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REVIEW

Senescent cells: Living or dying is a matter of NK cells

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Abstract

NK cells are lymphocytes of the innate immune system, which are able to deal promptly with stressed cells. Cellular senescence is a cell stress response leading to cell cycle arrest that plays a key role during tissue homeostasis and carcinogenesis. In this review, how senescent cells trigger an immune response and, in particular, the ability of NK cells to recognize and clear senescent cells are discussed. Special attention is given to the NK cell-mediated clearance of senescent tumor cells. NK cells kill senescent cells through a mechanism involving perforin- and granzyme-containing granule exocytosis, and produce IFN-γ following senescent cell interaction, leading to hypothesize that NK cell-mediated immune clearance of senescent cells not only relies on direct killing but also on cytokine production, that in turn can promote macrophage activation. These aspects, as well as the ability of the senescence-associated secretory phenotype and senescent cell-produced extracellular vesicles to modulate NK cell effector functions, are described.

KEYWORDS

cellular senescence, DNAM-1, extracellular vesicles, immune surveillance, NKG2D, SASP

1 | INTRODUCTION

NK cells are lymphocytes of the innate immunity endowed with cytolytic activity. They can target virus-infected, neoplastic, and, more in general, "stressed" cells. Indeed, NK cells display a wide array of activating/inhibitory receptors, which are able to engage MHC class I and class I-like molecules that serve as indicators of cellular stress in injured and damaged cells. Among the activating receptors, NKG2D and DNAM-1 are of great relevance as their ligands are promptly induced in response to stress conditions[1–3] and are largely expressed on a variety of tumor cells.[4,5] In humans, the ligands of NKG2D are MICA, MICB, and ULBP1-6, while murine NKG2D ligands include RAE-1 (five different isoforms), MULT-1, and H60 (three different isoforms).[6] The ligands of DNAM-1 are PVR (CD155) and Nectin-2 (CD112).[7] Expression of both NKG2D and DNAM-1 ligands can be mediated by the DNA damage response (DDR) pathway via ATM and ATR and occurs at the transcriptional level.[8–10] Drug-induced transcription of *MICA* and *PVR* genes involves the transcriptional factor E2F and is dependent on the cellular redox state.[11] Notably, NKG2D and DNAM-1 ligands have been shown to be expressed by senescent cells and drug-induced senescent tumor cells, unmasking an important role of NK cells for the immune surveillance of senescent cells.[10,12,13]

Senescence is a cellular program based on long-lasting cell cycle arrest upon replicative, genotoxic, or oncogenic insult (for a review on cellular senescence see Ref. 14). Senescent cells are apoptotic resistant and metabolically active, producing large amounts of soluble factors collectively called senescence-associated secretory phenotype (SASP). The composition of SASP is not unique but is context-dependent since it is subjected to the influence of several extrinsic and intrinsic factors. SASP composition includes cytokines, chemokines, growth factors, and proteases. In this way, senescent cells participate in tissue remodeling during embryogenesis,[15,16] wound healing,[17,18] and cancer.[19] As senescence is a barrier to exceeding cell proliferation, it is considered a tumor suppressive mechanism. On the other hand, the proinflammatory feature of SASP facilitates tumor progression.[20,21] Indeed, its proinflammatory activity results in enhanced proliferation and tumorigenesis of epithelial cells, stimulation of angiogenesis, triggering of epithelial to mesenchymal transition, promotion of cancer cell invasion, increased growth of xenograft tumors in vivo, and, in general, is responsible for multiple aging-related pathologies.[22–24]

In this regard, the life span of senescent cells seems to be the compelling factor. "Acute" senescence, when senescent cells are promptly

