Feed-forward regulation between cellular senescence and immunosuppression promotes the aging process and age-related diseases

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ABSTRACT
Aging is a progressive degenerative process involving a chronic low-grade inflammation and the accumulation of senescent cells. One major issue is to reveal the mechanisms which promote the deposition of pro-inflammatory senescent cells within tissues. The accumulation involves mechanisms which increase cellular senescence as well as those inhibiting the clearance of senescent cells from tissues. It is known that a persistent inflammatory state evokes a compensatory immunosuppression which inhibits pro-inflammatory processes by impairing the functions of effector immune cells, e.g., macrophages, T cells and natural killer (NK) cells. Unfortunately, these cells are indispensable for immune surveillance and the subsequent clearance of senescent cells, i.e., the inflammation-induced countering immunosuppression prevents the cleansing of host tissues. Moreover, senescent cells can also repress their own clearance by expressing inhibitors of immune surveillance and releasing the ligands of NKG2D receptors which impair their surveillance by NK and cytotoxic CD8+ T cells. It seems that cellular senescence and immunosuppression establish a feed-forward process which promotes the aging process and age-related diseases. I will examine in detail the immunosuppressive mechanisms which impair the surveillance and clearance of pro-inflammatory senescent cells with aging. In addition, I will discuss several therapeutic strategies which could potentially halt the degenerative feed-forward circuit associated with the aging process and age-related diseases.

1. Introduction

The primary cause of aging is still a mystery although it is known that the number of senescent cells increases in tissues and there exists a chronic low-grade inflammation, commonly called the inflammaging state (Franceschi et al., 2000; Fulop et al., 2018a). Interestingly, senescent cells express a pro-inflammatory phenotype which might induce the remodelling of the immune system occurring during the aging process. Currently it is not known whether cellular senescence is the only source of the age-related inflammation since many cellular stresses, unrelated to cellular senescence, can also trigger the secretion of pro-inflammatory mediators, e.g., endoplasmic reticulum (ER) stress (Zhang and Kaufman, 2008), oxidative stress (Forrester et al., 2018), and hypoxic exposure (Imtiyaz and Simon, 2010). It is evident that persistent inflammation induces counteracting anti-inflammatory responses with many immunosuppressive activities, also occurring in the aging process (Franceschi et al., 2007, Mincuillo et al., 2016; Fulop et al., 2018a; Salminen, 2020). The aging process is associated with an increase in the levels of myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg), and anti-inflammatory M2 macrophages (Mreg/M2c) in both the circulation and the tissues (Section 5). Immunosuppressive cells inhibit the functions of effector immune cells, e.g., T cells, natural killer (NK) cells, and macrophages. A decline in the function of immune system with aging also impairs the surveillance of senescent cells by NK cells and CD8+ T cells, the two major immune cells involved in the surveillance process (Fig. 1) (Section 6). This decline in the clearance of senescent cells leads to an accumulation of pro-inflammatory senescent cells and thus further augments the counteracting anti-inflammatory/immunosuppressive responses in aging tissues. It seems that there exists a feed-forward regulation between cellular senescence and immunosuppression with aging (Fig. 2). I will examine in detail the immunosuppressive mechanisms which impair the surveillance and clearance of senescent cells, thus permitting the accumulation of pro-inflammatory senescent cells within tissues. Moreover, I will discuss several therapeutic strategies which could potentially halt the feed-forward process and thus prevent the accumulation of senescent cells within tissues during aging and age-related diseases.
2. Cellular senescence is a hallmark of the aging process

Cellular senescence represents a cellular state characterized by the irreversible arrest of the cell cycle accompanied by many morphological and functional changes which distinguish it from reversible quiescence and terminal cell differentiation. The hallmarks of cellular senescence have been extensively discussed and reviewed elsewhere (Campisi, 2005; Kuilman et al., 2010; Sikora et al., 2013; Hernandez-Segura et al., 2018). Briefly, diverse cellular stresses, e.g., DNA damage and mitochondrial dysfunctions, induce the activation of distinct tumor suppressor pathways, such as p53 and p16INK4a, which inhibit the proliferation of cells. Several oncogenes, e.g., the activation of H-RAS and the deletion of Phosphatase and tensin homolog (PTEN), can provoke the onco- gene-induced senescence (OIS), probably in an attempt to suppress tumor growth. However, OIS can also promote tumorigenesis through its inflammatory phenotype (Coppe et al., 2010). Epigenetic mechanisms are believed to be involved in the regulation of cellular senescence, e.g., in the activation of the p16INK4A/ARF locus (Agherbi et al., 2009). Telomere shortening is a well-known hallmark of cellular senescence (Bonafe et al., 2020). Moreover, there are clear changes in the chromatrin structure, e.g., the formation of senescence-associated heterochromatin foci (SAHF). In cell culture, senescent cells display a flat, enlarged, and vacuolized morphology. There are also significant changes in the functions of senescent cells, e.g., in their autophagic activity (Tai et al., 2017), mitochondrial integrity (Chapman et al., 2019), and their responses to ER stress (Kim et al., 2019). Currently, it is not known whether these changes represent the causes or consequences of the senescent state. However, senescent cells display a pro-inflammatory phenotype, called the senescence-associated secretory phenotype (SASP), which is a common characteristic of senescent cells (Section 3). Single cell analyses of senescent cells have revealed that there exists significant cell-to-cell variability among senescent cells, not only between differently induced senescent cells but also among the cell population exposed to the same treatment (Hernandez-Segura et al., 2017; Wiley et al., 2017).

