CHAPTER TWO

# Targeting the stress support network regulated by autophagy and senescence for cancer treatment

**Jaejin Kim[†], Yeonghyeon Lee[†], Kyeonghwan Roh, Mi-Sung Kim, and Chanhee Kang***

School of Biological Sciences, Seoul National University, Seoul, South Korea
*Corresponding author: e-mail address: chanhee.kang@snu.ac.kr

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[†] These authors contributed equally.

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## Abstract

Autophagy and cellular senescence are two potent tumor suppressive mechanisms activated by various cellular stresses, including the expression of activated oncogenes. However, emerging evidence has also indicated their pro-tumorigenic activities, strengthening the case for the complexity of tumorigenesis. More specifically, tumorigenesis is a systemic process emanating from the combined accumulation of changes in the tumor support pathways, many of which cannot cause cancer on their own but might still provide excellent therapeutic targets for cancer treatment. In this review, we discuss the dual roles of autophagy and senescence during tumorigenesis, with a specific focus on the stress support networks in cancer cells modulated by these processes. A deeper understanding of such context-dependent roles may help to enhance the effectiveness of cancer therapies targeting autophagy and senescence, while limiting their potential side effects. This will steer and accelerate the pace of research and drug development for cancer treatment.

## 1. Introduction

Tumorigenesis is considered a multistep process that requires normal cells to progressively acquire several genetic changes, circumventing multiple barriers to tumor formation and progression (Hanahan & Weinberg, 2000, 2011). Cancer cells that have evaded such barriers display a specific set of hallmarks, which can be categorized into three types according to their characteristics: (1) growth-related hallmarks (sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality); (2) survival-related hallmarks (resisting cell death, avoiding immune destruction); and (3) support-related hallmarks (inducing angiogenesis, activating invasion and metastasis, genome instability and mutation, deregulating cellular energetics, and tumor-promoting inflammation). Numerous biological processes have been identified to modulate these hallmarks, yet only a few can affect all types of cancer hallmarks. Macroautophagy (hereafter "autophagy") and cellular senescence (hereafter "senescence") are two rare representative processes that can exert such pleiotropic effects in a context-dependent manner during tumorigenesis (Coppe, Desprez, Krtolica, & Campisi, 2010; Doria, Gatto, & Punzi, 2013; Lee & Schmitt, 2019; Levine & Kroemer, 2019; White, 2015).

Autophagy is a major lysosomal degradation pathway that is essential for cellular and organismal homeostasis (Doria et al., 2013; Levine & Kroemer, 2019; Mizushima & Komatsu, 2011). Autophagy can randomly degrade a portion of the cytoplasm (general autophagy) as well as

selectively target several cellular macromolecules such as damaged organelles, protein aggregates, and invading pathogens (selective autophagy) (Anding & Baehrecke, 2017; Johansen & Lamark, 2020; Kirkin, 2020). Recent studies also suggest that selective autophagy can degrade an individual protein to modulate specific biological processes, including stress responses (Belaid, Ndiaye, Klionsky, Hofman, & Mograbi, 2013; Kang & Elledge, 2016; Kang et al., 2015; Sanchez-Martin & Komatsu, 2020). Autophagy is intricately modulated by multiple regulators, including autophagy-related genes (ATG), and their mutations have been linked to an increased risk of developing several types of cancer. For example, mice carrying inactivated alleles of BECN1 (Beclin-1, a mammalian homolog of Atg6) display increased susceptibility to cancer (Levine & Klionsky, 2004), suggesting a role for autophagy in tumor suppression under basal conditions. However, under stressful conditions such as poor vascularization and chemotherapy, autophagy is induced in cancer cells and protects cells from apoptosis. These observations have informed the concept that autophagy may play dual roles in tumorigenesis, depending on the timing of autophagy activation and the type of autophagy/its target substrates (White, 2015).

Senescence is a cellular defense mechanism that prevents premalignant cells from further proliferation by ensuing stable cell cycle arrest, acting as a key barrier to tumorigenesis (Coppe et al., 2010; Gorgoulis et al., 2019; He & Sharpless, 2017; Herranz & Gil, 2018; Kuilman, Michaloglou, Mooi, & Peeper, 2010; Munoz-Espin & Serrano, 2014). Consistently, senescent cells are frequently observed to accumulate in premalignant lesions, yet are rarely found in the fully developed cancer region. However, this view only represents the surface of the complex relationship between senescence and tumorigenesis, as in the case of autophagy. Senescent cells are metabolically active and extensively secrete many pro-inflammatory cytokines, chemokines, growth factors, and proteases that can affect neighboring cells and the tissue microenvironment. This feature is collectively termed the senescence-associated secretory phenotype (SASP) (Coppe et al., 2008). The SASP is a built-in checkpoint for the removal of senescent cells by the immune system to coordinate senescence-associated biological processes in a systemic manner (e.g., tissue repair (Demaria et al., 2014; Krizhanovsky et al., 2008)). However, when this process is not correctly executed, the SASP can promote nearly every aspect of tumorigenesis: cytokines and chemokines for immunosuppressive chronic inflammation, growth factors for tumor growth, and proteases for cancer metastasis

(Coppe et al., 2010; Gonzalez-Meljem, Apps, Fraser, & Martinez-Barbera, 2018). Thus, senescence may toggle the balance of anti- and pro-tumorigenic mechanisms in a context-dependent manner. Targeting senescence for cancer treatment therefore needs to be carefully tailored.

In addition to the pleiotropic effects of autophagy and senescence in tumorigenesis, autophagy and senescence have been shown to be intertwined, which should also be considered when designing therapeutic strategies to target autophagy and senescence for cancer treatment (Gewirtz, 2013; Kang & Elledge, 2016). In this review, we discuss the context-dependent roles of autophagy and senescence in tumorigenesis, including their established functions in cell growth, cell survival, and stress homeostasis. Furthermore, we catalog cellular and molecular markers that can be exploited to guide a customized therapeutic strategy to enhance the effectiveness of therapies targeting autophagy and senescence for treating cancer.

## 2. Overview of autophagy and senescence

Autophagy and senescence are sophisticatedly regulated biological processes, and understanding how they are regulated took decades to unravel. Now, we have a near complete picture of the core regulatory pathways for autophagy and senescence, including transcriptional regulation, epigenetic modulation, post-translational modification, and regulated protein stability. In addition, their effector programs have been rapidly expanding, such as cellular and tissue homeostasis, development, stem cell maintenance, cell growth control, metabolism, immune modulation, tissue regeneration, development, and aging (Chan & Narita, 2019; DesMarais & Costa, 2019; Gorgoulis et al., 2019; He & Sharpless, 2017; Herranz & Gil, 2018; Higuchi-Sanabria, Frankino, Paul, Tronnes, & Dillin, 2018; Leidal, Levine, & Debnath, 2018; Levine & Kroemer, 2019).

### 2.1 General autophagy and selective autophagy

Autophagy is a complex yet tightly orchestrated process, which is initiated by the engulfment of a portion of the cytoplasm with a double membrane vesicle called the autophagosome. The autophagosome subsequently fuses with a lysosome to degrade and recycle its engulfed contents. The core autophagy machinery was originally characterized from yeast genetic screens, identifying over 30 autophagy-related genes (ATGs) that mainly control autophagosome formation. This regulatory mechanism has been vastly expanded, as different types of autophagy that act under specific

conditions have been added to the autophagy regulatory network (Levine & Klionsky, 2004; Levine & Kroemer, 2019).

Starvation is the best-studied inducer of autophagy, mainly acting through several nutrient and energy sensing pathways, such as the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) pathways. In addition, many cellular stresses implicated in cancer have also been shown to stimulate autophagy, which has multifaceted roles in tumorigenesis. For example, oxidative stress, the DNA damage response (DDR), the unfolded protein response (UPR), hypoxia, and inflammation can potently activate autophagy through various signaling transducers (Kroemer, Marino, & Levine, 2010). In most cases, such autophagy protects cells from damage-induced pathological responses, including transformation and cell death. However, as we discuss below, these protective roles of autophagy can also be operational in cancer cells, maintaining homeostasis and paradoxically promoting tumorigenesis.

