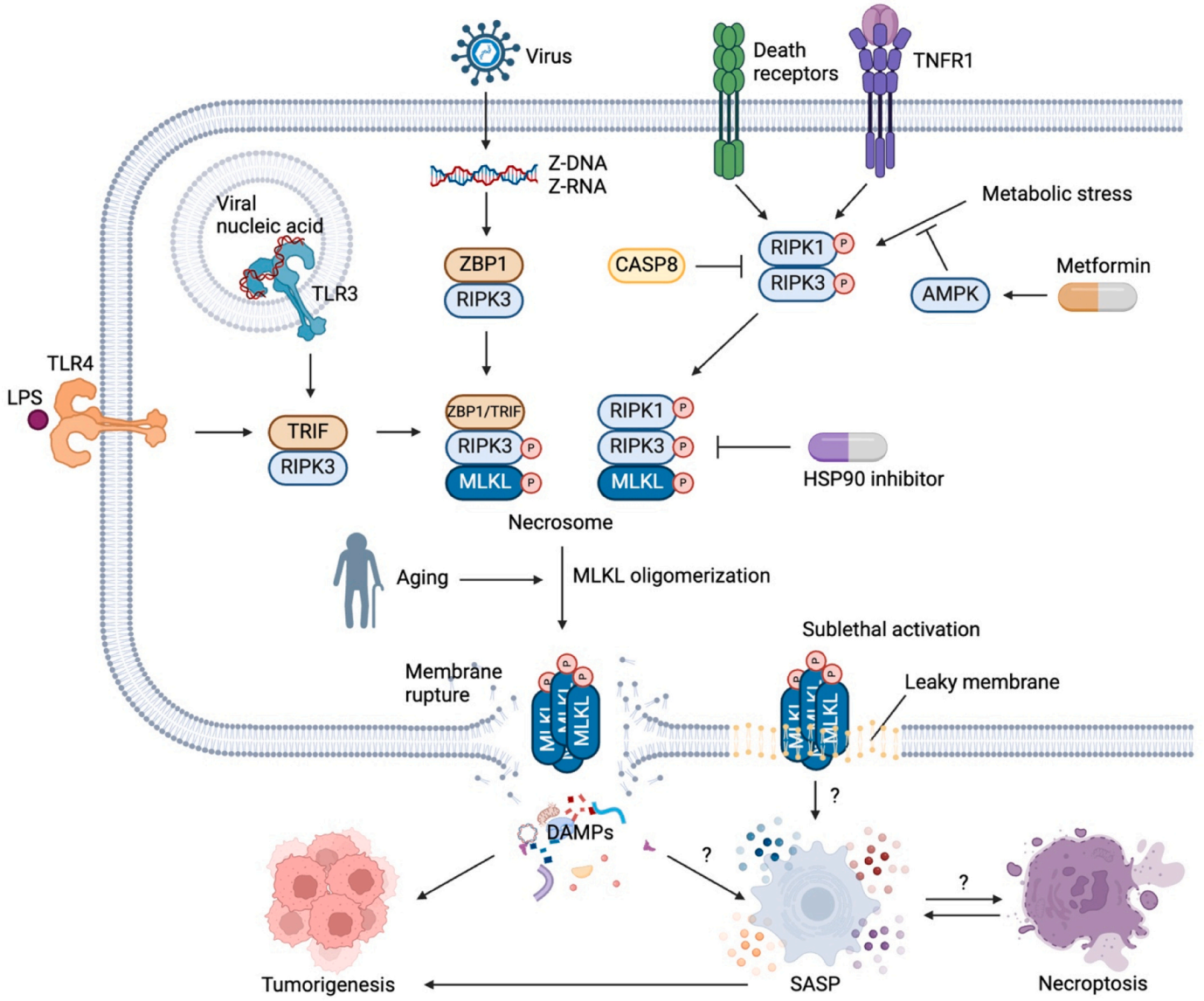

Fig. 3. Necroptotic pathway and crosstalk with aging-related changes. Activation of death receptors and TLRs, or viral infection, leads to the interaction of RIPK1, TRIF, or ZBP1 with RIPK3 through the RHIM domain, when CASP8 activation is limited. These interactions induce the activation of RIPK3, which in turn phosphorylates MLKL. Phosphorylated MLKL forms oligomers that translocate to the plasma membrane, causing membrane rupture and release of DAMPs. The levels of necroptotic DAMPs increase with aging. Sublethal activation of the necroptotic core machinery may be associated with cellular senescence and phenotype. Metformin and HSP90 inhibitors may exert senomorphic effects by inhibiting the necroptotic pathway.

TNF-mediated apoptosis of fetal liver hematopoietic cells. Although the interplay between senescence and autophagy is not yet fully understood [20], the activation of autophagy under certain conditions contributes to sustaining the protein synthesis of SASP factors [95,96] and buffering the toxicity of misfolded SASP factors [97]. Likewise, the enhanced autophagic process in senescent cells may prolong SASP factor production by detoxifying TNF cytotoxicity, including autocrine signaling. This also may partly explain why the mTOR inhibitor rapamycin exerts a senomorphic effect and extends life span [98–101].

C-FLIP is the major pro-survival gene targeted by NF-κB to protect against extrinsic pathway-induced apoptosis; therefore, targeting c-FLIP has great potential for sensitizing cancer cells to extrinsic apoptosis [102,103]. Importantly, CRISPR/Cas9-based genetic screens in several therapy-induced senescence models for cancer cells revealed that the loss of c-FLIP is a promising common vulnerability of senescent cancer cells [104]. Mechanistically, NF-κB activation in senescent cancer cells across different tissues upregulates TRAIL-R2 and its ligand to drive the extrinsic pathway. However, the co-upregulation of c-FLIP allows the maintenance of cell survival. Therefore, suppressing c-FLIP expression by BRD2 pharmacological inhibition using NEO2734 and TRAIL-R2 activation with an agonist antibody, conatumumab, can sensitize senescent cancer cells to senolysis (Fig. 2).