Cellular senescence is one of the hallmarks of the aging process and there are observations indicating that senescent cells gradually accumulate into tissues during the aging process (Dimri et al., 1995; Krishnamurthy et al., 2004; Wang et al., 2009; Biran et al., 2017). It seems that the accumulation of senescent cells enhances both the aging process and age-related diseases. Interestingly, there are observations that senescent cells can induce a paracrine senescence in neighbouring cells (Nelson et al., 2012; da Silva et al., 2019). The mechanisms underpinning bystander senescence still need to be clarified. Mensa et al. (2020) demonstrated that senescent human endothelial cells (HUVEC) secreted small extracellular vesicles, commonly called exosomes, which evoked the characteristics of cellular senescence in the recipient, normal HUVEC cells. They revealed that these exosomes contained several pro-senescence signals, e.g., miR-21 and miR-217, which controlled the DNA methylation and cell proliferation of recipient cells. Terlecki-Zaiewicz et al. (2018) reported that senescent human dermal fibroblasts secreted exosomes with various miRNAs, e.g., miR-23a and miR-137, which targeted mRNAs of pro-apoptotic proteins, thus reducing the apoptotic activity of the recipient cells. In fact, resistance to apoptosis is a common property of senescent cells (Salminen et al., 2011b). In addition to exosomes, there are several other mechanisms which can expand the senescence in aging tissues. For instance, Acosta et al. (2013) demonstrated that the SASP components, especially the members of TGF-β family, inducible the paracrine senescence both in cultured human fibroblasts and in mouse models of OIS in vivo. Especially, the activation of inflammasomes and the secretion of IL-1α induced the paracrine transmission of cellular senescence. Given that the pro-inflammatory SASP compounds can induce a counteracting immunosuppression (Section 4), it seems that TGF-β and other immunosuppressive factors have a key role in the expansion of senescence in tissues. For instance, it is known that TGF-β stimulates the expression of cyclin-dependent kinase inhibitors, e.g., p16INK4a and p21/WAF1, which consequently evoke cellular senescence (Tominaga and Suzuki, 2019).
3. Inflammatory phenotype of senescent cells

Abnormal senescent cells pose a threat to the homeostasis of aging tissues and probably for that reason, they adopt an inflammatory SASP state to alert the immune system to eliminate these cells from tissues. The secretome of senescent cells contains several pro-inflammatory factors, such as interleukines, chemokines, and colony-stimulating factors, as well as many growth factors and matrix metalloproteinases. The secreted components have been described in detail in the original reports (Kuilman et al., 2008; Rodier et al., 2009; Acosta et al., 2013; Wiley et al., 2016) and reviewed elsewhere (Coppe et al., 2010; Freund et al., 2010; Lasry and Ben-Neriah, 2015). Interestingly, the secretion profiles seem to be significantly dependent to the stress stimuli and the cell types involved. For instance, the so-called mitochondrial dysfunction-associated senescence (MiDAS) displays the SASP with a failure to secrete interleukins of the IL-1 family (Wiley et al., 2016). The ports (Kuilman et al., 2008; Rodier et al., 2009; Acosta et al., 2013; tors, as well as many growth factors and matrix metalloproteinases. The tissues and probably for that reason, they adopt an inflammatory SASP phenotype.

3. Inflammatory phenotype of senescent cells

3.1. Inflammatory SASP

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p53 through the activation of AMPK. It is known that p53 suppresses the secretion of both IL-1α and IL-1β cytokines via the activation of inflammasomes (Wiggins et al., 2019). In contrast, Coppe et al. (2011) revealed that the ectopic expression of p16INK4a and p21WAF1 evoked the senescent phenotype but not the SASP response in human fibroblasts which indicates that the growth arrest itself did not induce the inflammatory SASP. The pro-inflammatory responses of SASP are mainly regulated by NF-κB signaling in co-operation with C/EBPβ (Cappello et al., 2009; Freund et al., 2010; Salminen et al., 2012). It is likely that the accumulation of senescent cells within tissues with aging is the primary source of inflammmating which enhances the remodelling of the immune system with aging (Section 5). Interestingly, colony-stimulating factors (CSF) and chemokines (CCL and CXCL subfamilies) are abundant components in the secretomes of senescent cells (Freund et al., 2010; Acosta et al., 2013; Lasry and Ben-Neriah, 2015). It seems that the inflammatory components of the SASP secretome can affect the hematopoietic stem cells in bone marrow and recruit immune cells into aging tissues. For instance, GM-CSF, MCP-1/CCL2, MCP-2/CCL8, MIP-1α/CCL3, GROα/CXCL1, GROβ/CXCL2, and GROγ/CXCL3 have been strongly (over 4-fold) upregulated in the secretomes of different senescence models (Freund et al., 2010). GM-CSF is a driver of chronic inflammation activating myeloid cells (Becher et al., 2016). GM-CSF also stimulates immunosuppression by promoting the expansion and differentiation of MDSCs (Park et al., 2019) and Tregs (Hotta et al., 2019). There are also observations that GM-CSF can enhance myelopoiesis and establish trained immunity (Mitroulis et al., 2018) which controls the responses of myeloid cells with aging. Accordingly, chemokines are chemoaatractants for myeloid cells and lymphocytes, triggering their infiltration into inflamed tissues. Chemokines are also able to modulate immune surveillance in tissues, e.g., in the tumor microenvironment (Vigilme and Richmond, 2019). Chemokines exert specific responses to different immune cells through the diverse set of chemokine receptors. For instance, chemokines can promote acute inflammation and enhance cellular surveillance by activating NK cells (Zang et al., 2019), whereas in chronic inflammatory conditions, chemokines recruit immunosuppressive cells and induce their expansion (Hotta et al., 2019; Park et al., 2019), thus reducing the activity of effector immune cells. CCL2 and CXCL2, the two chemokines most extensively secreted by senescent cells (see above), are important agents since they direct the chemotaxis and expansion of Tregs and MDSCs (Katoh et al., 2013; Chang et al., 2016). It seems that senescent cells are able to trigger acute inflammatory responses but subsequently they induce a counteracting immunosuppressive state (Fig. 2), as observed in the aging process (Section 5).