Autophagy can be largely divided into two types according to its cargo selectivity: general and selective autophagy (Johansen & Lamark, 2020; Kirkin, 2020). General (or bulk) autophagy degrades a portion of the cytoplasm in a random manner upon induction. The best-known role for general autophagy is to provide building blocks and energy for supporting metabolic homeostasis, and thus cell survival, in response to nutrient starvation. Basal levels of general autophagy are also essential for protein homeostasis (proteostasis), especially in either slowly proliferating cells (e.g., stem cells) or fully differentiated/non-dividing cells (e.g., neurons and senescent cells). Suppressing basal autophagy is deleterious to these cells, either disrupting their functions or sensitizing them to cell death (Levine & Kroemer, 2019; Murrow & Debnath, 2013). Diverse components of the cell can also be selectively targeted for degradation by autophagy on demand. Numerous studies have reported that selective autophagy degrades various cellular organelles, including mitochondria, endoplasmic reticulum (ER), peroxisomes, ribosomes, and lipid droplets, as well as protein aggregates, invading pathogens, and individual proteins (Johansen & Lamark, 2020; Kirkin, 2020). The cargo selection for selective autophagy is mainly mediated by its direct or indirect binding to the ATG8 family of proteins (MAP1LC3s or GABARAPSs) that are conjugated to the autophagosomal membrane. The LC3-interacting region or LIR motif plays a key role in these types of recognition, as the cargo itself contains the motif (direct recognition) or several autophagy receptors, such as p62, NBR1, NDP52, and OPTN. These receptors carry the LIR motif

to bridge between the cargo and the ATG8 family of proteins (indirect recognition). Most cargoes recognized through autophagy receptors need to be labeled with ubiquitin (Ji & Kwon, 2017; Kirkin, 2020; Pohl & Dikic, 2019), and how such modification is modulated for selective autophagy is an active area of research.

Selective autophagy has enormously expanded the physiological role of autophagy beyond metabolic homeostasis during nutrient stress. Mitophagy, for example, selectively degrades damaged mitochondria, preventing the accumulation of reactive oxygen species (ROS) and thus maintaining redox homeostasis (Youle & Narendra, 2011). Upon proteotoxic stress, such as the massive synthesis of proteins frequently observed in cancer cells, ER-phagy targets a portion of the endoplasmic reticulum (ER) network to maintain proteostasis (Chino & Mizushima, 2020). Other homeostatic functions of selective autophagy include the DDR, inflammatory signaling, hypoxia, and immune modulation, many of which are implicated in tumorigenesis (Levine & Kroemer, 2019).

## 2.2 Cellular senescence and its intrinsic and extrinsic features

Senescence is characterized by several intrinsic and extrinsic features that can crosstalk with each other, even across individual cells. It is generally assumed that its intrinsic features contribute to the development of the senescent state and support its extrinsic features, which in turn exert systemic effects on neighboring cells, the tissue microenvironment, and even the immune system of the host (Gorgoulis et al., 2019; He & Sharpless, 2017; Herranz & Gil, 2018; Kuilman et al., 2010).

The best-characterized intrinsic feature of senescence is stable growth arrest, in which two tumor suppressive pathways, the p53-p21 and p16-Rb pathways, play a major role. Upon senescence induction, p53 is stabilized to induce the CDK inhibitor p21, which immediately halts the cell cycle of damaged cells. Subsequently, if the damage is irreparable, this cell cycle arrest is potentiated by increased expression of p16, another CDK inhibitor involved in senescence. This in turn induces the retinoblastoma (Rb)-mediated senescence-associated heterochromatic foci that stably repress E2F target genes, contributing to stable growth arrest in senescent cells (Kuilman et al., 2010). Remodeling of the nuclear lamina structure in senescent cells contributes to the relaxation of preexisting heterochromatin regions and thus increases transcriptional noise during senescence. The ER-Golgi network is massively reorganized in senescent cells, which might be necessary for the SASP, a prominent extrinsic feature of senescent cells, as discussed below (Hernandez-Segura et al., 2017). Although it is not

well characterized, another noticeable feature of senescence is senescent hypertrophy, which increases the volume of the cell with a flattened morphology. Currently, the functional consequence of senescent hypertrophy remains elusive, but it might be related to the expansion of the ER-Golgi network to support the massive secretory phenotype in senescent cells (Hernandez-Segura, Nehme, & Demaria, 2018).

The notable extrinsic feature of senescence is the SASP, which involves robust secretion of pro-inflammatory cytokines, chemokines, proteases, and growth factors, as well as other non-proteinous molecules including exosomes (Basisty et al., 2020; Coppe et al., 2010). The composition of the SASP can be highly varied depending on the cell type undergoing senescence, tissue of origin, and the inducer of senescence. In addition, many SASP factors are not exclusive to senescence but can have well-characterized roles in other biological contexts. For example, the inflammatory arm of the SASP, such as IL-1A and IL-6, is well known to be activated during acute inflammation. The key difference between the SASP and acute inflammation is the kinetics of each response. The SASP is a delayed response that takes several days to be fully developed upon senescence induction. The SASP is also very stable through the positive feed-forward activation loop, and thus can be maintained until senescent cells are physically removed by the immune system, including macrophages, natural killer cells (NK), and T lymphocytes (Bataller & Brenner, 2005; Brighton et al., 2017; Egashira et al., 2017; Kang et al., 2011; Lujambio et al., 2013; Mevorach et al., 2010; Munoz et al., 2019; Pereira et al., 2019). As the SASP consists of a wide-range of factors, it is not surprising to find that the SASP has pleiotropic effects on the tissue microenvironment. The SASP can affect senescence reinforcement in both autocrine and paracrine manners (Acosta et al., 2008, 2013; Coppe et al., 2008), proliferation, migration, and stemness of neighboring cells (Mosteiro et al., 2016; Ritschka et al., 2017), angiogenesis (Ruscetti et al., 2020), and immune modulation, such as macrophage differentiation and recruitment of innate and adaptive immune cells (He & Sharpless, 2017; Herranz & Gil, 2018). All of these features are closely associated with tumorigenesis. Currently, functional characterization of each SASP factor has gained attention, as this may provide a therapeutic option to preserve the beneficial role of senescence while decreasing its deleterious effect; this will be discussed below in the case of tumorigenesis. Although recent studies indicated a role for senescence-associated exosomes as a part of senescent secretome (Basisty et al., 2020; Takasugi et al., 2017), other non-proteinous, intracellular signaling molecules (e.g., metabolites) are yet to be discovered.

During the last decade, great advances have been made in understanding how the SASP is regulated at the transcriptional and post-transcriptional levels. Several transcriptional factors and epigenetic regulators, including nuclear factor-κB (NF-κB) (Chien et al., 2011), CCAAT/enhancer-binding protein-β (C/EBP-β) (Acosta et al., 2008), GATA4 (Kang et al., 2015; Mazzucco et al., 2017), NOTCH1 (Hoare et al., 2016), HMGB2 (Aird et al., 2016), and BRD4 (Tasdemir et al., 2016), have been identified to modulate the SASP at the transcriptional level. In addition, cytoplasmic chromatin fragments (CCFs) that pinch off from intact nuclei of senescent cells and LINE-1 elements reactivated during senescence stimulate the cGAS-STING pathway to activate the interferon 1 (IFN-1) response and thus maintain the SASP (De Cecco et al., 2019; Dou et al., 2015, 2017). At the post-transcriptional level, the mTOR pathway plays a central role in modulating the SASP. The TOR-autophagy spatial coupling compartment (TASCC), where the autolysosome and mTOR accumulate, facilitates the massive synthesis of secretory proteins by supplying amino acids to stimulate mTOR activity (Young, Narita, & Narita, 2011). The mTOR pathway preferentially stimulates translation of specific SASP factors and modulates the mRNA stability of SASP factors (Herranz et al., 2015; Laberge et al., 2015). Interestingly, it has been shown that senescent cells maintain a higher level of autophagy activity under this enhanced mTOR activity, which generally acts as a potent suppressor of autophagy (Dunlop & Tee, 2014). How such an uncoupling between autophagy and the mTOR pathway occurs currently remains unknown; considering the current therapeutic interest in modulating the activities of autophagy and the mTOR pathway for aging treatment, this will be an important topic in future research. This set of discoveries provides a molecular basis for developing therapeutic strategies to modulate the SASP, recently termed senostatics or senomorphics (Gorgoulis et al., 2019; Kang, 2019; Kirkland & Tchkonia, 2017; van Deursen, 2019), which will increase the repertoire of senescence-based therapies in a wide range of age-related diseases, including cancer.