3. Necroptosis and senescence

Necroptosis is caspase-independent programmed cell death initiated when pathogens or genetic backgrounds block the apoptotic pathway. In contrast to apoptosis, necroptosis is a lytic form of cell death accompanied by the abundant release of DAMPs and cytokines. Therefore, necroptosis is a highly pro-inflammatory mode of cell death that contributes to host defense mechanisms, including an antitumor immune response. The transient necroptosis of specific cells or the resulting released factors can induce repopulation for tissue regeneration, such as remyelination in the central nervous system and muscle regeneration by

Tenascin-C release [105,106]. While there are several beneficial effects, uncontrolled and continuous necroptosis promotes the pathogenesis of infectious diseases, various inflammatory diseases, tissue damage, and common age-related diseases, including cancer [107]. Thus, there has been a growing interest in the pharmacological management of necroptotic machinery as a therapeutic target. Mechanistically, necroptosis initiated through TNFR1 has been intensively studied. Because activated caspase-8 upon TNF stimulation counteracts the necroptosis pathway by cleaving the key mediators RIPK1 and RIPK3, under conditions of caspase-8 inhibition, activated RIPK1 can bind to RIPK3. MLKL is then recruited to the RIPK1-RIPK3 complex to form the nanoscale architecture called the necrosome, where activated RIPK3 mediates the phosphorylation and oligomerization of MLKL to execute necroptosis with plasma membrane rupture. Other death receptors besides TNFR1, including Fas and TRAIL-R1/2, can also mediate necroptosis. In addition, the activation of Toll-like receptor 3 (TLR3) and TLR4 upon exposure to viral nucleic acids and bacterial lipopolysaccharide (LPS), respectively, can lead to necroptosis by promoting the binding of TIR domain-containing adaptor-inducing interferon-β (TRIF), instead of RIPK1, to RIPK3. Like the RIPK1–RIPK3 interaction, this binding is also mediated by the receptor-interacting protein homotypic interaction motif (RHIM)–RHIM homotypic interaction. Upon Z-DNA or Z-RNA detection by Z-DNA binding protein 1 (ZBP1), another RHIM-containing protein, RIPK3, is recruited to activate the necroptotic pathway (Fig. 3).

The DAMPs released from necroptotic cells include high mobility group box 1 (HMGB1), S100 proteins, IL-1α, IL-33, long genomic DNA, and mtDNA [108,109]. Interestingly, circulating mtDNA levels increase with age, which correlates with the increased inflammatory status of older people characterized by plasma cytokines: TNF, IL-6, RANTES (CCL5), and IL-1 receptor agonist (IL-1RN) [110]. With advancing age, the expression of HMGB1 decreases, while secretory acetylated HMGB1 increases [111]. In addition, the concentration of S100B in the cerebrospinal fluid reportedly increases with age in healthy individuals [112]. Consistent with these age-related increases in the levels of circulating DAMPs, enhanced necroptosis and inflammation, likely due to MLKL protein levels, are observed in the epididymal white adipose tissue of aged mice [113,114]. At the cellular level, the interplay between cellular senescence and necroptosis remains to be elucidated. However, since TNF is one of the SASP factors, as well as a necroptosis inducer, it is not surprising that the accumulation of senescent cells with age is involved in the age-associated increase in necroptosis [113]. In addition, NF-κB signaling, a central pathway for SASP establishment [115,116], can be activated by a series of necroptotic DAMPs [109]. In cells undergoing senescence, HMGB1 translocates from the nucleus to the cytoplasm and is subsequently secreted for autocrine/paracrine stimulation [21,117]. Therefore, senescent and necroptotic cells may accumulate reciprocally and synergistically with aging (Fig. 3).

Importantly, DAMPs derived from necroptosis promote inflammation-associated cancer growth and metastasis [118]. Pharmacological inhibition or genetic ablation of RIPK3 suppressed cytoplasmic translocation of HMGB1 in mouse skin and attenuated the tissue inflammatory response, resulting in delayed chemical carcinogenesis [119]. No carcinogenesis was observed in NMRs harboring loss-of-function mutations in the RIPK3 and MLKL genes in the same experimental setting, suggesting that the cancer resistance mechanism in NMRs relies on a dampened inflammatory response due to necroptosis deficiency. Of note, low RIPK3 expression enables sublethal necroptosis with leaky membrane in hepatocytes, which promotes NF-κB-driven inflammation and hepatocarcinogenesis through prolonged cytokine and chemokine release [120]. This study also suggested that the pharmacological reprogramming of the necroptotic state from sublethal to lethal is an anticancer strategy in the liver. Given that the downregulation of core necroptosis mediators, including RIPK3, MLKL, and CYLD deubiquitinase, has been reported in a variety of cancers [118], persistent sublethal necroptosis signaling may contribute to cancer progression in general (Fig. 3). In line with this, PFK-15, a 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) inhibitor, can induce necroptosis-associated cytotoxicity and genotoxicity in colorectal cancer cells by upregulating RIPK1, RIPK3, and MLKL [121]. In addition, necroptotic cells can efficiently activate $CD8^+$ T cells by cross-priming, resulting in antitumor immunity [122]. Intriguingly, a recent study argued that the innate immune sensing of DNA damage by cGAS, in concert with the DNA double-strand break sensor Meiotic recombination 11 homolog (MRE11), promotes post-mitotic arrest in the context of *Trp53* deficiency [123]. Furthermore, MRE11-driven activation of cGAS–STING signaling prevents the oncogenic transformation of preneoplasia by inducing ZBP1-dependent necroptosis. Therefore, age-associated necroptosis can be induced under stress that causes DNA damage and cellular senescence, and thus warrants further exploration of its clinical implications and impact on anti-cancer treatments.