4. Inflammatory mediators evoke compensatory immunosuppression

The acute inflammation-induced compensatory immunosuppressive state has been commonly studied in pathogen-induced sepsis, traumatic injuries, and autoimmune diseases. Systemic inflammatory responses are associated with the compensatory anti-inflammatory response syndrome (CARS) (Gentile et al., 2012; Hazeldine et al., 2015), more recently called the persistent inflammation, immunosuppression and catabolism syndrome (PICS) (Mira et al., 2017). In general, the CARS state overlaps with pro-inflammatory response but it persists much longer than the pro-inflammatory phase, even in situations when the inflammation may have been resolved. The common characteristics of the compensatory anti-inflammatory state involve (i) the induction of myeloid-biased emergency myelopoiesis, (ii) the expansion and activation of immunosuppressive cells, e.g., MDSCs, Tregs, and M2 macrophages, and (iii) the increased expression of anti-inflammatory cytokines TGFB, and IL-10 (Brudecki et al., 2012; Gentile et al., 2012; Mira et al., 2017). There are studies indicating that the CCL2 chemokine is a potent trigger of the immunosuppressive CARS state, e.g., in mouse pancreatitis (Takahashi et al., 2006), and it can impair mouse antibacterial resistance (Tsuda et al., 2004). CCL2 possesses many immunomodulatory properties beyond chemotaxis, i.e., it enhances the polarization of macrophages to the anti-inflammatory M2 phenotype and it also stimulates the expansion of MDSCs and Tregs (Gschwandtner et al., 2019). However, it is not only systemic inflammatory disorders but also local persistent inflammatory conditions, such as the environment in tumor sites, which can induce the immunosuppressive state countering pro-inflammatory responses (Kanerman et al., 2012; Wang and DuBois, 2015; Amadio et al., 2019). Interestingly, the inflamming process is also associated with anti-inflammatory responses, e.g., it increases the levels of anti-inflammatory cytokines (Franceschi et al., 2007; Mincillo et al., 2016). Given that the perpetra-dor cannot be resolved, pro-inflammatory and compensatory immunosuppressive responses seem to overlap in the aging process, as appears also to be the situation in autoimmune diseases.

Chronic inflammation, such as in inflammingaging, affects the hematopoietic system inducing the myeloid-biased shift towards myelopoiesis (Pang et al., 2011). Inflammatory factors, e.g., CSFs and interferons, regulate the expansion of the myelocyte lineage and can trigger the formation of MDSCs from the myelopoietic pathway (Millrud et al., 2017). MDSCs are immature myeloid cells which are able to evoke the differentiation of immunosuppressive Tregs from effector T cells (Huang et al., 2006). Immunomodulatory mediators not only recruit pro-inflammatory cells but also immunosuppressive MDSCs and Tregs into inflamed tissues. The remarkable plasticity of immune cells makes possible the modification of their phenotypes and properties according to the requirements of their microenvironments, a process called immune education (Gabrilovich et al., 2012; Fang et al., 2018). Immunosuppressive cells establish a co-operative network which prevents the cellular injuries caused by acute inflammation. The immunosuppressive phenotypes of immune cells are commonly called regulatory subtypes, i.e., the regulatory T cells (Treg), B cells (Breg), DC cells (DCreg), NK cells (NKreg), NKT cells (type II NKT), and macrophages (M2 phenotype, also called Mreg). I have recently reviewed the properties of these subtypes and described how there is an activation of an immunosuppressive network in the aging process (Salminen, 2020). It seems that cellular senescence is a driver of the inflammingaging process which evokes the compensatory immunosuppression and thus it enhances the remodelling of immune system with aging (Fig. 2). For instance, immunosuppressive cells reduce the activity of effector T cells, NK cells, and dendritic cells (Trzonkowski et al., 2006; Pedroza-Pacheco et al., 2013; Wang and DuBois, 2015), which further impairs the immunosurveillance of senescent cells.
5. Immunosuppression increases with aging

There are two simultaneous age-related immune processes, i.e. inflamming and immunosenescence, which reflect the age-related remodelling of the immune system (Fulop et al., 2018a). Moreover, there is convincing evidence that the presence of immunosuppressive cells increases with aging which indicates that the inflamming process activates the immunosuppressive network (Salminen, 2020). For instance, with aging, the numbers of MDSCs increase in the circulation of humans (Verschoor et al., 2013) and mice (Eniontina et al., 2011). There exists a significant age-related accumulation of MDSCs in mouse bone marrow, spleen, and lymph nodes (Grizzle et al., 2007; Eniontina et al., 2011; Flores et al., 2017). The immunosuppressive activity of MDSCs also increases with aging in mouse bone marrow and spleen. Accordingly, there is a significant increase in the numbers of Tregs in the circulation with aging, both in humans and mice (Gregg et al., 2005; Sharma et al., 2006; Jagger et al., 2014). In addition, the occurrence of Tregs increases with aging in mouse skin (Agius et al., 2009) and adipose tissue (Kalathokounkel Antony et al., 2018). Interestingly, Ruhland et al. (2016) demonstrated that the senescent stromal cells in mouse skin induced a local inflammation which recruited immunosuppressive MDSCs and Tregs into senescent skin. Biochemical assays have revealed that senescent skin contained an increased level of pro-inflammatory factors, e.g., IL-6, CCL2, CXCL1, and GM-CSF, as well as immunosuppressive markers IL-10, TGF-β, and Arginine 1 (Arg1). Ruhland et al. (2016) also reported that the skin of elderly humans had elevated levels of senescent, INK4a-positive cells and immunosuppressive MDSCs as compared to those of younger donors. Many studies have also revealed a significant age-related increase in the numbers of M2 macrophages in several tissues, e.g., mouse bone marrow, spleen, lungs, and skeletal muscles (Jackaman et al., 2013; Wang et al., 2015a). For instance, Jackaman et al. (2013) demonstrated that the M2 macrophages from geriatric mice displayed robust immunosuppressive activity by secreting an increased level of TGF-β and IL-10 cytokines in comparison with their young counterparts.

There is substantial evidence that a decline in the function of immune system with aging impairs the immunosurveillance and clearance of aberrant cells, e.g., cancer cells and senescent cells (Ovadya et al., 2018; Perez-Lanzon et al., 2019; Tarazona et al., 2020). There are significant changes in the phenotypes of NK and CD8+ T cells with aging which might disturb the surveillance of cancer cells and infections in elderly patients (Nikolich-Zugich et al., 2012; Tarazona et al., 2020). For instance, Tarazona et al. (2020) have detailed the major changes in NK cells, i.e., (i) decreased percentage of the CD56bright cell subset, (ii) decline of activating receptors in the CD56dim NK subtype, (iii) down-regulation in cytokine production, and (iv) reduced activity in terms of cytotoxicity. The age-related alterations in the cytotoxic CD8+ T cell population include a decrease in proliferation capacity, a reduced recruitment and recognition ability, and a decline in target cell lysis (Nikolich-Zugich et al., 2012). The mechanisms underpinning these age-related changes are currently unknown although we have pointed out that immunosenescence and the MDSC-driven immunosuppression generate very similar changes in the phenotypes of NK and T cells (Salminen et al., 2019a). This will be discussed more thoroughly in Section 6.2.