# 3. Autophagy in tumors

## 3.1 Autophagy and tumor suppression

### *3.1.1 Metabolic stress and autophagy*

It has been well established that cancer cells significantly rewire cellular metabolism to match the demand of their high growth rate, which includes

increased levels of glycolysis, glutaminolysis, amino acid and lipid metabolism, and macromolecule biosynthesis (Ward & Thompson, 2012). Interestingly, several genetic mutations in metabolic enzymes are reported to be associated with tumorigenesis including succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase 1/2 (IDH1/2) (Morin, Letouze, Gimenez-Roqueplo, & Favier, 2014). Although a single mutation in metabolic enzymes does not recapitulate all metabolic changes in cancer cells, these findings strongly suggest that metabolic stress can promote tumorigenesis in certain cases. For example, nutrient deprivation increases ROS production and causes an imbalance in the thiol redox state, resulting in oxidative stress that can promote tumorigenesis (Filomeni, De Zio, & Cecconi, 2015). Thus, autophagy may protect cells from tumorigenesis by alleviating metabolic stress. However, this might be coupled with other homeostatic functions of autophagy, such as mitochondrial homeostasis (mitophagy) or lipid droplet mobilization (lipophagy).

### 3.1.2 Oxidative stress and autophagy

Oxidative stress can damage cellular macromolecules such as DNA, RNA, proteins, and lipids, which create pro-tumorigenic environments by introducing oncogenic mutations and activating pro-survival pathways, such as the NF-κB pathway. Oxidative stress induces autophagy through multiple mechanisms, including mTOR, protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), c-Jun N-terminal kinase (JNK), and p53. Upon activation, autophagy can relieve oxidative stress at multiple levels (Filomeni et al., 2015). As mitochondria are the main source of cellular oxidative stress, autophagy suppresses oxidative stress by removing damaged mitochondria through mitophagy (Galluzzi et al., 2017). Consistently, mice deficient in the key regulators of autophagy, such as Beclin-1, ATG5, and ATG7, harbor abnormal mitochondria associated with increased oxidative damage (Takamura et al., 2011). In addition, autophagy can remove protein aggregates caused by oxidative stress, maintaining proteostasis during oxidative stress (Filomeni et al., 2015). Lastly, autophagy can promote the DDR to repair DNA lesions caused by oxidative stress, maintaining genome integrity and suppressing oncogenic mutations (Gomes, Menck, & Leandro, 2017).

Autophagy is also involved in modulating cellular antioxidant programs to protect cells from oxidative stress. Upon oxidative stress, the autophagy receptor p62 (also known as SQSTM1) binds to kelch-like ECH associated protein 1 (KEAP1), an E3 ligase adaptor for NF-E2-related factor 2 (NRF2), and either sequesters KEAP1 from NRF2 or targets KEAP1 for autophagic degradation (Komatsu et al., 2010). NRF2 then translocates to the nucleus

and triggers the expression of antioxidant genes and detoxifying enzymes, enhancing redox homeostasis and cell survival. Collectively, it is plausible to assume that autophagy deficiency causes the oxidative stress that drives tumorigenesis. Indeed, autophagy deficiency is reported to promote hepatocellular adenoma/carcinoma with elevated levels of oxidative stress and damaged mitochondria in a manner dependent on the p62-KEAP1-NRF2 axis (Inami et al., 2011). Deletion of either p62 or NRF2 largely reverses the tumorigenic phenotypes observed in autophagy- deficient mice, suggesting that a dysregulated antioxidant program of the NRF2 pathway plays a major role (Ni et al., 2014; Takamura et al., 2011). Indeed, NRF2 also positively regulates genes involved in cancer metabolism, including the pentose phosphate pathway, purine-nucleotide synthesis, and glutaminolysis, redirecting glucose and glutamine into anabolic pathways (Mitsuishi et al., 2012).

### 3.1.3 The DDR and autophagy

Genome instability is one of the key hallmarks of cancers. Genetic mutations in genes related to DNA damage repair evoke so-called mutator phenotypes, which are predisposed to multiple types of cancer. It has been well established that multiple genotoxic stresses activate autophagy mostly, but not exclusively, in a DDR-dependent manner (Eliopoulos, Havaki, & Gorgoulis, 2016). The DNA damage response is also a potent inducer of senescence, suggesting a role for autophagy as an effector program of senescence (Hernandez-Segura et al., 2018). A major sensor kinase of double-strand breaks, ataxia-telangiectasia mutated (ATM), activates AMP-activated protein kinase (AMPK), which in turn suppresses mTOR by activating tuberous sclerosis complex 2 (TSC2) and relieves its inhibitory action on autophagy. In addition, ATM directly activates Unc-51 like autophagy activating kinase 1 (ULK1), which modulates early steps of autophagosome formation. ATM-checkpoint kinase 2 (CHK2) or ataxia telangiectasia and Rad3-related protein (ATR)-checkpoint kinase 1 (CHK1) pathways, a key DDR pathway, activates p53, which transcriptionally induces genes involved in autophagy, including ATG2, ATG4, ATG7, ATG10, and ULK1 (Kenzelmann Broz et al., 2013). Additionally, p53 upregulates Sestrin 1/2, which modulates the AMPK-mTOR-autophagy axis (Budanov & Karin, 2008). Sestrin 1/2 also inhibits mTOR via GAP activity toward Rags (GATOR) 1-GATOR 2 in an amino acid leucine-dependent manner, activating autophagy (Wolfson et al., 2016).

Upon activation, autophagy promotes DNA damage repair by enhancing a wide range of DNA repair pathways, including homologous

recombination (HR) and nucleotide exchange repair (NER) (Gillespie & Ryan, 2016; Hewitt et al., 2016; Qiang et al., 2016; Wang et al., 2016). Autophagy degrades p62, which binds to and inhibits an E3 ligase for histone H2A, RNF168. RNF168 then ubiquitinates H2A, which is necessary for recruiting DNA repair proteins such as breast cancer type 1 (BRCA1) and RAD51 to promote HR. Furthermore, autophagy targets Kruppel-associated box domain-containing zinc finger protein 1 (KAP1) for degradation (Tsuruma et al., 2008). KAP1 is a suppressor of signal transducer and activator of transcription 3 (STAT3), which upregulates BRCA1 during the DDR. Thus, autophagy activates the STAT3-BRCA1 axis to promote HR. Autophagy also positively regulates NER by enhancing DNA damage recognition through the Xeroderma pigmentosum complementation group C (XPC) and DNA damage binding protein 2 (DDB2) (Qiang et al., 2016). Autophagy deficiency stabilizes the transcription factor TWIST1, which activates the transcriptional repressor complex E2F4-RBL2. E2F4-RBL2 then suppresses XPC. TWIST1 also inhibits the histone acetyltransferase EP300, which impairs the recruitment of DDB2 to UV-induced DNA lesions (Qiang et al., 2014, 2016). In support of DNA repair functions of autophagy, autophagy-deficient cells display a high level of DNA damage under basal condition, likely because they tip the balance of DNA repair into an error-prone nonhomologous end joining (NHEJ) pathway (Gillespie & Ryan, 2016; Liu et al., 2015). Collectively, autophagy can suppress tumorigenesis by maintaining genome integrity.

### 3.1.4 The UPR and autophagy

Cancer cells generally have a high level of protein and lipid synthesis to match their proliferation rate, which leads to ER stress (Hsu et al., 2019). The UPR is triggered to relieve ER stress and sustain cell viability. The UPR consists of three branches of ER stress sensors: inositol requiring enzyme 1 (IRE1), protein kinase RNA-activated-like ER kinase (PERK), and activating transcription factor 6 (ATF6). These sensors suppress protein translation, increase chaperone proteins, and activate endoplasmic reticulum-associated protein degradation (ERAD) and autophagy in a coordinated manner.

Increasing evidence suggests that ER stress and UPR activation contribute to tumorigenesis in several types of cancer, including prostate, breast, and colon cancer (Dejeans, Barroso, Fernandez-Zapico, Samali, & Chevet, 2015). The UPR supports neoplastic transformation by increasing protein folding capacity and activating pro-survival pathways. The UPR allows

tumor cells to overcome hypoxia and nutrient deprivation during tumor establishment by promoting angiogenesis and rewiring metabolic pathways. In addition, the UPR promotes metastasis by increasing epithelial-to-mesenchymal transition (EMT) and decreasing cell-cell contact. Lastly, the UPR protects cancer cells from chemotherapies by activating pro-survival pathways, increasing drug efflux, and maintaining cancer stem cells (Hsu et al., 2019).