It is unclear whether the necroptotic machinery leading to membrane disruption, such as MLKL, can directly contribute to the secretion of SASP factors in senescent cells. However, the discovery that HSP90 inhibitors significantly block necroptosis is interesting, for their potential as senomorphic drugs (Fig. 3) [124,125]. Indeed, HSP90 inhibition can modulate SASP establishment and SASP factor secretion [72]. For example, the inhibition of HSP90 by STA-9090 (ganetespib) during chemotherapeutic treatment attenuated the SASP-like oncogenic secretome of malignant pleural mesothelioma (MPM), resulting in chemosensitizing effects [126]. This HSP90 inhibition can enhance apoptotic signaling in MPM cells; however, the impact on the necroptotic pathway has not been examined. SASP production is also reduced by compounds that modulate NF-κB signaling, such as metformin [127,128]. Metformin is a widely used drug for type 2 diabetes and is known to activate AMP-activated protein kinase (AMPK) [129]. Notably, a recent study found that AMPK-mediated phosphorylation of RIPK1 suppresses metabolic stress-induced cell death, including necroptosis and apoptosis [130]. In addition, metformin acts as a cardioprotective agent that inhibits aging-induced ischemic necroptosis through the restoration of autophagy flux [131]. Therefore, the possibility that the senomorphic activity of metformin is attributable to the regulation of RIPK1-dependent cell death cannot be excluded (Fig. 3).

4. Pyroptosis and senescence

Pyroptosis is an inflammatory mode of regulated cell death caused by gasdermin pore formation in the plasma membrane. It is primarily observed in barrier epithelia [132,133] and professional phagocytic cells (i.e., macrophages, monocytes, dendritic cells) upon infection [40,41]. In this process, caspase-1 activation in the inflammasome complexes is a crucial event, which is initiated through the recognition of pathogen-associated molecular patterns (PAMPs) and DAMPs by a series of pattern recognition receptors (PRRs): NLRP1, CARD8, NAIP/NLRC4, NLRP3, AIM2, Pyrin, and NLRP6. The caspase recruitment domain (CARD)-containing proteins NLRP1, CARD8, and NAIP/NLRC4 can recruit caspase-1 through CARD-CARD interactions. The pyrin domain (PYD)-containing proteins, such as NLRP3, AIM2, Pyrin, and NLRP6, utilize the PYD and CARD domains of the adaptor protein ASC to assemble caspase-1-activating inflammasomes. In addition, intracellular LPS presentation directly activates caspase-4/5 in humans and caspase-11 in mice, as non-canonical inflammasomes. These inflammatory caspases cleave GSDMD to remove the autoinhibitory C-terminal domain, leading to pore formation by the N-terminal domain protomers and enabling the release of small DAMPs such as caspase-1-generated mature IL-1β and IL-18. Moreover, caspase-8 can also cleave GSDMD to drive pyroptosis. This pathway is reportedly initiated through TAK1 inhibition by the Yersinia virulence effector protein YopJ [134]. Such GSDMD-mediated pore formation, cytokine release, and subsequent pyroptotic cell death are dampened by the endosomal sorting complex required for transport (ESCRT)-dependent membrane repair system [135]. During pyroptosis, ninjurin-1 (NINJ1), a cell surface protein with