Abbreviations: ADAM10, a disintegrin and metalloproteinase 10; ATM, ataxia telangiectasia mutated protein; ATR, ataxia telangiectasia and Rad3-related protein; CDK, cyclin-dependent kinase; DDR, DNA damage response; DNAM-1, DNAX accessory molecule-1; DPP4, dipeptidyl peptidase 4; EnSC, endometrial stromal cell; EV, extracellular vesicle; FOXO1, forkhead box protein O1; H60, histocompatibility 60; IL-15RA, interleukin 15 receptor subunit alpha; M-CSF, macrophage colony-stimulating factor; MDSC, myeloid-derived suppressor cell; MICA/B, MHC class I chain-related proteins A/B; miRNA, micro RNA; MM, multiple myeloma; MULT-1, murine ULBP-like transcript-1; NKG2D, natural-killer group 2 member D; PVR, poliovirus receptor; RAE-1, retinoic acid early inducible protein-1; RAS, rat sarcoma; SASP, senescence-associated secretory phenotype; ULBP, UL16-binding protein

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removed from organs, contributes to tissue repair, while "chronic" senescence, due to the persistence of senescent cells in tissues, promotes tissue ageing and inflammation, thus, enhancing tumorigenesis. This double aspect of senescence has arisen much interest in uncovering the faith of senescent cells in tissues, especially in cancer settings, as it has become clear that the efficacy of certain chemotherapeutic drugs relies on the induction of senescence[25,26] and prosenescence therapy is approaching.[27] So, targeting senescent cells is now a major issue of the scientific community. Beside the development of senolytic drugs,[28] the immune surveillance of senescent cells is another aspect that is under investigation. So far, different cellular types of the immune system have been involved in the clearance of senescent cells, with phagocytes and NK cells playing an essential role.[29,30] In particular, macrophages have been implicated in the removal of senescent cells during embryogenesis[15,16] and in the clearance of senescent red blood cells,[31] as well as premalignant/malignant senescent cells.[32–34] Neutrophils have been also shown to participate in tumor clearance after senescence induction due to p53 reactivation in hepatocarcinoma cells.[34] On the other hand, NK cells have been described to efficiently target senescent hepatic stellate cells,[35,36] senescent hepatocarcinoma cells after p53 restoration,[12,34] and drug-induced senescent multiple myeloma cells.[10,37] Finally, premalignant N-RAS-expressing senescent hepatocytes have been reported to be controlled by a CD4 T lymphocyte-mediated immune response, that likely then supports macrophages and NK cells.[33] It is worth mentioning that nevi contain numerous senescent melanocytes without any immune clearance for unknown reasons.[38]

This review focuses on the ability of NK cells to recognize and clear senescent cells both in physiological and in pathological conditions, as well as it describes the latest studies showing the way senescent cells modulate NK cell effector functions.

2 | RECOGNITION OF SENESCENT CELLS BY NK CELLS DRIVES TISSUE HOMEOSTASIS

Nowadays, it is clear that cellular senescence plays a role in tissue homeostasis. This aspect has been clearly addressed in a model of liver fibrosis, where hepatic damage is caused by CCl_4 treatment. After liver injury, hepatic stellate cells (HSCs, also called Ito cells) proliferate and promote organ repair producing extracellular matrix. Excessive HSC activity leads to fibrosis, eventually triggering liver cirrhosis.[39] Krizhanovsky and colleagues have demonstrated that activated HSCs undergo cellular senescence to limit matrix deposition. Senescent HSCs reduce secretion of extracellular matrix, enhance secretion of matrix-degrading enzymes, and, at the same time, stimulate an immune response aimed at HSC removal, thus, promoting the resolution of fibrosis. NK cells largely characterize this immune response (Fig. 1).[35] Curiously, the natural compound curcumin has been reported to foster HSC senescence.[40] Senescent HSCs upregulate IL-8 (CXCL8), the adhesion molecule CD58, and the NKG2D ligands MICA and ULBP2, thereby, supporting NK cell engagement.[35] The specific killing of senescent HSCs by NK cells is mediated by granule exocytosis, while death receptor signaling is not required. To partially account for this mechanism, expression of the decoy death receptor DCR2 is observed on senescent HSCs.[36] Quiescent mouse HSCs do not express the NKG2D ligand RAE-1, making NKG2D ligand expression peculiar of the senescence condition rather than cell cycle arrest related.[41]