6. Immunosuppression impairs the clearance of senescent cells

Immune surveillance has a crucial role in the maintenance of tissue homeostasis since distinct immune cells can recognize and eliminate foreign pathogens, transformed cancer cells, and unhealthy host cells (Jannello and Raulet, 2013; Semovilla et al., 2013). There is convincing evidence that the immune system can also evoke the clearance of senescent cells (Sagiv and Krizhanovsky, 2013; Burton and Stolzing, 2018). NK cells and cytotoxic CD8+ T cells are the major surveying immune cells but also γδ T cells, invariant NKT cells, and tissue-resident innate lymphoid cells (ILC) can sense and induce the elimination of unhealthy cells (Lo Presti et al., 2018; Stamatiadis and Li, 2019; Diaz-Basabe et al., 2020). However, studies on tumors and inflammatory diseases have revealed that immunosuppression can inhibit the function of those immune cells driving immune surveillance, e.g., NK cells and CD8+ T cells (Section 6.2). There are interesting observations indicating that both the MDSC-driven immunosuppression and immunosenescence evoke very similar declines in the functions of NK cells and CD8+ T cells, i.e., they decrease the responses of these cells to cytokines and reduce their cytotoxic activity (Jergovic et al., 2018; Salminen et al., 2019a). Moreover, senescent cells can repress their own immune surveillance which increases their accumulation and can even promote tumorigenesis (Egger et al., 2016; Ruhland et al., 2016). Egger et al. (2016) reported that oncogene-induced senescent hepatocytes recruited CCR2-positive myeloid cells into mouse liver by secreting the CCL2 chemokine. They observed that immunosuppressive myeloid cells inhibited the activity of NK cells in both mouse and human peritumoral tissues. These studies indicate that immunosuppressive cells can prevent the clearance of senescent cells and induce their accumulation within aged tissues.

6.1. Immune surveillance of senescent cells by NK and CD8+ T cells

There is substantial evidence that NK and CD8+ T cells have a major role in the immune surveillance of tumor cells (Ostroumov et al., 2018; Meza Guzman et al., 2020). Several other immune cells are also involved in the control of their cytotoxic activity and contribute to the clearance process. In their seminal study, Sagiv et al. (2013) demonstrated that NK cells were able to target and induce the death of senescent human fibroblasts. The killing of senescent cells required the exocytosis of perforin, a pore forming cytolytic protein present in the granules of NK and CD8+ T cells. Perforin is located in the granules which contain granzymes, i.e. serine proteinases which induce the apoptosis of target cells. It is known that NK and CD8+ T cells utilize the perforin/granzyme mechanism to kill transformed cancer cells (Cullen et al., 2010). Sagiv et al. (2013) also reported that the signaling of Fasl and TRAIL, the death receptors, was not required in the targeting of senescent human fibroblasts by NK cells. Subsequently, Ovadya et al. (2018) demonstrated that the impaired immune surveillance increased the accumulation of senescent cells within several tissues in the knockout mice of perforin (Prf1−/−) gene. They also observed that a perforin deficiency augmented chronic inflammation with aging and promoted the age-related disorders. The critical role of NK and CD8+ T cells in the immune clearance of senescent cells has been confirmed in several studies (Sagiv et al., 2016; Pereira et al., 2019). Immune surveillance of senescent cells and the contribution of other immune cells to the subsequent apoptosis and clearance processes have been described in several review articles (Sagiv and Krizhanovsky, 2013; Burton and Stolzing, 2018; Antonangeli et al., 2019; Kale et al., 2020).

6.2. Immunosuppressive cells impair the function of NK and CD8+ T cells

The development of an immunosuppressive microenvironment into tumors prevents the clearance of transformed cancer cells (Umansky et al., 2017). The surveillance process by NK and CD8+ T cells has been impaired by the infiltration and expansion of immunosuppressive cells, e.g. MDSCs, Tregs, and tumor-associated macrophages (TAM). Chronic inflammation is an important inducer of an immunosuppressive state in the growth of tumors. There is extensive evidence that both MDSCs and Tregs inhibit the functions of NK and CD8+ T cells by impairing their surveillance capacity and cytotoxic activity (Ghiringhelli et al., 2006; Trzonkowski et al., 2006; Hoechst et al., 2009). Cytokines have a key role in the control of phenotypes and functions of NK cells (Wu et al., 2017). For instance, anti-inflammatory cytokines, e.g., IL-10 and TGF-β, suppress the cytotoxic activity of NK and CD8+ T cells (Scott et al., 2006; Crane et al., 2010; Littwitz-Salomon et al., 2018) (Fig. 1). Moreover,
immunosuppressive cells can convert NK cells into the NKreg phenotype which display distinct immunosuppressive properties (Zhang et al., 2006; Michel et al., 2016). The CD56\textsuperscript{High} phenotype represents the NKRg subtype, whereas CD56\textsuperscript{dim} cells act as cytotoxic cells, robustly expressing perforin and granzymes. Accordingly, NKRg cells are able to suppress the antigen-specific responses of CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells (Deniz et al., 2008; Ehlers et al., 2012). In tumors, NK cells can even be converted to MDCSs (Park et al., 2013) or ILC-1 cells (Gao et al., 2017). These observations indicate that NK cells possess substantial plasticity and thus can regulate inflammatory processes by controlling immune surveillance and cytotoxicity.