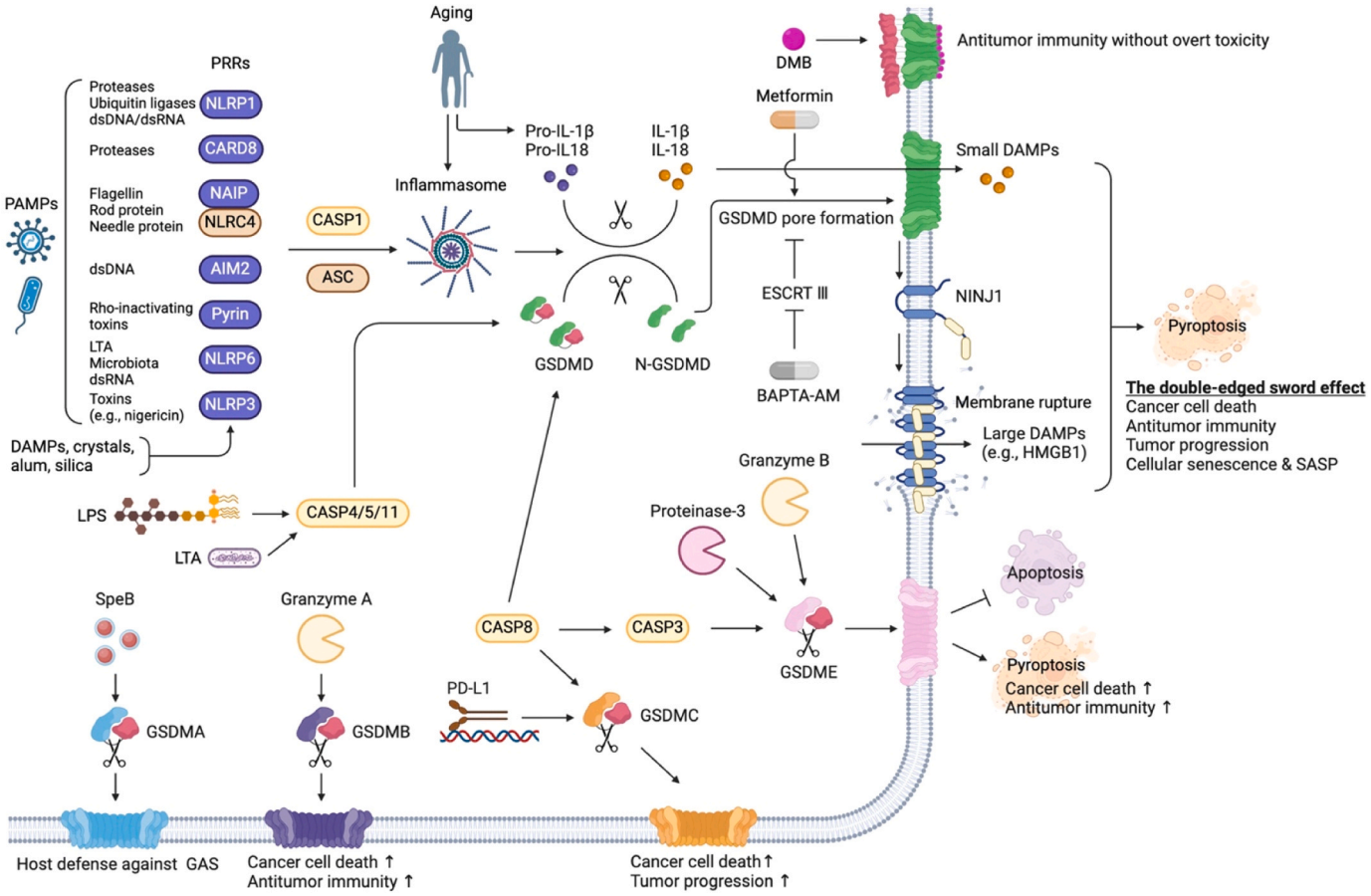

Fig. 4. Pyroptotic pathway and crosstalk with aging-related changes. Sensing various PAMPs or DAMPs by PRRs induces the recruitment of an adaptor protein (ASC or NLRC4) and the assembly of inflammasomes to activate CASP1. CARD8 is an exception, as it can bind and activate CASP1 without adaptor proteins. Intracellular LPS can form a non-canonical inflammasome to activate human CASP4/5 and mouse CASP11. These inflammatory caspases cleave GSDMD to separate the inhibitory C- and active N-terminal domains. N-GSDMD oligomerizes and forms pores in the plasma membrane, releasing mature IL-1β and IL-18. This membrane disruption promotes NINJ1-driven membrane rupture with the release of large DAMPs. N-terminal cleaved fragments of GSDMA, GSDMB, GSDMC, and GSDME can also mediate pyroptotic cell death. The expression of specific inflammasome components and genes related to inflammasome activity increases with aging, and may be involved in cellular senescence. A Ca^{2+} chelator, BAPTA-AM, and metformin can induce GSDMD-mediated cancer cell pyroptosis. SpeB, Streptococcal pyrogenic exotoxin B; GAS, group A *Streptococcus*; DMB, 6,7-dichloro-2-methylsulfonyl-3-N-tert-butylaminoquinoxaline.

two transmembrane domains, polymerizes into branched filaments, resulting in plasma membrane rupture downstream of GSDMD [136, 137]. This membrane rupture allows the release of large DAMPs, such as HMGB1. In certain situations, the TLR and TNFR1 signaling pathways participate in the activation of the noncanonical NLRP3 inflammasome via RIPK1, RIPK3, caspase-8, and their scaffolding proteins [138–140]. For example, in human monocytes, the alternative axis-mediated NLRP3 inflammasome can induce the release of active IL-1β without pyroptotic cell death [141], indicating that the intricate interplay between regulated cell death pathways can elicit different pathological outcomes. In mammals, the other gasdermin family members, including GSDMA, GSDMB, GSDMC, and GSDME, also mediate pyroptotic cell death in response to a variety of pathogens or downstream of apoptotic and necroptotic signaling [142] (Fig. 4).

Pyroptosis is a highly immunogenic cell death process that limits the spread of infection and boosts the immune system against cancer, suggesting potential therapeutic utility. Macrophages derived from *Nlrp1b*-transgenic mice undergo pyroptotic cell death without IL-1β or IL-1α release (denoted as $Pyro^{-1}$) upon stimulation with anthrax lethal toxin (LeTox). Interestingly, a recent study on the pyroptotic secretome demonstrated that the *de novo* synthesis and secretion of oxylipins such as PGE_2 are upregulated in the $Pyro^{-1}$ form of cell death, which promotes wound healing *in vivo* [143]. This may provide a potential strategy for therapeutic intervention in aging-associated inflammation and cancer. In tumors, GSDME, activated by caspase-3 or cytotoxic lymphocyte-derived granzyme B, can reprogram noninflammatory apoptosis to pyroptosis, promoting antitumor immunity and cancer cell death, and is therefore considered a tumor suppressor [144,145]. Indeed, GSDME expression is epigenetically silenced in many types of cancer [144,146–148], and numerous cancer-associated GSDME mutations impair its pore-forming ability [145], resulting in resistance to irradiation and chemotherapy treatment [149,150]. GSDMB cleaved by granzyme A from killer lymphocytes can also induce cancer cell pyroptosis and promote the efficacy of immunotherapy using the antibody against programmed cell death 1 (PD-1) [151]. The administration of the GSDMD protein and an ESCRT inhibitor via a bacteria-based delivery system synergistically drove tumor pyroptosis, improving immune checkpoint blockade therapies against multiple tumor models [152]. In addition, 6,7-dichloro-2-methylsulfonyl-3-N-tert-butylaminoquinoxaline (DMB) reportedly functions as a selective GSDMD agonist that induces cleavage-independent GSDMD pore formation and pyroptosis in cancer cells, which can stimulate antitumor immunity without overt toxicity [153]. However, pyroptosis is a double-edged sword, as it can also exert pro-tumorigenic activities (Fig. 4). For instance, GSDMC expression is up-regulated by PD-L1 translocated into the nucleus under hypoxic conditions, which switches apoptosis to GSDMC/caspase-8-mediated pyroptosis in cancer cells, causing tumor necrosis [154]. This may generate a chronic inflammatory environment