Involvement of NKG2D ligands for senescent cell targeting has been confirmed also in human fibroblast IMR-90 cells induced to senescence by DNA damage with etoposide treatment, by replicative senescence through prolonged cell culture, and by *H-RAS* overexpression. MICA, ULBP1, and ULBP2 are constantly upregulated in all the investigated settings. ULBP2 expression is ATM signaling dependent, while MICA expression has been ascribed to ERK activity. As IL-6, IL-8, CXCL1, CXCL10, and CCL2 (MCP-1) expression in the senescent secretome requires ERK activity too, ERK seems to be a key factor for NK cell engagement upon senescent cell interaction.[13]

Regarding pancreatitis, senescence of pancreatic stellate cells has been found to increase their susceptibility to immune cell cytotoxicity, including NK cell activity. Nevertheless, NK cell contribution to the pancreatic wound healing seems not essential, as fibrosis is not affected by NK cell depletion.[42]

A pivotal role for senescent cells and their clearance by NK cells in tissue homeostasis has been well described during tissue remodeling of cycling human endometrium.[43] Replication stress of rapid endometrial growth during the proliferative phase induces senescence in a pool of decidualizing endometrial stromal cells (EnSCs). The transcription factor FOXO1, inducing cell cycle exit of EnSCs, not only drives differentiation into decidual cells but also forces a pool of EnSCs to enter senescence, that in turn, is supported in an autocrine/paracrine way by the secretion of IL-8 by the senescent decidual cells themselves.[43,44] The SASP of senescent decidual cells encompasses IL-8, IL-6, and CXCL1 secretion, supporting the transient inflammatory state observed during decidualization. In parallel, differentiated decidual cells secrete IL-15, a key cytokine for NK cell proliferation and activation, in order to activate uterine NK cells, thus, regulating the clearance of their senescent counterpart. Accordingly, NK cells target senescent EnSCs only after decidualization, when IL-15 levels support NK cell activity. Also in this setting, NK cells eliminate senescent cells through perforin- and granzyme-containing granule exocytosis upon NKG2D engagement.[43] Efficacy of senescent decidual cell removal by uterine NK cells regulates endometrial remodeling and assures homeostasis in cycling endometrium (Fig. 1).

3 | NK CELL-MEDIATED CLEARANCE OF SENESCENT TUMOR CELLS

The first evidence of senescent tumor cell recognition and killing by NK cells stems from the discovery by Scott-Lowe's group that p53 restoration in murine liver carcinoma results in tumor regression due to the clearance of senescent tumor cells by an innate immune response that includes NK cells.[34] This study has changed the perspective about senescence. Cellular senescence is not only a cell-autonomous mechanism imposing a barrier to cell proliferation, but is a process that strongly involves the recognition of the