The pool of NK cells in the body contains heterogenous subtypes with different cell surface receptors and functional properties (Freud et al., 2017). In addition, there are significant differences between the conventional NK cells of the spleen and circulation compared to the tissue-resident NK cells (Melsen et al., 2016; Peng and Tian, 2017). Normally, CD56\textsuperscript{dim} cells are more frequent in circulation, whereas tissue-resident NK cells display the CD56\textsuperscript{Bright} phenotype. However, pathological microenvironments exert major effects on the phenotype of NK subsets, e.g., those cells involved in chronic inflammation (Paris et al., 2017). In fact, cellular stress activates NK cells (Chan et al., 2014) and subsequently NK cells function as the sensors of stressed cells, especially via their NKG2D receptors (Lopez-Larrea et al., 2009) (Section 6.3). There is an extensive literature on the effects of the aging process on the phenotypes of NK cells, mostly involving changes in the receptor repertoire (Almeida-Oliveira et al., 2011; Solana et al., 2012; Hazeldine and Lord, 2013). However, these studies have not investigated changes occurring in the tissue-resident NK cells of peripheral tissues since all experiments are mostly focused on the blood and rarely on the spleen. In brief, it seems that the functional capacities of circulating NK cells (Solana et al., 2012; Hazeldine and Lord, 2013) as well as those of CD8\textsuperscript{−} T cells (Jergovic et al., 2018) decline with aging in both humans and mice. Nair et al. (2015) reported that the age-related defects in mouse NK cells (Fernandez-Sanchez et al., 2013). Moreover, the exposure of TGF-β impaired the function of NKG2D receptors and the cytokine secretion of NK cells by down-regulating the expression of DAP10 (Lee et al., 2011; Regis et al., 2020). In addition, the endocytosis and trafficking of NKG2D receptors can also control cytotoxicity, e.g., by inducing a hypo-responsive state in NK cells (Molfetta et al., 2017).

Human NKG2D ligands consist of two MHC class I polypeptide-related sequence A (MICA) and B (MICB) proteins as well as six functional UL16-binding proteins 1–6 (ULBP1–6) (Rautel et al., 2013). The expression of NKG2D ligands is induced by common stress-related transcription factors, e.g., NF-κB, p53, and HSF1 (Cerboni et al., 2007; Lin et al., 2012; Rautel et al., 2013). In fact, the expression of NKG2D ligands and their presence at the cell surface have been regulated at multiple levels including microRNA and posttranslational mechanisms (Elias and Mandelboim, 2012; Zingoni et al., 2018). The clearance of stressed cells via the NKG2D/NKG2D ligand pathway is a double-edged mechanism since many abnormal cells, such as transformed and infected cells, can escape apoptotic cleansing by releasing NKG2D ligands from their cell surfaces (Fig. 1). There are two ways to dispose NKG2D ligand proteins; one is the proteolytic shedding of NKG2D ligands (Chitadze et al., 2013) and another is the packaging of NKG2D ligands into exosomal vesicles (Soriani et al., 2020). Both secretory pathways establish an immunosuppressive state which permits the immune evasion by the abnormal cells instead of their clearance by apoptosis. The disintegrin and metalloproteases (ADAM), especially ADAM10 and ADAM17, are the major sheddases of NKG2D ligands (Zingoni et al., 2020). For instance, the genotoxic stress-induced senescence of myeloma cells promoted the ADAM10-dependent release of soluble MICB ligands (Zingoni et al., 2015). Moreover, it was demonstrated that matrix metalloproteinasises (MMP), especially MMP-9, are potent sheddases of NKG2D ligands from cancer cells (Shiraiishi et al., 2016). It is known that a long-term exposure to soluble NKG2D ligands down-regulates the expression NKG2D receptors and the cytotoxicity of NK and CD8\textsuperscript{+} T cells (Song et al., 2006; Cerboni et al., 2009).

Soluble NKG2D ligands not only have immunosuppressive effects on NK and CD8\textsuperscript{+} T cells but these ligands can also stimulate immunosuppressive cells in stressed or senescent tissues (Fig. 1). Xiao et al. (2015) demonstrated that soluble MIC ligands promoted the expansion of MDCSs and skewed macrophages towards the immunosuppressive M2 phenotype. For instance, they reported that the intraperitoneal injection of soluble MICB proteins provided the accumulation of MDCSs and M2 macrophages into mouse peritoneal fluid. They also revealed that soluble MICB protein induced the expansion and activation of mouse MDCSs in vitro conditions. The stimulation was dependent on the activation of NKG2D receptors and the signaling via STAT3, the crucial inducer of MDCS function. The STAT3 activation by soluble MICB also shifted macrophages towards the M2 phenotype. Accordingly, Zhang et al. (2019) reported that the treatment with the antibody targeted to soluble MIC induced the enrichment of antigen-specific CD8\textsuperscript{+} T cells in a
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mouse MIC-positive tumor model. The antibody exposure allowed tumors to respond to the Programmed cell death protein 1 (PD1)/PD-ligand 1 (PD-L1) blockade therapy. It seems that it is not only the soluble ligands but also the surface-bound ligands can activate MDSCs. Qian et al. (2017) reported that the membrane-bound RAE1e protein (NKG2D ligand of mouse) was able to induce a robust expansion of MDSCs, both in mouse spleen and blood. MDSCs displayed a significant increase in their immunosuppressive activity, e.g., the expression of ARG1 and the secretion of IL-4 and IL-10 cytokines. They also revealed that RAE1e ligands induced the expansion of MDSCs through the NKG2D signaling. These observations indicate that the increased expression of NKG2D ligands, either soluble or intact, can promote immunosuppression and prevent the NKG2D-dependent surveillance and clearance (Fig. 1).