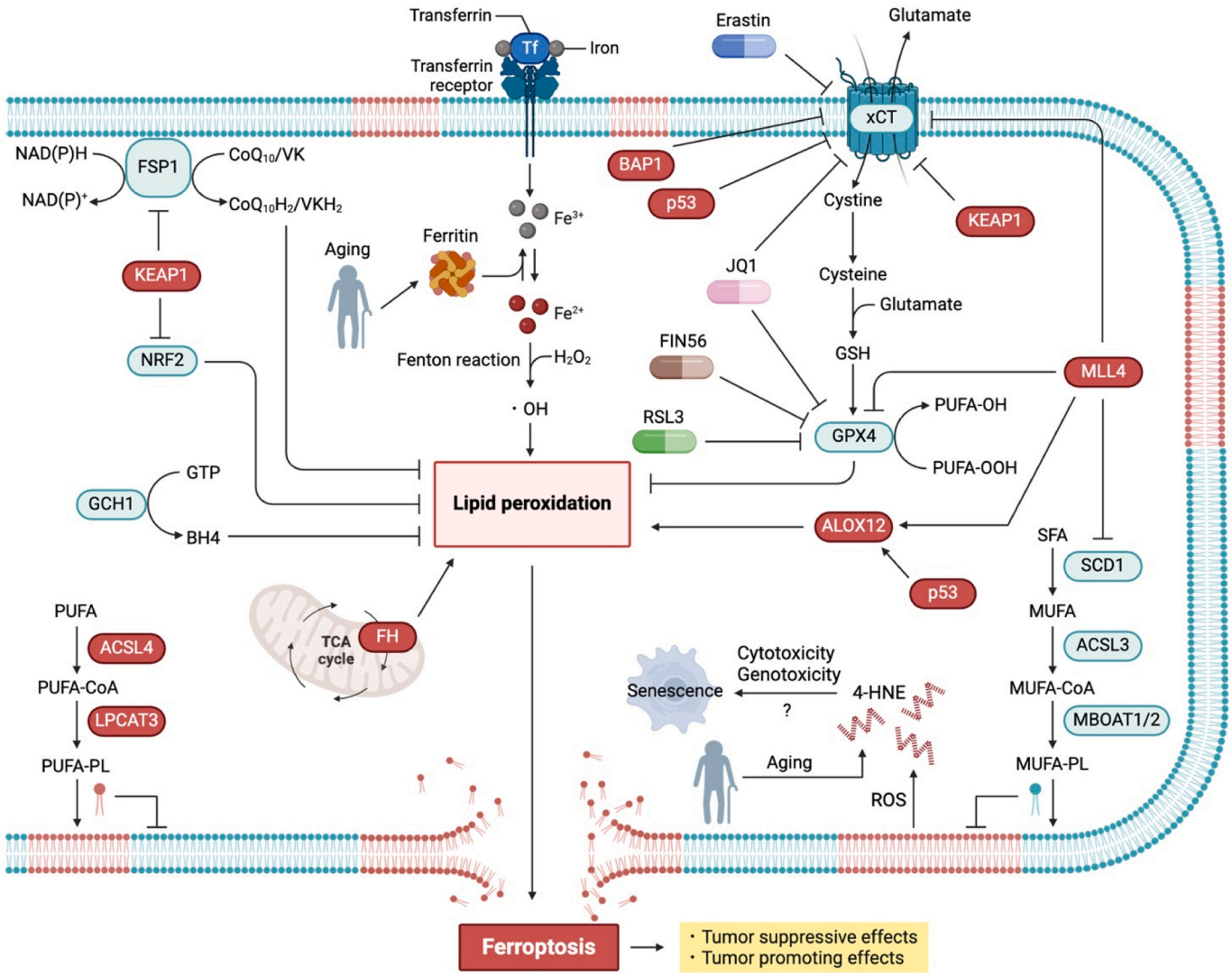

Fig. 5. Ferroptotic pathway and crosstalk with aging-related changes. Transcending the lethal levels of phospholipid hydroperoxides in membranes results in ferroptotic cell death with membrane rupture. Ferroptosis sensitivity depends on (1) the availability of Fe^{2+} for the Fenton reaction to promote membrane phospholipid oxidation, (2) the availability of oxidizable membrane phospholipids, which is increased by the ASCL4-LPCAT3 axis, and decreased by the SCD1-ACSL3-MBOAT1/2 axis, and (3) the cellular antioxidant systems controlled by xCT, GPX4, FSP1, NRF2, GCH1, etc. In tumors, p53, KEAP1, BAP1, FH, and MLL4 can induce ferroptosis. Age-related accumulation of iron and 4-HNE may be associated with increased senescent cells. Several compounds, such as FIN56 and JQ1, may be utilized as senolytic drugs by promoting ferroptotic cell death.

to enhance tumor progression [155]. High expression of GSDMC indeed correlates with poor survival in human breast cancer [154].

Although the mechanisms of the age-related increase in pyroptotic cell death and its involvement in cancer development have not been clearly described yet, the enhanced expression of inflammasome components, such as NLRC4 and NLRC5, as well as genes related to inflammasome activity including IL-1β, IL-1RN, TLR5/6/8, and interferon α/β receptor α chain (IFNAR1), was observed in the Stanford–Ellison longitudinal cohort depending on individual aging [156]. Of note, the expression levels of inflammasome-related genes correlated with health and longevity. Mechanistically, in the elderly group with high inflammasome-related gene expression, nucleotide metabolites such as adenine and N^4-acetylcytidine, which can be produced downstream of oxidative stress, prime and activate the NLRC4 inflammasome, leading to the constitutive expression of IL-1β [156].