The UPR is a potent stimulus of autophagy, and all three branches of ER stress sensors are involved in this process. PERK transcriptionally activates genes involved in autophagy, including LC3 and ATG5, via ATF4 and CHOP, respectively. PERK can also stimulate autophagy through the sestrin-mTOR pathway (Rashid, Yadav, Kim, & Chae, 2015). ATF6 can upregulate transcription of ATG3, ATG12, ATG5, and other autophagy genes. IRE1 activates the JNK pathway through the TRAF2-ASK1 axis, stimulating autophagy (Heath-Engel, Chang, & Shore, 2008; Wei, Pattingre, Sinha, Bassik, & Levine, 2008). Upon activation, autophagy relieves ER stress by degrading protein aggregates and frequently a portion of ER clusters that include unfolded proteins through ER-phagy (Loi, Fregno, Guerra, & Molinari, 2018). ER-phagy is mediated by a set of specialized autophagy receptors including FAM134B, RTN3L, ATL3, SEC62, CCPG1, and TEX264, each of which modulates a different part of the ER (Kirkin, 2020). Since autophagy can quickly relieve ER stress, it is plausible to assume that autophagy may prevent the pro-tumorigenic activities of the UPR. However, caution is needed to predict the role of autophagy during UPR-induced tumorigenesis, since autophagy can promote its pro-tumorigenic activities in a context-dependent manner. For example, autophagy induced by the UPR in a fully established cancer can support its metabolic demand and promote resistance to chemotherapy (see below).

### 3.1.5 Cell death and autophagy

Cell death plays an essential role in suppressing tumorigenesis by deleting pre-malignant cells. Apoptosis is the best characterized form of cell death, which depends on a caspase-dependent system to execute cell death. Accordingly, pre-malignant and malignant cells need to overcome apoptosis to become a fully developed cancer. Indeed, many apoptosis-related pathways are found to be mutated or dysregulated in most, if not all, types of human cancer, including the p53 pathway and anti-apoptotic BCL2 family of proteins (Pfeffer & Singh, 2018). When apoptosis is disabled,

compensatory backup mechanisms ensure that pre-malignant or damaged cells are removed by non-apoptotic cell death, including autophagic cell death. The role of autophagy in cell death has been debated, yet it can be largely defined as follows based on recently published guidelines (Denton & Kumar, 2019): (1) autophagy-associated cell death, (2) autophagy-mediated cell death, and (3) autophagy-dependent cell death (ACD). In autophagy-associated cell death, autophagy is induced during cell death but plays a negligible role, as its inhibition does not affect the progress of cell death. Autophagy can trigger or support apoptosis in autophagy-mediated cell death, yet autophagy induces cell death independently of apoptosis or necrosis in ACD. Both types of autophagic cell death can act as a tumor-suppressive mechanism, but only ACD can cover apoptosis to remove premalignant cells when apoptosis is disabled.

Expression of oncogenic H-Ras$^{V12}$ in ovarian epithelial cells induces caspase-independent cell death with features of autophagy, and autophagy inhibition rescues this ACD to promote the transforming potential of oncogenic forms of Ras (Elgendy, Sheridan, Brumatti, & Martin, 2011). In A549 lung cancer cells, treatment with resveratrol, a natural polyphenol that activates autophagy, induces cell death via autophagy induction in the absence of several apoptotic markers such as caspase activation (Dasari et al., 2017). Autophagy inhibition by knockdown of key autophagy components rescued cell death induced by resveratrol, indicating that ACD is executed upon resveratrol treatment. Treatment with *Z*-VAD-FMK, a pan-caspase inhibitor, induced cell death in human leukemia cells (Yu et al., 2004). Knockdown of ATG7 and Beclin 1 reversed this autophagic cell death. This set of data suggests that ACD can function as both a natural barrier to tumorigenesis and a treatment option for fully established cancer. How ACD induces cell death remains elusive except for autosis, which depends on the plasma membrane $Na^+/K^+$-ATPase but has not been associated with cancer (Liu et al., 2013). It is possible that excessive consumption of cytoplasmic components, including cellular organelles during ACD, leads to cell death. Alternatively, autophagy may selectively target specific survival factors for degradation to induce ACD (Denton & Kumar, 2019).

### 3.1.6 Immune regulation and autophagy

Autophagy suppresses tumorigenesis in a cell non-autonomous manner by modulating the immune surveillance of cancer cells. Autophagy has been shown to promote MHC class I-dependent cross-presentation of tumor antigens and activation of $CD8^+$ T cells (Crotzer & Blum, 2009).

Autophagy is induced in tumor cells undergoing tumorigenesis-related cellular stresses, which engulfs tumor antigens and is subsequently released into the extracellular environment. Dendritic cells (DCs) internalize secreted autophagosomes and present tumor peptides with MHC class I molecules to activate $CD8^+$ T cells. In addition, autophagy processes cytosolic and nuclear tumor antigens and subsequently delivers them to the lysosome for association with MHC class II molecules (Li et al., 2008; Munz, 2016). Further processing of cytosolic and nuclear tumor antigens may occur prior to binding to MHC class II molecules by lysosomal proteases. Displayed tumor antigens stimulate $CD4^+$ T cells and increase tumor immune surveillance. In addition, autophagy has been shown to increase the release of ATP from cancer cells during chemotherapy, which recruits DCs and T cells that exert a tumor-suppressive mechanism (Michaud et al., 2011).

## 3.2 Autophagy and tumor promotion

Genetic inhibition of autophagy in several tumor models generally causes less aggressive types of cancer, indicating that autophagy may be necessary for tumors to progress to malignancy. Indeed, increasing evidence suggests that autophagy turns on its heel once a tumor is established, maintaining the homeostatic state of cancer cells and promoting tumor progression.

### *3.2.1 Autophagy relieves metabolic stress in cancer cells*

In most established tumors, autophagy is frequently hyperactivated to support cancer metabolism, which is essential for cancer cells that have a higher rate of proliferation and cell growth. This could be achieved by autophagic recycling of cellular components through general autophagy, ribophagy (autophagic degradation of the ribosomes), glycophagy (autophagic degradation of glycogen), or lipophagy (autophagic degradation of lipid droplets) to supply mitochondria with their substrates (e.g., amino acids and lipids), generating cellular energy under nutrient-poor conditions (Goldsmith, Levine, & Debnath, 2014). Consistent with this, inhibition of autophagy in most cancer cells is associated with a buildup of both structurally and functionally defective mitochondria. Mitochondrial defects could be due to either impaired metabolic substrate recycling or decreased mitophagy, or both (Galluzzi et al., 2015). Supplementation of pyruvate or glutamine rescues the survival of autophagy-deficient cells in several types of cancer, including pancreatic cancer, supporting this notion. Another cancer metabolism supported by autophagy is enhancing glycolysis. Cancer cells frequently shift their metabolism from oxidative phosphorylation to aerobic

glycolysis for producing ATP from glucose, directing glycolytic intermediates toward biosynthetic pathways in a process known as the Warburg effect (Ward & Thompson, 2012). Inhibition of autophagy in HRas-transformed mouse embryonic fibroblasts (MEFs) or mouse breast cancer cells decreases glucose uptake and reduces de novo production of lactate, suggesting a role for autophagy in glycolytic flux (Lock et al., 2011). Thus, autophagy deficiency greatly sensitizes these transformed or cancer cells to reduced levels of glucose. Consistent with the metabolic support role of autophagy in cancer, activation of oncogenes, including expression of oncogenic Ras, upregulates basal levels of autophagy (Guo et al., 2011).