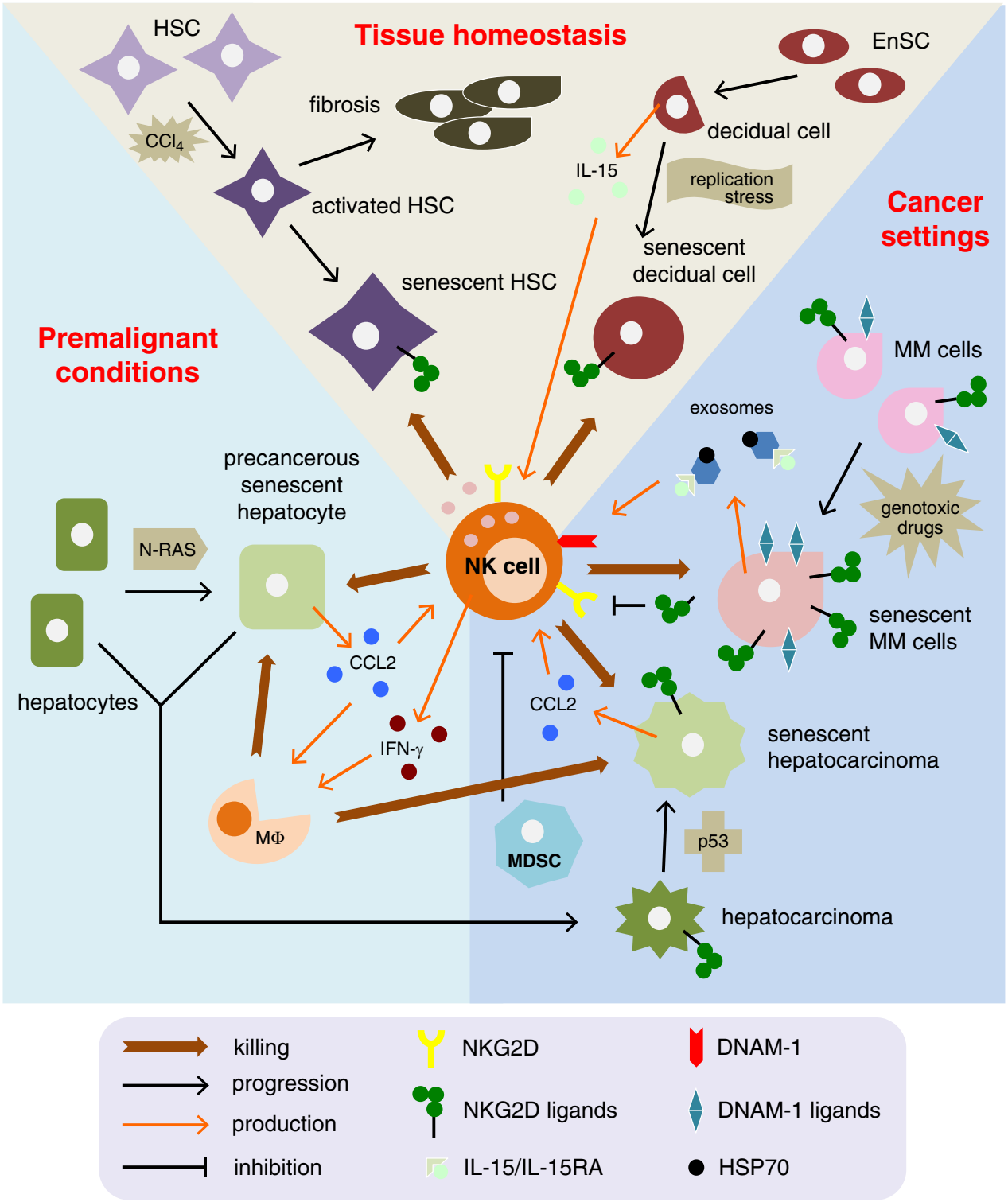

FIGURE 1 **Schematic representation of NK cell response against senescent cells in different settings.** NK cells target senescent cells in liver and endometrium promoting tissue remodeling (upper side). NK cells, as well as macrophages, perform immune surveillance of premalignant senescent cells contributing to cancer prevention (left side). NK cells recognize and clear senescent tumor cells during prosenescence therapies against cancer cells (right side). HSC, hepatic stellate cell; EnSC, endometrial stromal cell; MΦ, macrophage; MDSC, myeloid-derived suppressor cell; MM cells, multiple myeloma cells

senescent cells by the immune system. Senescent cells and cells of the immune system interact with each other and deeply shape tissue homeostasis, performing tissue remodeling during carcinogenesis and tumor progression.

From a mechanistic point of view, the model of p53 reactivation in hepatocarcinoma cells has shown the requirement of NK cells for tumor regression after the induction of senescence, as NK cell depletion strongly delays tumor eradication.[12,34] In line with this evidence,

abrogation of the senescence program because of additional p53 mutations causes aggressive hepatocarcinoma development.[45]

Targeting of the senescent cells occurs via NKG2D recognition of its ligands on tumor cells. Indeed, NKG2D blocking antibodies can prevent tumor clearance.[12] In this tumor model, NKG2D ligand expression on senescent cells is not enhanced by p53. Instead, p53 restoration is associated with increased chemokine secretion. In particular, senescent tumor cells, through the SASP, release CCL2, CCL3, CCL4, CCL5, CXCL1 (GROα), and CXCL2. Among these, CCL2 is essential for NK cell recruitment to the tumor site (Fig. 1).[12]