A recent report demonstrated that caspase-4 and GSDMD contribute to cellular senescence induced by cytoplasmic LPS. Notably, the caspase-4 noncanonical inflammasome is formed in reaction to oncogenic RAS-mediated OIS, which establishes SASP [157]. Of note, lipoteichoic acid (LTA), a component of gut microbiota cell wall, is accumulated in the liver of mice fed with a high-fat diet, which induces caspase-11 activation followed by GSDMD-mediated release of IL-33 from senescent hepatic stellate cells, promoting obesity-associated hepatocellular carcinoma [158]. In aging neutrophils, proteinase-3- and caspase-3-mediated cleavage of GSDME dictates pro-inflammatory responses by promoting pyroptosis instead of efferocytosis of apoptotic neutrophils [159]. Notably, protein levels of inflammasome components, including NLRP3, ASC, and caspase-1, are increased in cells undergoing OIS, which contributes to SASP expression via IL-1 signaling, further mediating paracrine senescence through TGF-β signaling [160]. The authors mentioned that it is worth investigating whether such propagation of cellular senescence in the surrounding tissue mediates the harmful effects on tumor progression. As described above, the pyroptotic machinery accumulates and activates in senescent cells to promote SASP under certain conditions. However, senolytic approaches targeting the pyroptotic pathway have not yet been established. Interestingly, metformin can induce GSDMD-mediated pyroptosis of esophageal cancer cells by an undefined mechanism, via the downregulation

of transcriptional coregulator proline-, glutamate- and leucine-rich protein 1 (PELP1) [161]. Thus, it is expected that pyroptosis-driven senolytics could be a new modality to eliminate senescent cells induced in environments prone to activating the pyroptotic pathway, such as barrier epithelia.

5. Ferroptosis and senescence

Ferroptosis is regulated cell death with membrane rupture mediated by iron-dependent lipid peroxidation. Hydroxyl radicals generated by Fe^{2+} and H_2O_2, known as the Fenton reaction, attack polyunsaturated fatty acids (PUFAs) to form lipid radicals, initiating the peroxidation of phospholipids in the ER, mitochondria, and plasma membrane. Although the exact mechanism by which excessive lipid peroxides compromise membrane integrity remains unclear, ferroptosis sensitivity is determined by the systems that regulate iron metabolism, phospholipid synthesis, and cellular redox capacity that protect against lipid peroxidation. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are enzymes required for the biosynthesis of PUFA-containing lipids, which can be substrates for peroxidation. In contrast, stearoyl-CoA desaturase (SCD1), ACSL3, and membrane-bound *O*-acyltransferase domain-containing (MBOAT)1/2 generate monounsaturated fatty acid (MUFA)-containing lipids that compete with PUFA-containing lipids for membrane composition, thereby reducing cellular sensitivity to ferroptosis [162]. The heterodimeric amino acid antiporter xCT imports extracellular cystine in exchange for exporting glutamate, which contributes to the synthesis of GSH. In addition to its well-established roles in apoptosis and senescence, p53 can also mediate ferroptosis by repressing *SLC7A11*, a key component of xCT, under conditions of ROS stress [163]. Notably, the selenoprotein glutathione peroxidase 4 (GPX4) protein directly protects lipids from peroxidation by using GSH to reduce lipid hydroperoxides to non-toxic lipid alcohols. Furthermore, ferroptosis suppressor protein 1 (FSP1) and GTP cyclohydrolase 1 (GCH1) can block lipid peroxidation and subsequent ferroptosis by generating radical-trapping antioxidants. FSP1 reduces coenzyme Q10 (CoQ10) and vitamin K (VK) to $CoQ10H_2$ and vitamin K hydroquinone (VKH_2), respectively. GCH1 also produces the lipophilic antioxidant tetrahydrobiopterin (BH4). Thus, unlike other forms of regulated cell death, ferroptosis is caused by the breakdown of the cellular antioxidant system, which is regulated at multiple levels (Fig. 5).

Ferroptosis has been implicated in neurodegenerative disease promotion [164,165] and multiple organ injury associated with oxidative stress or iron overload [166]. Neuroferritinopathy is a dominantly inherited movement disorder characterized by brain iron accumulation, and its causative variants of L-ferritin, an iron storage protein, increase the labile iron pool and induce iron-dependent cell death [164]. A recent study in a cohort of intensive care unit (ICU) patients showed that the severity of multiorgan dysfunction and the mortality were positively correlated with plasma levels of catalytic iron and malondialdehyde, a marker of lipid peroxidation [167]. These reports provide a rationale for inhibiting ferroptosis as a treatment strategy for aging-associated disorders.