### 3.2.2 Autophagy maintains redox homeostasis in cancer cells

At the early stage of tumorigenesis when blood supply is limited, a large portion of the cancer region is deprived of nutrients and oxygen under hypoxic conditions. Under these conditions, the mitochondrial respiratory chain produces nitric oxide (NO), which further generates other ROS including reactive nitrogen species (RNS), reactive aldehyde-malondialdehyde (MDA), and 4-hydroxynonenal (4-HNE) (Cipak Gasparovic et al., 2019). Thus, cancer cells need to maintain redox homeostasis for their survival. In addition, genome instability frequently observed in cancer cells causes protein imbalance in the mitochondrial respiratory chain, contributing to mitochondrial dysfunction and oxidative stress (Ward & Thompson, 2012). Autophagy plays a crucial role in maintaining redox homeostasis under this condition, similar to its action in normal cells. Consistent with this, autophagy is observed to be hyperactivated in the hypoxic region of tumors, and its inhibition sensitizes tumor cells to cell death (Degenhardt et al., 2006). As discussed above, autophagy removes dysfunctional mitochondria, which are a main source of ROS via mitophagy, enhancing redox homeostasis (Weinberg et al., 2010). p62-mediated selective autophagy also plays a critical role in redox homeostasis in cancer, by degrading KEAP1 and subsequently activating the NRF2 anti-oxidant program. In activated KRas– and BRaf–driven lung cancers, autophagy contributes to ROS detoxification via the p62-KEAP1-NRF2 axis (DeNicola et al., 2011). Consistently, mutational signatures in multiple tumors indicate an activation signature for NRF2, which is opposite to an inactivation signature for KEAP1 (Hayes & McMahon, 2009).

### 3.2.3 Autophagy promotes therapeutic resistance to DNA-damaging chemotherapies

As most cancer cells are subject to severe genome instability, they need to disable certain DNA damage pathways for their survival. Genotoxic drugs

used for chemotherapies target such vulnerability of cancer cells, increasing the burden of DNA damage to surpass their threshold to induce cell death (Swift & Golsteyn, 2014). Given its cytoprotective role during the DDR, it has been extensively studied that autophagy inhibition augments cytotoxicity in combination with several anticancer agents. Thus, readers interested in the role of autophagy during chemotherapies can refer to excellent recent reviews on this topic (Mulcahy Levy & Thorburn, 2020; Perez-Hernandez et al., 2019).

#### 3.2.4 Autophagy maintains proteostasis in cancer cells for their survival

Tumor cells proliferate in an accelerated manner, requiring a high flux of protein and lipid synthesis to match their growth rate. This, in turn, causes a high level of proteotoxic stress. In addition, genome instability, such as aneuploidy, provides another important source of proteotoxic stress, as it can generate unbalanced protein complexes that can lead to protein aggregates. Autophagy can relieve such proteotoxic stress via aggrephagy (selective degradation of protein aggregates) or ER-phagy, aiding the survival of tumor cells. In aggrephagy, polyubiquitinated proteins coalesce to form aggresomal particles that are transported toward the microtubule organizing center (MTOC) in a histone deacetylase 6 (HDAC6)-dependent manner, where aggresomes are targeted for autophagic degradation (Losson, Schnekenburger, Dicato, & Diederich, 2020). Inhibition of HDAC6 using the specific inhibitor ACY-1215 might provide a therapeutic option for combinatorial treatments with inhibition of proteasome or other protein quality systems to induce cell death in cancer, as exemplified in multiple myeloma. The role of ER-phagy in tumorigenesis has not been revealed. However, the fact that FAM134B and SEC62, two autophagy receptors for ER-phagy, have been linked to several types of cancer indicates that ER homeostasis via autophagy plays a role in tumorigenesis (Wilkinson, 2020).

#### 3.2.5 Autophagy modulates a cancer cell survival pathway

Autophagy can promote cancer cell survival under various stressful conditions as a stress-activated mechanism, as discussed above. In addition, autophagy can prevent cancer cell death by directly modulating factors related to apoptosis or necrosis. For example, autophagy promotes degradation of the active tyrosine kinase Src using an E3 ligase c-Cbl as an autophagy receptor, enhancing tumor cell survival in squamous carcinoma (Sandilands et al., 2011). Colon cancer cells deficient for the pro-apoptotic protein BAX are known to be resistant to TNF-related apoptosis-inducing ligand

(TRAIL)-induced cell death when autophagy is disabled (Sharma & Almasan, 2018). Mechanistically, TRAIL increases autophagy, which counterbalances TRAIL-mediated apoptosis in cancer cells by sequestrating caspase-8 into the autophagosome for subsequent lysosomal degradation. Autophagy can regulate tumor cell survival in a cell non-autonomous manner. Autophagy in normal endothelial cells in the tumor region mediates the secretion of high mobility group box 1 (HMGB1), which in turn interacts with the receptor for advanced glycosylation end products (RAGE) on pancreatic cancer cells to induce autophagy and promote survival and resistance to apoptosis (Kang et al., 2010).

### 3.2.6 Autophagy promotes immune evasion of cancer cells

Cancer cells need to overcome detection by the immune system for their survival. One such mechanism by which they avoid detection is the autophagy-dependent downregulation of tumor-specific antigen presentation. In pancreatic ductal adenocarcinoma (PDAC), MHC class I molecules that are required for antigen presentation are subject to NBR1-dependent selective autophagy, promoting immune evasion (Yamamoto et al., 2020). Inhibition of autophagy enhanced the surface display of MHC class I molecules, rescuing the susceptibility of PDAC to cytotoxic T lymphocytes (CTLs)-mediated cell death. Autophagy is also involved in modulating cytolytic granule-mediated tumor cell death (Thiery et al., 2011). Hypoxia activates autophagy in MCF-7 breast cancer cells, which in turn suppresses Natural killer (NK) cell-mediated cancer cell lysis. Mechanistically, autophagy targets granzyme B and perforin granules for lysosomal degradation in a p62-dependent manner (Baginska et al., 2013), thus promoting immune evasion of cancer cells. Autophagy can disrupt the immune synapse between NK cells and hypoxic melanoma cells by selectively degrading gap-junctional connexin 43, which in turn impairs NK-mediated tumor cell death (Tittarelli, Janji, Van Moer, Noman, & Chouaib, 2015). Autophagy indirectly contributes to tumor immune evasion by modulating proteasome-dependent degradation of STAT3, an important factor in the expression of several immunosuppressive genes (Noman et al., 2009). In lung carcinoma, hypoxia activates autophagy, degrading the autophagy substrate protein, p62. When autophagy is inhibited, p62 accumulates to promote STAT3 degradation in a proteasome-dependent manner, thus increasing the susceptibility of tumor cells to CTLs (Noman et al., 2011). Lastly, autophagy targets inflammasomes, reducing the secretion of cytokines/chemokines and thus preventing immune cell recruitment. Inhibition of autophagy causes a high

level of IL-6 secretion, which is necessary for massive macrophage infiltration to suppress tumorigenesis (Degenhardt et al., 2006). Collectively, these findings support a role for autophagy in the immune evasion of cancer by modulating CTL and NK cells-mediated tumor cell death.

### 3.3 Cataloging properties of the stress support network associated with autophagy addiction for cancer treatment

Several studies have demonstrated that autophagy plays a dual role in tumorigenesis (Fig. 1). Thus, understanding the context-dependent roles of autophagy in tumorigenesis is essential for developing therapeutic strategies to target autophagy for cancer treatment. The timing of autophagy activation, what causes such autophagy activation, and its cellular targets should be considered for autophagy-based cancer therapies.

Cancer cells metabolically addicted to autophagy should be judged by the following criteria: (1) autophagy is activated at the early stage of tumorigenesis when blood supply is not reestablished around an emerging tumor region; (2) nutrient deprivation is accompanied by autophagy activation, in which case the rate of glucose transport might be a good surrogate marker, or the status of energy sensing pathways such as AMPK could be assessed upon autophagy inhibition; and (3) general autophagy, ribophagy, and lipophagy could occur in this situation. Although autophagy inhibition is favored for

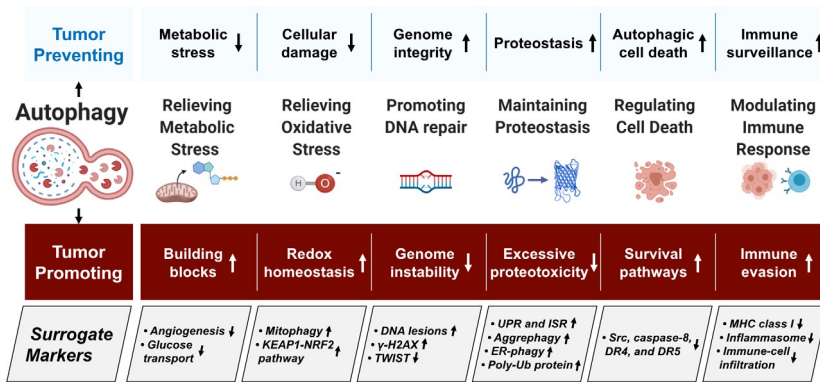


**Fig. 1** Dual roles of autophagy in tumorigenesis. Autophagy prevents tumorigenesis by (1) relieving metabolic stress, (2) reducing cellular damage, (3) maintaining genome integrity, (4) promoting proteostasis, (5) serving as a backup cell death mechanism, and (6) enhancing immune surveillance. Autophagy promotes tumorigenesis by (1) providing cellular energy and building blocks, (2) maintaining redox homeostasis, (3) suppressing excessive DNA damage, (4) reducing proteotoxicity, (5) inhibiting cell death pathways, and (6) increasing immune evasion (created with BioRender.com).

cancer treatment when the above criteria are fulfilled, caution should be taken as excessive starvation caused by autophagy inhibition can promote metastasis.