The ability of NK cells to recognize and clear senescent cells and the association between senescent cells and NKG2D ligands have been largely addressed by our group in a model of drug-induced senescence. In this context, multiple myeloma (MM) cell lines and patient-derived malignant plasma cells treated with sublethal (not apoptotic) doses of chemotherapeutic drugs, namely doxorubicin and melphalan, become senescent with increased cell surface expression of the NKG2D ligands (MICA/B and ULBP1-3) and DNAM-1 ligands (PVR and Nectin-2).[10] Similarly, in a mouse model of MM, low doses of melphalan promote the in vivo establishment of a senescent tumor cell population, harboring high levels of the stress-induced ligands RAE-1 and PVR.[37] Remarkably, engagement of NKG2D and DNAM-1 not only targets senescent tumor cells to NK cell-mediated cytotoxicity,[10,37] but also triggers NK cell production of IFN-γ, that in turn can elicit macrophage activity, thus, contributing to the clearance of senescent cells (Fig. 1).[11] NKG2D and DNAM-1 ligand upregulation is p53-independent but dependent on the redox state, as doxorubicin and melphalan DDR triggering is based on ROS signaling.[11] Induction of tumor senescence associated to increased oxidative stress has been reported also in breast cancer due to protein acyltransferase dysregulation.[46] The resulting SASP, characterized by the secretion of CCL2, CXCL1, CXCL16, and IL-8, recruits antitumor "M1-like" macrophages and NK cells leading to reduced tumor growth.[46]

It should be taken into consideration that the release of NKG2D ligands from the cell surface in their soluble form by proteolytic cleavage plays an important role in tumor cell escape from NKG2D-dependent immune surveillance.[47] Interestingly, it has been demonstrated that genotoxic stress-induced upregulation of *ADAM10* expression and soluble MICB secretion are primarily associated with senescent cells.[48] Thus, the release of soluble NKG2D ligands has been proposed to be a component of tumor cell SASP, contributing to the creation of a microenvironment suitable for tumor escape (Fig. 1).[48] Strategies aimed at targeting metalloproteases or that encompass antibody-mediated blocking of MICA ligand release in conjunction with chemotherapy could be successful to preserve NKG2D ligands on the cell surface of senescent cells.[49]

CCL2 plays a central role in NK cell, as well as monocyte/macrophage recruitment to the tumor site and CCL2–CCR2 axis has been shown to be crucial in the senescence surveillance of premalignant hepatocytes. Premalignant N-RAS-expressing senescent hepatocytes produce a large amount of CCL2 driving CCR2$^+$ myeloid cell accumulation and maturation in the senescent liver, where differentiated macrophages can perform precancerous senescent hepatocyte clearance, achieving anticancer effects.[32] Strikingly, if premalignant hepatocytes escape or bypass senescence (or if senescent hepatocytes are not efficiently removed) leading to hepatocellular carcinoma growth, the SASP-driven effect of oncogene-induced senescent hepatocytes is to recruit immature myeloid cells that, in a tumor context, do not differentiate into macrophages but induce an immunosuppressive environment.[32] Tumor-infiltrating NK cells are strongly inhibited by myeloid-derived suppressor cells (MDSCs), with reduced IFN-γ release and cytotoxic capacity.[50] Thereby, the SASP can exert opposite jobs, procancer as well as anticancer functions, depending on the efficacy of senescent cell clearance by the immune system (Fig. 1).

Supporting this statement, senescent stromal cells that accumulate in aged skin, likely because of reduced immune clearance, create, through the SASP factor IL-6, a myeloid-driven immunosuppressive environment that does not restrain tumor formation.[51] Thus, accumulation of senescent cells in tissues is able to establish a chronic inflammatory state that is tumor permissive.

Many findings highlight the opposing functions of SASP as a procancer as well as anticancer mechanism. To ensure that the established SASP promotes antitumor immunity, a possible innovative approach is to reprogram the SASP from procancer toward anticancer effector function. In this regard, a work by Toso and colleagues has provided evidence of the possibility of reprogramming the SASP to restore an immune response.[52] *Pten*-null senescent prostate tumor cells are characterized by an immunosuppressive SASP, but Jak2/Stat3 genetic or pharmacological inhibition changes the profile of cytokine secretome, reducing CXCL2, M-CSF, GM-CSF, IL-10, IL-13, and increasing CCL2, CXCL10, thus, reactivating senescence surveillance by NK cells. This work highlights also the importance of the genetic background of senescent cells for the feature of SASP and, consequently, for the efficacy of chemotherapy that relies on antitumor immunity.[52] An interesting strategy to erase the side effects of SASP has been exploited by Georgilis and colleagues. Through a large-scale RNA interference library screen in RAS-driven senescent human diploid fibroblasts, the authors have identified and targeted transcripts associated to the SASP pathway without interfering with the senescent cell growth arrest.[53] All together, these studies focus on the importance of SASP-associated cytokines and chemokines to drive the immune surveillance of senescent cancer cells, but recent evidence has shown that also SASP-derived extracellular vesicles (EVs) can significantly contribute to this effect.