6.4. NKG2D triggers the clearance of senescent cells

In 2016, Sagiv et al. demonstrated that the expression of NKG2D ligands, especially MICA and ULBP2, was robustly upregulated in the senescent cells induced by different treatments of several cultured cell types. They also confirmed that the increase in the level of NKG2D ligands was located on the surface of senescent cells. The upregulation of NKG2D ligands was present only in senescent cells but not in quiescent cells. Next, they revealed that NK cells evoked the cytotoxicity of senescent cells via the activation of NKG2D receptors, as observed in tumor and infected cells (Section 6.3). The MEK/ERK signaling pathway induced the upregulation of MICA and ULBP2 in the senescent cells provoked by DNA-damage. Given that the common components of SASP, e.g., IL-6, IL-8, CXCL1, and CCL2, were also increased which indicated that the induction of NKG2D ligands was involved in the senescence program. Soriani et al. (2009) demonstrated that doxorubicin and melphalan, the therapeutic drugs of human multiple myeloma (MM), induced significant increase in the expression of NKG2D ligands, MICA and MICB, in the drug-induced senescent MM cells. Accordingly, the upregulation of MICA and MICB expression in senescent MM cells provoked the degranulation of NK cells indicating that the NKG2D/NKG2D ligand system controls the immunosurveillance and clearance of human senescent cancer cells. Munoz et al. (2019) demonstrated that an increase in the expression of MICA/B and ULBP1–3 after genotoxic stress was independent of the expression of p53 and p16, the markers of cell-cycle arrest, in human fibroblasts. They also reported that the genotoxic chemotherapy significantly increased the expression of MICA ligands in several tumors. Sagiv et al. (2016) also demonstrated that the NKG2D receptor-ligand interactions in vivo induced the elimination of senescent hepatic stellate cells in mouse fibrotic liver, thus reducing the level of hepatic fibrosis. These studies indicate that the ligands of NKG2D, i.e., “kill me” signals, have a key role in the clearance of senescent cells. Thus, the expression of NKG2D ligands can be exploited in the clearance of injured/degenerating cells. For instance, Davies et al. (2019) demonstrated that a crush injury of mouse peripheral nerves upregulated the infiltration of NK cells and the expression of RAE1 ligand in the injured sensory axons. Consequently, the damaged parts of sensory axons were removed due to the activation of NKG2D-dependent cytotoxicity. This elimination process might have a crucial role in Wallerian degeneration, thus maintaining the homeostasis of neuronal networks. The clearance process itself involving the phagocytosis of apoptotic bodies is known to be carried out mostly by monocytes/macrophages and neutrophils.

6.5. Immunosuppression impairs the NKG2D-mediated clearance of senescent cells

Given that senescent cells display a robust expression of NKG2D ligands, the progressive accumulation of senescent cells within tissues with aging indicates that the surveillance potential of NK and CD8+ T cells does decline with aging. There are several age-related potential mechanisms which are able to impair the cytotoxicity of NK and CD8+ T cells based on the recognition system of the NKG2D/NKG2D ligand axis (Fig. 1). A chronic increase in the number of senescent cells with the augmented level of NKG2D ligands might induce the down-regulation of NKG2D receptors, especially at the cell surfaces of surveying cells, as discussed above (Section 6.3). Moreover, an increased amount of soluble NKG2D ligands could modify the tolerance of NKG2D receptors to NKG2D ligands. Munoz et al. (2019) reported that senescent human fibroblasts and epithelial cells secreted MICA ligands into cell cultures. Accordingly, the long-term culture of senescent cells with peripheral blood mononuclear cells (PBMC), including the surveying cells, significantly increased the amount of soluble NKG2D ligands in the medium, whereas the level of NKG2D ligands on the cell-surface was markedly reduced. This indicates that senescent cells were able to prevent immune surveillance by shedding NKG2D ligands from their cell surfaces, although the total level of cellular expression was not decreased. They also revealed that senescent cells robustly expressed several members of MMPs and accordingly, the inhibition of MMPs restored the clearance of senescent cells in co-culture with PBMCs. These observations indicate that senescent cells can evade the surveillance and subsequently prevent their clearance by shedding the NKG2D ligands from their cell surfaces. It is known that MMPs have a crucial role in the remodelling of extracellular matrix (ECM) with aging (Freitas-Rodriguez et al., 2017) but simultaneously, they might prevent the immunosurveillance of senescent cells and augment the accumulation of senescent cells within tissues.

Senescent cells possess another route to release NKG2D ligands, i.e., the secretion in exosomal vesicles. It is known that cellular senescence robustly increases the secretion of extracellular vesicles from several cell types, e.g. dermal fibroblasts (Terlecki-Zaniewicz et al., 2018) and endothelial cells (Mensa et al., 2020). Fernandez-Messina et al. (2010) reported that there was a difference between NKG2D ligands depending on whether they were secreted through the cleavage by MMPs or in exosomal vesicles, i.e., ULBP2 was cleaved by MMPs, whereas ULBP3 was released in exosomes from CHO cells. Moreover, exosomal ULBP3 induced a more potent down-regulation of NKG2D receptors in NK cells than was seen with soluble ULBP2 ligands. It is known that the tumor-derived exosomal NKG2D ligands have a crucial role in the down-regulation of NKG2D receptors in both NK and CD8+ T cells, thus enhancing the immune evasion of cancer cells (Lundholm et al., 2014; Vulpis et al., 2019). In addition to NKG2D ligands, exosomal vesicles contain several other components, e.g., miRNAs, enzymes, and cytoxins, which augment the immunosuppressive state not only by inhibiting NK, dendritic, and effector T cells but by inducing the expansion of immunosuppressive MDSCs, Tregs, and Bregs as well as enhancing the polarization of macrophages towards the M2 phenotype (Whiteside, 2016). Interestingly, there are several studies indicating that the exosomal TGF-β cytokines, both soluble and membrane-bound forms, can induce the down-regulation of NKG2D receptors and impair the cytotoxicity of NK cells (Clayton et al., 2008; Berchem et al., 2015; Lazarova and Steinle, 2019). It is most probable that distinct exosomal miRNAs secreted by senescent cells can target the mRNAs controlling the NKG2D recognition and perforin/granzyme exocytosis, although currently the nature of these miRNAs needs to be clarified.