Cancer cells addicted to autophagy for redox homeostasis should be judged by the following criteria: (1) signature of mitophagy such as autophagosome with engulfed mitochondria, or activation of the PINK-PARKIN pathway, which is known to modulate mitophagy (Narendra, Tanaka, Suen, & Youle, 2008), is enriched; and (2) the level of KEAP1 is reduced, and the activation signature of the NRF2 pathway is observed together with autophagy activation. Inhibition of general autophagy can increase ROS in normal cells, and thus targeting autophagy should be carefully conducted to target cancer cells addicted to autophagy for redox homeostasis. This could be achieved if the extent of autophagy inhibition is carefully controlled, or if tumor-specific selective autophagy of KEAP1 can be targeted.

Cancer cells addicted to autophagy for the DDR should be judged by the following criteria: (1) tumor mutational burden should be relatively high; (2) activation of molecules associated with the DDR, such as gamma-H2AX, is readily detected; and (3) selective autophagy targets that negatively modulate DNA damage repair, including TWIST, should be expressed at lower levels. In this case, autophagy inhibition combined with chemotherapies that cause additional DNA damage could be considered to enhance the effectiveness of treatment.

Cancer cells addicted to autophagy for proteostasis should be judged by the following criteria: (1) the UPR pathway and integrated stress response (ISR) are activated; (2) aggrephagy and ER-phagy are frequently observed, as assessed by aggresome formation and decreased levels of ER-phagy receptors, including FAM134B and SEC62, respectively; and (3) polyubiquitinated proteins are greatly accumulated. In this case, autophagy inhibition combined with proteasome inhibition could be explored for a better response.

Cancer cells addicted to autophagy for cell survival pathways should be judged by checking selective autophagy targets for modulating cell survival pathways, such as Src, caspase-8, DR4, and DR5, to determine whether they are downregulated at the protein level. If the apoptosis pathway is disabled, caution must be taken, as ACD can act as a back-up cell death pathway in such cancer cells. In this case, stimulating autophagy could be considered to enhance the effectiveness of treatment.

Cancer cells addicted to autophagy for immune surveillance should be judged by the following criteria: (1) expression of MHC class I molecules

is downregulated; (2) inflammasome formation is greatly reduced, with a lower level of immune-stimulating inflammatory response; and (3) immune cell infiltration is lower. Since autophagy can also promote immune surveillance of cancer, caution should be taken when autophagy inhibition suppresses immune cell activation, including $CD4^+$ and $CD8^+$ T cells.

## 4. Senescence in tumors

### 4.1 Tumor-suppressive roles of senescence

Senescence was originally identified as a tumor suppressor mechanism that can restrict the expansion of damaged or premalignant cells by installing stable growth arrest, which is triggered after a finite number of replications. This type of senescence, called "replicative senescence," is mainly regulated by the DDR due to critically shortened telomeres (Harley, Futcher, & Greider, 1990). Later, other types of senescence related to tumorigenesis, including oncogene-induced senescence (OIS) and therapy-induced senescence (TIS), are also shown to be mainly regulated by the DDR (Wang, Kohli, & Demaria, 2020).

#### *4.1.1 Oncogene-induced senescence*

Tumors are primarily driven by driver mutations that confer growth advantage on the cells carrying them and have been positively selected during tumorigenesis. Oncogene activation and tumor suppressor inactivation are two representatives of such driver mutations (Braig et al., 2005; Chen et al., 2005). However, additional mutations besides driver mutations are generally necessary for malignant transformation, because aberrant activation of oncogenic signaling triggers oncogene-induced senescence (OIS). For example, overexpression of oncogenic Ras in primary human fibroblasts induces hyperactivation of proliferation followed by senescence, which depends on ROS generation and the DDR. Consistently, treatment with the antioxidant *N*-acetyl-cysteine (NAC) or inhibition of the DDR suppresses OIS (Di Micco et al., 2006; Serrano, Lin, McCurrach, Beach, & Lowe, 1997). Although OIS shares several characteristics with other types of senescence, including replicative senescence, OIS can also have unique features depending on how OIS is activated. For example, oncogenic Ras expression induces OIS with full activation of the SASP, yet a tumor suppressor PTEN deletion drives OIS without the SASP (Perez-Mancera, Young, & Narita, 2014). Since the SASP is closely associated with several aspects of tumorigenesis, such differences should be considered for senescence-based cancer treatments.

### 4.1.2 Therapy-induced senescence

Most, if not all, chemotherapeutic agents exert their tumor suppressive effects by inducing cancer cell death or senescence. Chemotherapeutics activate senescence mostly by inhibiting DNA repair pathways or by causing DNA lesions. Doxorubicin, etoposide, and camptothecin are inhibitors of topoisomerase, which induce DNA breaks and cause torsional stress during replication. These drugs are effective in several types of cancers, including lung cancers, lymphoma, and breast cancers (Thorn et al., 2011). Bleomycin, another widely used chemotherapeutic agent, directly oxidizes DNA and causes DNA double- and single-strand breaks. It is effective in several cancers, including Hodgkin's lymphoma, non-Hodgkin's lymphoma, and testicular cancers (Chen, Ghorai, Kenney, & Stubbe, 2008; Scheule, Perkins, Hamilton, & Holian, 1992). Radiotherapy induces DNA lesions by transferring a high amount of energy through electrically charged ions, causing senescence. These types of treatments lack specificity and thus can be generally used, regardless of cancer type (Baskar, Lee, Yeo, & Yeoh, 2012). However, whether the p53 pathway is intact in cancer cells is crucial for effective treatment, as such DNA damage agents act through the p53 pathway to induce senescence or apoptosis in most cases. For example, in glioblastoma carrying loss-of-function p53 proteins, radiotherapy is marginally effective in inducing senescence (Quick & Gewirtz, 2006).

Targeted therapy for activating senescence in cancer has recently been developed, which can reduce potential side effects frequently observed in traditional chemotherapy, and is similarly effective in reducing tumor growth. Palbociclib, ribociclib, and abemaciclib are inhibitors of CDK4 and CDK6, which are essential for cell cycle progression from G1 to S phase (O'Leary, Finn, & Turner, 2016). Inhibition of CDK4/6 mimics the state of cell cycle arrest induced by p16, including increased senescence-associated beta-galactosidase (SA-β-Gal) activity and stable growth arrest. However, it is possible that such CDK4/6 inhibitor-induced senescence lacks the activation of the SASP axis, analogous to the one induced by overexpression of p16 (Coppe et al., 2011). Because the SASP can either promote or suppress tumorigenesis and the efficacy of tumor immune surveillance in a context-dependent manner, caution should be taken when considering this promising senescence-based targeted therapy.

### 4.1.3 Paracrine senescence and immune surveillance

In contrast to quiescent cells that also freeze their cell cycle, senescent cells are metabolically active and display a massive secretory phenotype.

The SASP exerts a pleiotropic effect of senescence, which includes two non-cell autonomous, tumor suppressive mechanisms: paracrine senescence and immune surveillance (Perez-Mancera et al., 2014). The SASP induces paracrine senescence in normal cells, where TGF-β secreted from primary senescent cells plays a major role in regulating p15 and p21 in normal receiving cells (Zhang, Alexander, & Wang, 2017). This paracrine activity ensures senescence growth arrest of potentially premalignant, yet partially damaged cells that are closely located to the primarily damaged cells (e.g., oncogene-activated senescent cells by cellular stressors), impacting tumor suppression (Acosta et al., 2013).