4 | EVs AS A KEY COMPONENT OF SASP MODULATE NK CELL FUNCTIONS

A large body of evidence shows that EVs, including exosomes and microvesicles, that are important mediators of intercellular communication, represent a key component of SASP.[54,55] In general, EVs carry and transfer a wide variety of molecules, such as micro RNAs (miRNAs), messenger RNAs, DNA, and proteins. Remarkably, EVs secreted from senescent cells have unique characteristics and contribute to regulate the behavior of recipient cells similarly to soluble SASP factors.[56,57] By analyzing EVs from senescent human dermal fibroblasts,

Terlecki-Zaniewicz and colleagues have identified a set of selectively retained or secreted miRNAs and have shown that senescent cell-derived EVs with their miRNA cargo contribute to an antiapoptotic environment in tissues where senescent cells accumulate.[58] Furthermore, ovarian cancer-derived exosomes expressing miRNA-433 have the potential to modulate the tumor microenvironment by inducing cellular senescence in neighboring cells.[59] In addition to miRNA pattern, also protein profile significantly changes in senescent cell-derived exosomes, as described by a proteomic study demonstrating that EVs derived from drug-induced senescent breast cancer cells contain proteins involved in cell proliferation, ATP depletion, and apoptosis.[60] Moreover, typical SASP components, such as soluble IL-6 receptor and ICAM-1, have been described in EVs.[61,62]

A number of studies have demonstrated that stress conditions, such as heat shock, oxidative stress, chemotherapy, irradiation, hypoxia, and hypothermia, which can induce cellular senescence, are reported to increase EV secretion and, in some circumstances, to induce remarkable changes in the compositions of EVs.[63–68] Mechanistically, the increased exosome secretion from senescent cells is mediated by p53 activation.[66,69] Similarly to SASP soluble factors, EVs can have both immunosuppressive and immunostimulating effects on NK cell-mediated functions. Exosomes derived from leukemia cells in response to oxidative stress express high levels of NKG2D ligands that have the capability to turn-off NKG2D, thus, reducing NK cell-mediated recognition of cancer cells.[65] On the other hand, EVs released by etoposide-treated hepatocellular carcinoma cells express high levels of HSPs and induce NK cell activation.[67] In line with these observations, our group has recently demonstrated that melphalan stimulates the secretion of exosomes from MM cells and that these nanovesicles have the capability to trigger IFN-γ production by NK cells with a mechanism dependent on HSP70/TLR2 interaction.[68] The immunostimulatory property of the exosomes from drug-induced senescent MM cells has been further proven by the finding that the exosomes express the IL-15/IL-15RA complex and can transpresent IL-15, thereby promoting NK cell activation and proliferation.[70] Collectively, these findings suggest a mechanism whereby chemotherapeutic drugs act in synergy with antitumor NK cell response by enhancing the release of nanovesicles exposing immunomodulating molecules (Fig. 1). Although the characterization of the immunomodulatory roles exerted by the EVs released from senescent cells is still largely unknown and need further investigation, senescence-associated EVs may have the potential to be a rational therapeutic target.