In contrast, accumulating evidence supports the role of ferroptosis in the fight against cancer. Several tumor suppressors, such as p53, Kelch-like ECH-associated protein 1 (KEAP1), BRCA1-associated protein 1 (BAP1), fumarate hydratase (FH), and myeloid/lymphoid or mixed-lineage leukemia 4 (MLL4), can induce ferroptosis in tumors [168] (Fig. 5). For example, p53 sensitizes cancer cells to ferroptosis by repressing xCT expression [163]. KEAP1 deficiency in lung cancer and glioma confers ferroptosis resistance through NRF2-mediated upregulation of FSP1 and xCT [169,170]. The epigenetic regulator MLL4 is frequently mutated in cutaneous squamous cell carcinoma, and the knockout mice develop precancerous skin lesions [171]. Importantly, *Mll4* deficiency in the mice skin resulted in transcriptional changes that suppress ferroptosis, such as the upregulation of anti-ferroptotic proteins (xCT, GPX4, and SCD1) and the downregulation of pro-ferroptotic lipoxygenases ALOXs (ALOX12, ALOX12B, and ALOXE3). In addition, ferroptosis induced in circulating melanoma cells can prevent metastatic spread [172,173]. Thus, the viability of certain cancers relies on anti-ferroptotic molecules, suggesting promising targets for cancer therapy. Indeed, ferroptosis was initially discovered by the death of cancer cells harboring oncogenic RAS mutations, which was induced by small molecules such as the xCT inhibitor erastin and the GPX4 inhibitor RSL3 [174,175]. A recent proteolysis-targeting chimera (PROTAC) strategy using the HSP90 chaperone complex, including E3 ligases, successfully induced the ubiquitin-proteasomal degradation of GPX4 and subsequent ferroptosis in HT-1080 cells and xenograft mice [176]. Despite the presence of ferroptosis-mediated tumor suppressive effects, neutrophil-induced ferroptosis by the transfer of myeloperoxidase-containing granules into tumor cells may exacerbate glioblastoma with an increased pro-inflammatory signature [177]. In addition to immunogenic DAMPs, immunosuppressive lipid mediators, such as PGE_2 and 15-hydroperoxyeicosaetetranoic acid (15-HpETE-PE), are released from cancer and tumor-associated immune cells undergoing ferroptosis [168,178,179]. In the tumor microenvironment, polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), a population of pathologically activated neutrophils, spontaneously die by fatty acid transporter 2 (FATP2)-driven ferroptosis and attenuate the antitumor immune response via the release of oxidized lipids [180]. Importantly, genetic and pharmacological inhibition of ferroptosis dampened the immunosuppressive activity of PMN-MDSCs and potentiated the efficacy of immune checkpoint therapy in multiple tumor models in mice. Given the dual immunologic role of ferroptosis in the tumor microenvironment, the selective induction of ferroptosis in immunosuppressive cells may be a promising anti-cancer treatment, warranting further exploration of its clinical implications.

Age-related iron accumulation in various tissues has been observed in multiple animal species, from nematodes (*C. elegans*) to humans. Consistently, aging tissues accumulate the iron storage protein ferritin [181,182]. Furthermore, reactive aldehydes such as 4-hydroxynonenal (4-HNE), generated by lipid peroxidation of PUFA, increase with age, probably due to the age-associated increase in oxidative stress and the limited detoxification capacity of antioxidant systems, including the NRF2 pathway [183]. 4-HNE can form cytotoxicity- and genotoxicity-related adducts with proteins, lipids, and DNA (Fig. 5). The age-dependent increase of physiologically ferroptotic cells in various organs was estimated by the iron deposition levels and an HNEJ-1 monoclonal antibody that detects 4-HNE-modified proteins [184].

Large amounts of intracellular iron accumulation, accompanied by changes in the levels of iron homeostasis proteins, were observed in senescent cells regardless of the methods used to induce cellular senescence [185–187]. Consistently, aging mice accumulated senescent cells in the liver with increased ferritin expression and iron deposition [185]. However, the age-related accumulation of senescent cells in the body may occur independently from the iron accumulation in aged tissues [188–193]. In an *in vitro* model, cellular senescence preceded iron accumulation and was not blocked by sustained iron chelation [185]. Notably, senescent cells were highly resistant to ferroptosis. Mechanistically, impaired ferritinophagy, a lysosomal process that mediates ferritin degradation, in senescent cells leads to enrichment of ferritin, thereby reducing the labile iron pool. However, promoting ferritinophagy by using the autophagy activator rapamycin failed to resensitize senescent cells to ferroptosis, even though decreases in transferrin receptor 1 (TfR1), ferritin, and intracellular iron were detected [185]. Recent reports indicated the utility of FIN56 [194], a specific inducer of ferroptosis by mediating GPX4 degradation and CoQ10 depletion, for the senolytic approach to eliminate multiple types of primary and paracrine senescent cells [187] and induce cancer cell ferroptosis [195–198] (Fig. 5). Furthermore, the BET family inhibitor JQ1 downregulated several ferroptosis resistance genes, such as *GPX4*, *SLC7A11* (xCT), and *NRF2*, in senescent cells but not proliferating cells. JQ1