Another non-autonomous tumor suppressive mechanism of senescence is promoting tumor immune surveillance. Most cells become senescent upon oncogenic activation, yet a few may escape OIS and become malignant. In this situation, senescent cells secrete the SASP, which includes many pro-inflammatory cytokines and chemokines that recruit immune cells to clear themselves and their neighboring premalignant/malignant cells (Childs, Baker, Kirkland, Campisi, & van Deursen, 2014; Lee & Schmitt, 2019). Innate immune response and CD4 T cell-mediated adaptive immune response are involved in such immune surveillance (Liu, Ding, & Meng, 2018). Thus, when the SASP or immune system is disabled, tumorigenesis is accelerated in the hepatocarcinoma mouse model (Kang et al., 2011). In addition, it was recently reported that the SASP promotes tumor angiogenesis, which in turn increases the delivery of immune checkpoint inhibitors to the tumor region. This reveals an unexpected therapeutic opportunity generated by the SASP (Ruscetti et al., 2020). In this study, the authors utilized a KRAS mutant PDAC model, which is characterized by extensive desmoplasia that promotes hypovascularity and resistance to chemotherapy and immunotherapy. Co-treatment with MEK and CDK4/6 inhibitors can induce RB-dependent senescence, suppressing the proliferation of PDACs. This senescence-inducing therapy also promotes tumor vascularization through the SASP, which in turn enhances drug delivery and efficacy of cytotoxic gemcitabine chemotherapy. In addition, the SASP stimulates the accumulation of CD8 T cells into tumor regions, greatly increasing the efficacy of the PD-1 checkpoint blockade for PDACs. It will be interesting to examine whether such therapy-induced senescence can sensitize other immunologically "cold" tumors to chemotherapies and immunotherapies through the SASP-dependent effects on the tumor vasculature and immune system.

## 4.2 Tumor-promoting roles of senescence

As senescence growth arrest is stable, tumor-promoting functions of senescence are generally emanated from its non-cell autonomous function, the SASP (Coppe et al., 2010).

### 4.2.1 Growth factors

The SASP includes a wide range of growth factors, such as insulin growth factor (IGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), amphiregulin (AREG), epiregulin (EREG), and neuregulin (NRG) (Coppe et al., 2010). These growth factors can stimulate the proliferation of neoplastic cells in various tissues (Witsch, Sela, & Yarden, 2010). Accordingly, coinjection of senescent fibroblasts, but not normal fibroblasts, stimulates proliferation of malignant epithelial cells in vivo. Consistently, targeting the SASP pathway abrogates tumor growth stimulated by senescent cells in vivo (Laberge et al., 2015).

### 4.2.2 Stress resistance

One characteristic of senescent cells is their stress resistance. Interestingly, this stress resistance can be relayed to their neighboring cells, including cancer cells, via the SASP, especially under therapy-induced stressful conditions. For example, IL-6 produced from senescent cells in the mouse thymus protects lymphoma cells from chemotherapy. Inhibition of IL-6 increases the efficacy of chemotherapy in a mouse lymphoma model (Gilbert & Hemann, 2010).

### 4.2.3 Tumor stemness

Cancer stem cells (CSCs) exhibit characteristics of both stem cells and cancer cells, including self-renewal and differentiation capacities. CSCs barely proliferate under normal conditions, yet increase their proliferation to repopulate cancer cells in a context-dependent manner, including cancer treatment (Nguyen, Vanner, Dirks, & Eaves, 2012). Recent studies suggest that senescence promotes the formation of CSCs and tumor relapse after targeted cancer therapy (Kurppa et al., 2020; Milanovic et al., 2018). Inhibition of the EGFR signaling by osimertinib and trametinib causes tumor stemness followed by relapse in EGFR mutant non-small cell lung cancers. CSCs display several characteristics of senescence, including high levels of SA-beta-Gal activity, a flattened morphology, and activation of the SASP. Abrogation of such a stemness state prevents tumor relapse after

cancer treatment, suggesting a crucial role for senescence-like cancer stem cells in tumorigenesis (Kurppa et al., 2020). How CSCs escape from senescence and resume their proliferation is unclear. However, it is possible that senescence is not fully installed under this condition as senescence is not a static status, but instead evolves over time.

#### 4.2.4 Angiogenesis and metastasis

The SASP promotes tumor angiogenesis by secreting vascular endothelial growth factor (VEGF), which supports tumor cells with oxygen and nutrients. In fact, senescent fibroblasts increase tumor vasculature when they are coinjected into mice with poorly malignant epithelial EpH4 cells (Coppe, Kauser, Campisi, & Beausejour, 2006). In addition, the SASP can also promote EMT in tumor cells, potentially increasing their invasion. Consistently, conditioned media from senescent fibroblasts induces EMT in breast cancer cells, which is partially mediated by IL-6 and IL-8 (Ortiz-Montero, Londono-Vallejo, & Vernot, 2017). Senescent cells also secrete various extracellular matrix (ECM) remodeling factors, including matrix metalloproteinase 1 (MMP1), MMP2, and MMP3, which directly influence metastasis (Coppe et al., 2010; Deryugina & Quigley, 2006). For example, MMP1 and MMP2 from senescent skin fibroblast cells can activate a serine/threonine protein kinase PAR-1 on tumorigenic keratinocytes and stimulate their invasion (Malaquin et al., 2013). In addition, MMPs can stimulate growth factor signaling in cancer cells by releasing growth factors entangled with ECMs. In fact, treatment with an MMP inhibitor GM6001 reverses the growth-promoting effects of senescent cells on xenograft tumors (Liu & Hornsby, 2007).

#### 4.2.5 Immune suppressive microenvironment

The SASP can also create immune suppressive environments in a context-dependent manner that drives tumorigenesis. This is somewhat perplexing, as the SASP is shown to be critical for tumor immune surveillance (Childs et al., 2014; Lee & Schmitt, 2019). The types of senescent cells (e.g., senescent cancer cells, senescent stromal cells) and the stage of tumorigenesis seem to be critical for understanding such complexity (Perez-Mancera et al., 2014). For example, in the hepatocellular carcinoma model, senescent stromal cells secrete CCL2, which promotes the recruitment of immunosuppressive myeloid cells. This in turn restrains NK-driven tumor cell clearance (Eggert et al., 2016). Other SASP factors that exert immunosuppressive functions are IL-6, IL-10, and TGF-β in the

PTEN-loss prostate cancer model. These SASP factors inhibit NK cells, recruit regulatory T cells, and polarize macrophages to the M2 state, suppressing tumor immune surveillance (Toso et al., 2014).

## 4.3 Senolytics and senostatics as anti-cancer strategies

As in the case of autophagy, senescence also has dual roles in tumorigenesis (Fig. 2). Therefore, to improve the efficacy of senescence-based cancer therapies, it is necessary to consider how to decrease the deleterious effects of senescence in tumorigenesis. In other words, it is a balancing act between the beneficial effects of senescence (e.g., tumor cell senescence, paracrine senescence, and tumor immune surveillance) and its deleterious effects (e.g., stromal cell senescence, immune suppression, and resistance to therapy). Currently, two approaches are available for this purpose: senolytics and senostatics (Kang, 2019; Short, Fielder, Miwa, & von Zglinicki, 2019). Senolytics are agents that selectively kill senescent cells. Analogous to the ones used for selectively killing cancer cells, senolytics generally target survival pathways specific to senescent cells. For example, navitoclax (also known as ABT-263) targets an anti-apoptotic BCL2 family of proteins that increases during senescence, inducing apoptosis in senescent cells (Zhu et al., 2016). Dasatinib and quercetin induce apoptosis of senescent cells by targeting the upregulated dependence receptor and

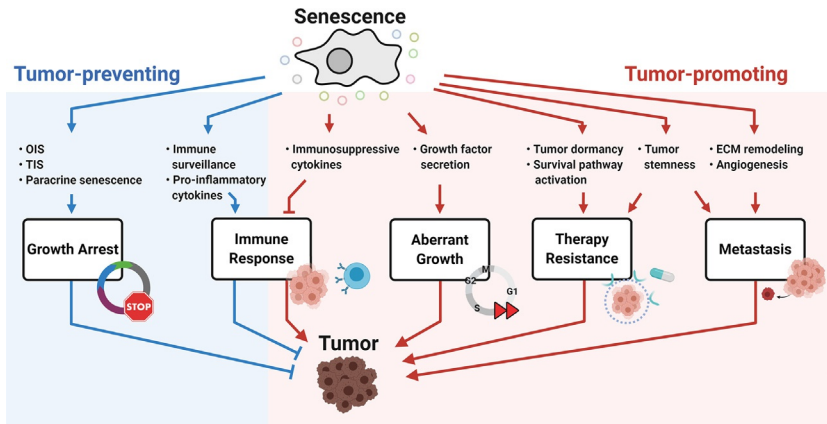


**Fig. 2** Dual roles of senescence in tumorigenesis. Senescence prevents tumorigenesis by (1) inhibiting cell growth and (2) promoting immune surveillance. Senescence promotes tumorigenesis by (1) providing tumor cells with trophic support, (2) promoting resistance to cancer therapy, (3) creating tumor-suppressive microenvironment, and (4) enhancing invasion and metastasis (created with BioRender.com).