EVs, as well as SASP composition can be affected by the metabolic state of the cell and senescent cells, undertaking relevant metabolic changes, affect many aspect of cellular physiology, including autophagy.[71] While it is widely recognized that senescent cells are resistant to apoptosis, the relationship between senescence and autophagy is much more controversial and a discussion about this topic is beyond the scope of the present paper (for a review on senescence and apoptosis see Ref. 72, for reviews on senescence and autophagy see Ref. 73,74). Of interest for NK cell biology, Baginska and colleagues have shown that the activation of autophagy in cancer cells due to hypoxic conditions leads to a reduced NK cell-mediated killing. This impairment has been ascribed not to a defect in tumor cell recognition by NK cells but to the degradation of NK cell-derived granzyme B in autophagosomes.[75] Considering the relevance of SASP for NK cell recruitment and activation, it is worth noting that stabilization of the transcription factor GATA4, that is necessary for SASP establishment, is mediated by the selective inhibition of GATA4 autophagic degradation. Under normal conditions, GATA4 is degraded by p62-mediated selective autophagy. During the senescence process, this regulation is abrogated and GATA4, through TRAF3IP2 and IL1A, sustains NF-κB activity to initiate the SASP.[76] Remarkably, the GATA4-NF-κB pathway for SASP induction relays on ATM/ATR while is independent of p53 or p16, thus, connecting autophagy and DDR to senescence independently of cell cycle arrest.[76] This finding confirms the strong interplay between senescence and autophagy.

5 | TYPE I INTERFERONS AT THE CROSSROAD BETWEEN SENESCENT AND VIRUS-INFECTED CELLS

Cytokines belonging to the family of type I IFN, including IFN-α and IFN-β, play a major role during antiviral response in concert with NK cells.[77] Notably, senescent cells secrete type I IFN[78] and long exposure to IFN-β has been reported to be sufficient to induce the state of senescence.[79] Therefore, senescent cells are able to stimulate and reinforce the senescent condition of neighboring cells also through the production of IFN-β. This finding, together with the observation that some viruses have developed strategies to overcome senescence,[80,81] can lead to the idea that cellular senescence may be evolved as an antiviral mechanism.[82] Undoubtedly, senescence is an important host defense mechanism against oncogenic virus effects.[83]

Recent studies highlight the link between cytosolic DNA sensing and the induction of cellular senescence, stressing the pivotal role of the cGAS-STING pathway, thus, providing the molecular basis for considering cellular senescence as a defense system against virus infection, as well as genomic/neoplastic insult.[84–87] Accordingly, type I IFNs result protective against retrotransposition events[88] and cells accumulating DNA damage produce endogenous IFN-β and become senescent.[89,90] Hence, it is reasonable that type I IFN signaling drives cellular response upon both virus infection and DNA damage to protect genome integrity, becoming actually a tumor suppressive mechanism.

In this context, Katlinskaya and colleagues have shown that the production of IFN-β by senescent cells contributes to the NK cell-mediated clearance of senescent cells not only acting on the effector cells, performing NK cells priming,[91,92] but also having effect on target senescent cells. Indeed, the engagement of the IFN pathway on senescent cells increases their expression of NKG2D ligands, that is, MICA and ULBP2, promoting NK-mediated killing.[93] Thereby, type I IFNs operate at different levels, inducing cellular senescence as a cell-autonomous safeguard mechanism and, at the same time, triggering the immune system, namely NK cells, as an extrinsic response.

NKG2D ligand coding genes do not belong to the *bonafide* IFN gene signature. From a molecular point of view, DDR and ROS signaling drive NK activating ligand expression, whether cellular stress comes from

direct DNA damage, such as genotoxic drugs or viral infection.[8,94] So, it is possible to speculate that NK cells recognize senescent cells and virus-infected cells in a similar way. However, little is known on how NK cells behave during the infection of senescent cells compared to uninfected senescent cells and further investigations are needed to clarify this point.

6 | CONCLUSIONS AND PERSPECTIVES

First studies paid attention to the proliferation arrest aspect of senescence, highlighting its implications as a tumor suppressive mechanism. Nowadays, cellular senescence is considered a more complex program, triggered by a plethora of stimuli during both physiological and pathological conditions. Senescent cells, via SASP, are able to evoke an immune response and to orchestrate important tissue remodeling. The effects of SASP are wide and may achieve even opposite results depending on the cellular context. In this regard, it is of great relevance if senescent cells are recognized and efficiently cleared by the immune system, or they persist in tissues, promoting chronic inflammation and, as a matter of fact, immune suppression, 2 characteristics of aged tissues. Recent works on the ability of senescence to promote stemness feature and tissue rejuvenation emphasize the importance of timing, opposing transient versus chronic SASP exposure.[95–97]