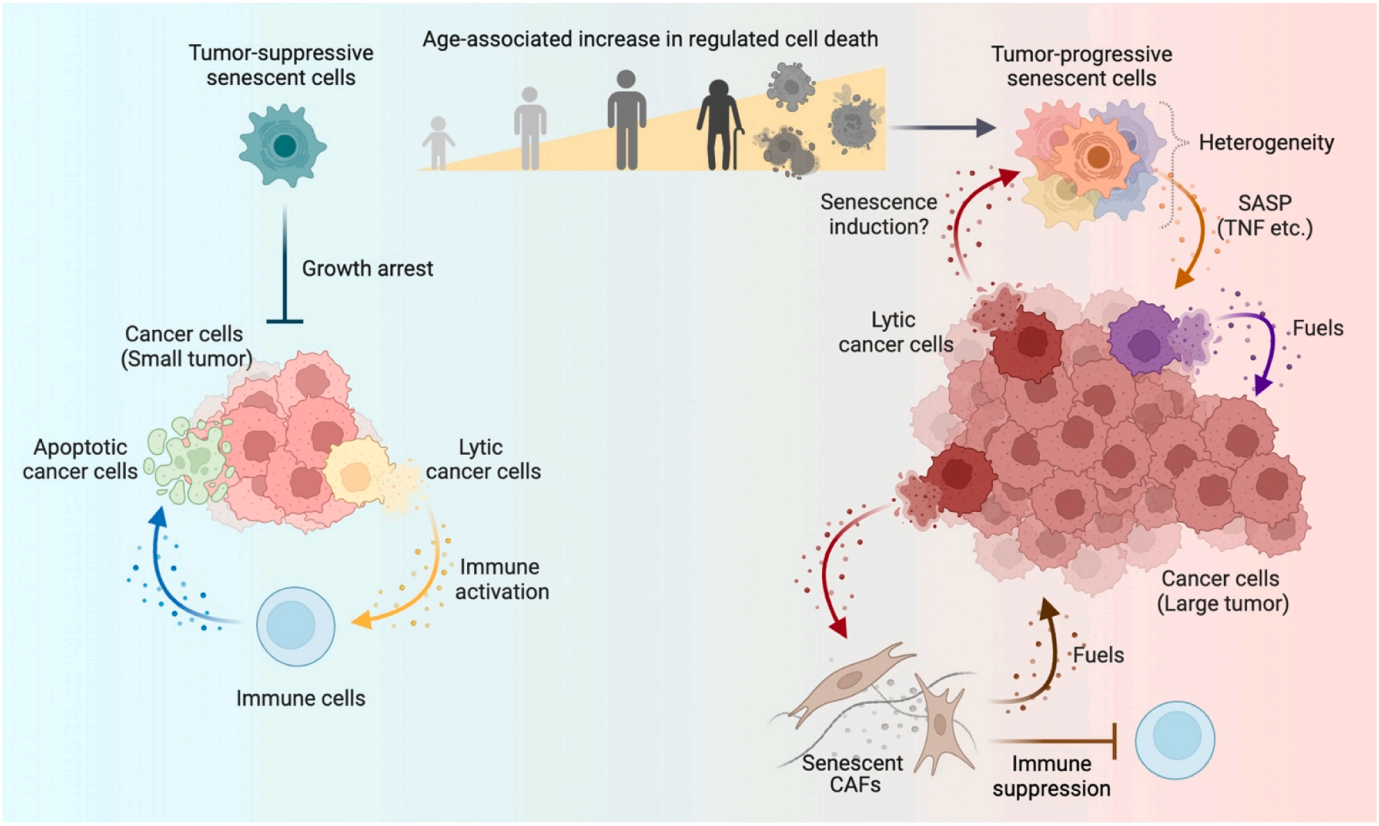

Fig. 6. Interplay between cell death and senescence in cancer. Increased cell death with aging may promote tumorigenesis via senescent cells. Furthermore, the numbers of both senescent cells and cancer cells undergoing lytic cell death may mutually increase and synergistically fuel tumor progression.

showed senolytic and anti-cancer activities by inducing ferroptosis [199, 200]; however, it should be noted that JQ1 also has properties that induce cellular senescence [201,202].

6. Conclusion and perspective

Accumulating evidence indicates that the signals of regulated cell death described in this review increase in aging, which may induce cellular senescence (Fig. 6). The majority of inflammatory cell death is essential for limiting tumor progression, such as through facilitating antitumor immunity. Conversely, intense or chronic inflammatory signals from such cell death may cause cellular senescence in surrounding tissues, eventually promoting tumor growth (Fig. 6). These consequences of cell death are the reason why cellular senescence acts as a double-edged sword in cancer. At present, there is little information on the mutual impacts of the immune landscape and regulated cell death during aging; however, the immunologically hot tumor microenvironment is likely to induce cancer cell death readily [39,203,204]. Another aspect to consider is whether immunogenic cell death can reactivate exhausted or senescent immune cells, especially T cells.

One of the hallmarks of senescent cells is their resistance to apoptosis. Therefore, the first challenge to targeting senescent cell death for cancer therapy is their undefined susceptibility to the lytic type of programmed cell death. The susceptibility of senescent cells to cell death is likely affected by the aging-associated changes in the expression and activity of each programmed cell death inducer, executioner, or inhibitor. As a therapeutically relevant example, the pharmacological induction of RIPK3 and MLKL expression can set a lower threshold for triggering necroptosis in cancer cells [39,205–207]. In this strategy, improving the specificity of the drug delivery system to the tumor or senescent cells would be required to minimize the adverse effects of unwanted cell death. The second challenge is the complexity and crosstalk of regulated cell death pathways, which make it difficult to target a specific pathway. Indeed, radiation therapy and chemotherapeutics causing DNA damage can induce necroptosis, pyroptosis, and ferroptosis, as well as intrinsic apoptosis [208]. In addition, like cancer cells, senescent cells are heterogeneous. Although certain senolytic reagents target specific populations of senescent cells [48,68], a more effective senolytic approach may be found by identifying the senescent cell susceptibilities specific to the tissue of origin, type of cancer, and surrounding environment. Thus, it will be essential to clarify how each cell death program is regulated in senescent cells with aging and how these programs differ among tissues or cancer types. This will lead to new interventions to inhibit cellular senescence and eliminate senescent cells based on the cell death pathways. In addition to miMOMP activation of the apoptotic pathway without death, this review also discussed the possibility that non-lethal activation of the necroptosis and pyroptosis machinery may promote SASP factor secretion in senescent cells. Clarification of this point will expand the targets for senomorphic approaches.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The author (H.I.) is a Guest Editor for *Seminars in Cancer Biology* and was not involved in the editorial review or the decision to publish this article.

Acknowledgements

This work was partly supported by funding from ACT-X, JST (JPMJAX2117 to K.S.) and MEXT/JSPS KAKENHI (JP20K16146 and JP22K07174 to K.S., and JP24K02242 and JP22K18385 to F.T.). The

figures in this manuscript were created using BioRender.

Data Availability

No data was used for the research described in the article.

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