PI3K/Akt pathways (Zhu et al., 2015). Although these first generation of senolytics have their own limitations, such as off-target effects and inconsistent efficacy depending on the type of senescent cells, they display promising effects on several age-related disease models, including cancer metastasis, idiopathic pulmonary fibrosis, atherosclerosis, liver cirrhosis, glomerulosclerosis, diabetes, sarcopenia, and osteoarthritis (Kang, 2019; Short et al., 2019). Senostatics are agents that do not kill senescent cells but modulate the SASP, especially its proinflammatory secretome, to dampen the deleterious, non-cell autonomous effects of senescence. The development of senostatics is at a very early stage, and no specific senostatics are available. Currently, inhibitors of NF-κB, multiple flavonoids and polyphenols, and inhibitors of the mTOR pathway are proposed to act as senostatics (Short et al., 2019). However, caution should be taken when considering some of these inhibitors for cancer treatment, as they can also affect other critical biological processes. For example, inhibitors of the mTOR pathway activate general autophagy (Dunlop & Tee, 2014), which could enhance tumor survival in a context-dependent manner, as described above. As we have recently gained insights into how the SASP is regulated, more tailored therapeutic strategies for targeting the SASP are expected to be discovered in the near future.

When senolytics and senostatics are applied to improve cancer treatment, the following information should be carefully considered: (1) the types of senescent cells involved; (2) the stages of tumorigenesis; (3) the types of immune cells recruited by senescent cells; and (4) the age of patients. Senescence-inducing therapies (e.g., chemotherapy, radiotherapy) can induce senescence in both cancer cells and their neighboring cells, including stromal cells (Wang et al., 2020). The SASP from senescent stromal cells either induces resistance to therapy by either providing cancer cells with trophic support or promoting an immunosuppressive microenvironment (Coppe et al., 2010; Perez-Mancera et al., 2014). Thus, if the ratio between senescent stromal cells and senescent tumor cells is relatively high after treatment, it would be better to apply either senolytics or senostatics as soon as possible at the expense of the beneficial SASP effects, including paracrine senescence and tumor immune surveillance. The SASP can promote cancer cell invasion and metastasis, suggesting that senescence induction in fully established cancers may increase the possibility of devastating metastasis. Therefore, in this case, senolytics and senostatics should be applied immediately after cancer treatment. Alternatively, inhibition of metastasis should be considered together at

the treatment of senescence-inducing therapy. However, at the early stage of cancer, it would be better to allow the beneficial effects of the SASP to be maximized first, following which senolytics and senostatics can be applied as a failsafe treatment. Another consideration is which immune modulatory axis of the SASP is ensued upon senescence-inducing therapy. The SASP includes both immune stimulating and suppressing factors, depending on senescent cell types, senescence-inducing stimuli, and the senescent stage. Thus, after senescence-inducing therapy, if immunosuppressive SASP factors such as IL-10 and TGF-β or tumor-promoting immune cells (e.g., M2 macrophages, regulatory T cells) are enriched in the tumor microenvironment, it would be better to apply senolytics and senostatics as soon as possible. Senolytics and senostatics can also be applied before cancer treatment to improve the tumor environment. For example, in aged patients, senescent stromal cells are already accumulated in the tumor region, decreasing the efficacy of senescence-inducing therapy (Baker et al., 2016). In this case, senolytics and senostatics can remove senescent stromal cells, suppressing the tumor-supporting microenvironment. Then, senescence-inducing therapy can be applied, and whether additional rounds of senolytics and senostatics are necessary can be determined after assessing the treatment response, as described above.

## 5. Interplay between autophagy and senescence

Many stressors that activate autophagy can also modulate senescence, and vice versa (Gewirtz, 2013). Indeed, autophagy has been shown to be a critical effector of senescence (Chan & Narita, 2019; Gorgoulis et al., 2019). This intertwined relationship should therefore be considered when autophagy and senescence are employed as therapeutic targets for cancer treatment.

### 5.1 Pro-senescence and anti-senescence roles of autophagy

The relationship between autophagy and senescence seems to be close to that between autophagy and cancer. Before senescence is induced (under normal conditions), autophagy acts to maintain cellular homeostasis, suppressing senescence in a passive manner. For example, autophagy targets dysfunctional mitochondria and protein aggregates for degradation to maintain redox homeostasis and proteostasis. In addition, autophagy maintains lysosomal integrity and resolves stress granules. Autophagy can also suppress senescence by directly targeting critical regulators of senescence.

For example, p62-dependent selective autophagy degrades a key regulator of the SASP, GATA4, suppressing the SASP and senescence (Kang & Elledge, 2016).

Once senescence is triggered, however, autophagy can contribute to senescence establishment. Autophagy functions as "non-senescence addiction" wherein senescence relies on autophagy, which is not a senescence-inducing process by itself. This dampens several senescence-associated stresses, thus maintaining the viability of senescent cells (Kwon, Kim, Jeoung, Kim, & Kang, 2017). In addition, autophagy provides amino acids to support the massive synthesis of SASP factors through the formation of TASCC (Narita et al., 2011). Lastly, autophagy can target negative regulators of senescence for degradation, thus actively causing senescence. Δ133p53α, an alternative splicing form of p53 (Horikawa et al., 2014), the nuclear lamina component Lamin B1 (Dou et al., 2015), and the histone deacetylase SIRT1 are such autophagy substrate targets (Xu et al., 2020). How such autophagy is modulated and why they need to be degraded during senescence are incompletely understood.

## 5.2 Context-specific regulation of autophagy and senescence for cancer treatment

As autophagy can either suppress or induce senescence in a context-dependent manner, targeting autophagy for cancer treatment should be carefully considered after examining whether it can modulate senescence under the same conditions. For example, autophagy inhibition could decrease the efficacy of chemotherapies to induce senescence. In addition, as autophagy is necessary for senescence maintenance, its inhibition after senescence-inducing treatment could escape severely damaged, potentially premalignant cells from senescence, rather accelerating, not suppressing, tumorigenesis.

Another consideration is the role of autophagy in controlling the SASP. Autophagy inhibition may potentiate activation of the SASP by accumulating GATA4 and sustaining cytoplasmic chromatin fragments that can be sensed by the cGAS-STING pathway (De Cecco et al., 2019; Dou et al., 2017; Gluck et al., 2017; Kang et al., 2015; Li & Chen, 2018; Yang, Wang, Ren, Chen, & Chen, 2017). Thus, it can boost paracrine senescence and immune surveillance after senescence-inducing treatment for cancer. Since GATA4 and the cGAS-STING pathways are mostly involved in the proinflammatory axis of the SASP, whether such modulation may increase immunosuppressive secretomes would be less of a concern; however, caution should be taken when applying these to treatment.

Autophagy modulation could also be considered for senolytics. Since senescent cells undergo very similar stress responses observed in cancer cells, including metabolic rewiring, proteotoxic stress, DNA damage, and oxidative stress, they might be vulnerable to autophagy inhibition (Soto-Gamez, Quax, & Demaria, 2019). In fact, autophagy inhibition sensitizes senescent cells to cell death by depleting cellular nutrients and energy (Dorr et al., 2013). This could provide additional options for enhancing senolytics during cancer treatment.

## 6. Concluding remarks and perspectives

The studies discussed above clearly demonstrate the complex functions of autophagy and senescence during tumorigenesis. Autophagy and senescence can either promote or suppress tumorigenesis in a context-dependent manner. Thus, we need to fully understand when, how, and why autophagy and senescence are activated during tumorigenesis and cancer treatment. For example, for over a decade, we have largely viewed senescence as stable growth arrest that suppresses tumorigenesis. Recent studies linking senescence to secretion have begun to highlight a completely novel non-cell autonomous role for senescence in tumorigenesis: paracrine senescence, immune surveillance and modulation, and trophic support. Further elucidation of autophagy and senescence programs, including their intertwined relationship, should provide insight into new therapeutic strategies for modulating autophagy and senescence in cancer.

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