NK cells exploit both activating and inhibitory receptors and co-stimulatory proteins in their immune surveillance and cytotoxic functions (Chester et al., 2015). Pereira et al. (2019) demonstrated that senescent human dermal fibroblasts expressed an increased level of HLA-E protein, a non-classical MHC class 1b molecule, which interacted with the inhibitory NKG2A receptor of NK and CD8+ T cells. The interaction of HLA-E and NKG2A proteins inhibited the immune surveillance of senescent fibroblasts and prevented their clearance. The expression of HLA-E protein was induced by p38 signaling which stimulated the expression of some pro-inflammatory cytokines, e.g., IL-6 and IL-8. Pereira et al. (2019) also revealed that NK and CD8+ T cells targeted senescent cells by promoting the NKG2D/MICA/B interaction which induced the clearance of senescent cells. However, the binding HLA-E
protein with the inhibitory NKG2A receptor prevented the NKG2D-mediated apoptotic death of senescent fibroblasts under \textit{in vitro} conditions. Subsequently, they observed that the expression of HLA-E protein was robustly increased in the skin of old healthy donors and was co-localized with the markers of cellular senescence. These results indicate that an increased expression of HLA-E protein in senescent cells might prevent their clearance and thus promote their accumulation into aging tissues (Fig. 1). In addition to the HLA-E protein, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) can also inhibit the NKG2D-mediated cytolytic function of NK cells (Hosomi et al., 2013). Sappino et al. (2012) revealed that DNA-damage stimulated the expression of CEACAM1 protein through the activation of ATM/p53 signaling in human MCF cells. An upregulation of CEACAM1 protein was required for the p53-mediated cellular senescence of MCF cells. Hosomi et al. (2013) demonstrated that the increase in the expression of CEACAM1 in the IL-2-activated mouse and human NK cells inhibited the NKG2D-induced cytolysis of those cells expressing CEACAM1 protein (Fig. 1). Interestingly, Elsiefeldt et al. (2019) observed that the expression of CEACAM1 was significantly upregulated with aging in human thoracic artery and murine aorta. They demonstrated that the expression of CEACAM1 and TNF-α created a positive feed-forward loop which maintained a chronic pro-inflammatory microenvironment in the aging vasculature. The increased expression of CEACAM1 was associated with oxidative stress, fibrosis, and endothelial dysfunction. However, they did not report on whether the enhanced expression of CEACAM1 with aging was associated with the accumulation of senescent cells.

There is convincing evidence that certain immunosuppressive cells, e.g., MDSCs, Tregs, and M2 macrophages, inhibit the cytotoxicity of NK cells (Ghiranghelli et al., 2006; Li et al., 2009; Kmetta et al., 2017; Geng et al., 2019) (Fig. 1). It is known that the TGF-β secreted by immunosuppressive cells inhibits the expression of NKG2D receptors in NK and CD8$^+$ T cells and subsequently impairs their cytotoxic activity (Lee et al., 2004; Kopp et al., 2009; Crane et al., 2010; Lazarova and Steine, 2019). MDSCs and Tregs suppress the NKG2D-mediated cytotoxicity in a contact-dependent manner through the membrane-bound TGF-β1 cytokines (Ghiranghelli et al., 2006; Li et al., 2009; Lazarova and Steine, 2019). Moreover, kynurenine, a catabolite of IDO activation, inhibits the surface expression of NKG2D and the cytotoxic activity of human NK cells (Della Chiesa et al., 2006). TGF-β also reduces the secretion of IFN-γ from NK cells and suppresses their proliferation (Ghiranghelli et al., 2006). It seems that immunosuppressive cells inhibit the surveillance and cytotoxicity of NK cells which might have harmful effects in many pathological conditions (Section 6.6).

6.6. Immunosenesence impairs the clearance of senescent cells in age-related diseases

It is known that the number of senescent cells is increased in many age-related diseases, e.g., in Alzheimer’s disease (Bhat et al., 2012), age-dependent hepatic steatosis (Ogrodnik et al., 2017), cardiovascular diseases (Olivieri et al., 2013), and many cancers (Prieto and Baker, 2019). There is convincing evidence that the increase in cellular senescence and inflamaging can aggravate many age-related diseases (Franceschi and Campisi, 2014; Ovadya and Krizhanovsky, 2014; Fulp et al., 2018b). For instance, Ogrodnik et al. (2017) demonstrated that the hepatocyte-specific senescence induced age-dependent hepatic steatosis in mice. There existed a close correlation between the upregulation of senescence markers and the accumulation of fat into mouse liver. The senolytic clearance of senescent cells reduced the development of fatty liver disease. There is substantial evidence that several age-related diseases are associated with the expansion of immunosuppressive MDSCs, e.g., atherosclerosis (Wang et al., 2015b), hepatic steatosis (Yao et al., 2016), osteoporosis (Zhang et al., 2015), and type 2 diabetic nephropathy (Islam et al., 2020). Immunosenesence is a common hallmark of the age-related diseases including neurodegenerative, cardiovascular, and metabolic diseases (Costantini et al., 2018; Barbe-Tuana et al., 2020). Interestingly, the phenotypes of age-related senescent immune cells are reminiscent to those induced by immunosuppressive cells, such as by MDSCs (Salminen et al., 2019a). The senescent phenotype of human NK cells displays alterations in the subsets of NK cells as well as functional changes, e.g., reduction in cytotoxic activity and decrease in the production of cytokines and chemokines (Gayoso et al., 2011). Hazelidine et al. (2012) demonstrated that the aging did not affect the expression of NKG2D but significantly reduced the secretion of perforin which induced the age-related decline in the cytotoxicity of NK cells. This indicates that the immunosuppression-induced immunosenesence impairs the clearance of senescent cells thus aggravating the pathogenesis of age-related diseases.