NK cells, together with macrophages, have been shown to play a major role in senescent cell immune surveillance. The activating receptors, NKG2D and DNAM-1, are able to promptly recognize stressed cells, make NK cells peculiar in their role of sentinels of senescent cells. Indeed, senescent cells have been demonstrated to upregulate NKG2D and DNAM-1 ligands and to secrete NK cell recruiting and activating factors. On the other hand, a role of the death receptor ligands FASL and TRAIL in the killing of senescent cells by NK cells has been ruled out in different settings. NK cells are observed in close proximity to senescent cells and, beyond their role in senescent cell clearance, can contribute to tissue remodeling due to their capacity of cytokine secretion. This aspect is exemplified by the endometrium physiology, where NK cells and senescent cells cooperate to assure tissue receptivity. All together, these findings support the concept of immunogenic senescence, a safety program through which senescent cells flag themselves as the target of the immune system to restore tissue integrity.[10]

Senescent cells are reported to accumulate in aging tissues, thus, contributing to tissue dysfunction.[98,99] The weakening of the immune system during ageing may account for this accrual, with immune cells no longer able to efficiently recognize senescent cells. In elderly individuals, a negative correlation between CD56^{bright} NK cells and CRP levels (assessed as a marker of inflammation) has been reported,[100] leading to speculate that NK cells contribute to control inflammation, likely performing senescent cell immune surveillance. Accordingly, a positive association between the total NK cells and healthy elderly individuals has been reported too.[100] It would be interesting to verify whether NK cell number negatively correlates with senescent cell accumulation in aging tissues. Cells of the immune system, including NK cells, display a senescent phenotype with increasing age, a process called immunosenescence.[101–103] The idea of ameliorate aged tissue functionality by killing senescent cells is supported by different studies.[104–106]

Anticancer prosenescence therapies are currently under investigation,[27,107,108] and recently approved drugs, such as CDK4/6 selective inhibitors, have been shown to induce tumor senescence.[25,26,109] Senescence induction in cancer cells may represent a valid approach to restrain tumor growth, but persistent senescent tumor cells may act as the silent factor for tumor relapse. For this reason, much effort is being spent in discovering tools and drugs that selectively target senescent cells.[28,106,110–113] Alternative approaches to target senescent cells have been explored. Georgilis and colleagues have split the unwanted protumorigenic effects from the beneficial proliferation arrest of senescent cells by specifically targeting the secretory pathway of SASP.[53] Notably, the suppression of SASP is associated with poor immune cell infiltration, apparently with no augmented risk of tumorigenesis, but further investigations are needed. Kim and colleagues, instead, identified dipeptidyl peptidase 4 (DPP4) or CD26 by MS analysis as a surface protein specifically expressed by senescent fibroblasts. This feature allowed them to sensitize senescent cells to ADCC by using an anti-DPP4 antibody, thereby targeting senescent cells, but not dividing fibroblasts, to NK cell clearance.[114]

The idea of making tumor cells more prone to NK cell killing is not new, but the finding that senescent cells are preferentially recognized and cleared by NK cells extends the field of application. NK cell-based anticancer therapies are promising[115,116] and NK cell immunotherapy should be considered as part of a prosenescence therapy. A combined treatment could be conceived in which tumor cells are forced to senescence and then removed by in vivo boosted NK cells or in vitro activated adoptively transferred NK cells. In line with this idea, a recent article by Ruscetti and colleagues clearly demonstrates how cytostatic agents used in cancer therapy, specifically a MAPK inhibitor (trametinib) and a CDK4/6 inhibitor (palbociclib), able to induce cellular senescence result cytotoxic because of the recruitment and activation of NK cells.[117,118]

AUTHORSHIP

F.A. and A.Z. searched for literature articles, conceived, and wrote the manuscript. A.L.S. and A.N.S. conceived and critically revised the manuscript. F.A., A.Z., A.L.S., and A.N.S. approved the final version of the manuscript.

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DISCLOSURE

The authors declare no conflicts of interest

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