7. Feed-forward regulation between cellular senescence and immunosuppression promotes the aging process

It seems that there exists a feed-forward regulation between cellular senescence and immunosuppression (Fig. 2). Cellular senescence promotes inflamaging, which consequently induces a counteracting immunosuppressive state involving the expansion of immunosuppressive cells within aging tissues. Subsequently, the immunosuppression impairs the clearance of senescent cells which further enhances the accumulation of senescent cells into aging tissues. This feed-forward circuit augments the appearance of a chronic inflammatory state and compensatory immunosuppression (Fig. 2). Currently, it is known that there are several inducers of cellular senescence, both endogenous and environmental insults, although the primary cause of cellular senescence in tissues with aging still needs to be revealed. The accumulation of senescent cells displaying SASP properties into aging tissues evokes the secretion of inflammatory mediators, e.g., colony-stimulating factors, cytokines, and chemokines, which stimulate myelopoiesis and subsequently evoke the recruitment of immune cells into the affected tissues. Immunosuppressive cells secrete reactive oxygen and nitrogen species (ROS/RNS) and anti-inflammatory cytokines, e.g., TGF-β, IL-4, and IL-10, which suppress the function of NK and CD8$^+$ T cells and thus inhibit the clearance of senescent cells. Senescent cells can also enhance their own accumulation within the aging tissues. The robust expression of cell-surface NKG2D ligands and their soluble cleavage products as well as the expression of surveillance inhibitors, e.g., HLA-E and CEACAM1, prevent the clearance of senescent cells by NK and CD8$^+$ T cells. These observations indicate that cellular senescence, inflamaging, and compensatory immunosuppression are partners in the feed-forward circuit which progressively promotes the aging process in tissues (Fig. 2).

Interestingly, this feed-forward circuit not only increases the numbers of senescent cells in aging tissues but the persistent occurrence of immunosuppressive cells also impairs tissue homeostasis and promotes tissue degeneration with aging (Salminen, 2021). For instance, some immunosuppressive cytokines, especially TGF-β, induce disturbances in the structures of the extracellular matrix (ECM), e.g., they increase the secretion of proteolytic enzymes and enhance fibrosis in many tissues (Kim et al., 2004; Meng et al., 2016). Moreover, senescent cells themselves can modify the structures of tissue ECM through their secretomes (Levi et al., 2020). Secreted proteinases, such as matrix metalloproteinases, collagenases, and elastases, produce many danger-associated molecular patterns from extracellular matrix (ECM-derived DAMP). For example, aggregan, biglycan, decorin as well as osteopontin- and elastin-derived peptides control innate immunity, i.e., they are able to induce inflammation and consequently enhance the aging process and age-related diseases (Shao et al., 2017; Prevert et al., 2018; Le Page et al., 2019). Shao et al. (2017) reported that osteopontin fragments stimulated the expansion of MDSCs. It is known that TGF-β1 signaling enhances cellular senescence but it can also aggravate the pathogenesis of many age-related diseases, e.g., muscle atrophy and...
cardiovascular diseases (Low et al., 2019; Tominaga and Suzuki, 2019). Moreover, IL-10 cytokine activates STAT3 signaling and in that way it enhances the function of certain immunosuppressive cells and augments the polarization of macrophages towards the immunosuppressive M2 phenotype after mouse myocardial infarction (Jung et al., 2017). STAT3 can also inhibit autophagy and thus disturb cellular homeostasis (You et al., 2015). The secretion of ROS/RNS compounds not only enhance immunosuppression in tissues but also exert a myriad of harmful effects during the aging process (Finkel and Holbrook, 2000). The expression of amino acid catabolizing enzymes ARGI and indoleamine 2,3-dioxygenase (IDO) is the third mechanism which immunosuppressive cells exploit to induce an immune suppressive state in tissues (Murray, 2016; Salminen, 2020). The increased expression of ARGI and IDO depletes L-arginine and tryptophan, respectively, from the tissue microenvironment and thus suppresses the proliferation of autotrophic effector immune cells. Consequently, the shortage of distinct amino acids impairs protein synthesis in the cells of host tissues. Moreover, L-arginine is also the substrate of nitric oxide synthase (NOS) enzymes (Rath et al., 2014) and thus a shortage of L-arginine impairs the generation of nitric oxide (NO) disturbing vascular homeostasis. Accordingly, the increased expression of IDO stimulates the kynurenine pathway producing a number of metabolites, e.g., kynurenine and quinolinic acid, which can exert a variety of pathological effects (Chen and Guillemin, 2009). It seems that the feed-forward circuit between cellular senescence and immunosuppression is not only able to promote the aging process but also aggravate age-related diseases.

8. Therapeutic prospects to halt the feed-forward process associated with aging

Given that senescent cells enhance the aging process in tissues, there are many research approaches to discover techniques to eliminate senescent cells from aging tissues, a process called senolysis (Childs et al., 2017; Ovadya and Krizhanovsky, 2018). It is not only the aging process but senolytic therapies might also alleviate many age-related diseases, e.g., cardiovascular diseases (Childs et al., 2018). In 2011, Baker et al., 2011 demonstrated that the genetic elimination of p16INK4a-positive cells prevented the appearance of several age-related disorders in the BubR1 progeroid mice. This proof-of-principle study revealed that the clearance of senescent cells could alleviate age-related sarcopenia and cataract as well as the loss of adiposity in the skin. Subsequently, Baker et al. (2016) reported that the elimination of senescent cells from wild-type mice extended the median lifespan of both males and females. The clearance of senescent cells delayed tumorigenesis and attenuated the age-related degeneration in heart, kidney, and adipose tissues. Currently there are many candidate drugs undergoing evaluation as senolytic therapies although these drugs do not specifically target senescent cells and they may have harmful off-target responses such as inducing inflammation and even atrophy in some tissues. For instance, Hickson et al. (2019) reported that the co-treatment with dasatinib and quercetin for three days significantly reduced the numbers of senescent cells in the adipose tissue and skin of patients with diabetic kidney disease. Dasatinib is a clinically-used drug in the treatment of chronic myeloid leukemia which could down-regulate the amount of Tregs, whereas the numbers of NK and CD8+ T cells as well the differentiation level of NK cells inversely correlated with the proportion of Tregs (Najima et al., 2018). Dasatinib also reduced the level of monocytic MDSCs in patients with chronic myeloid leukemia (Giallongo et al., 2018). These observations imply that the effect of dasatinib on senescent cells could be mediated through a reduction in immunosuppression which increased the surveillance and clearance capacity of NK and CD8+ T cells. However, dasatinib, a protein kinase inhibitor, has several harmful side-effects and thus it seems that this drug is a far from optimal choice for anti-aging therapy.

In the future, the elimination of senescent cells with aging may entail specific targeting and immune-mediated clearance of these cells. Currently, the genetically engineered immunotherapies exploiting the chimeric antigen receptor T cell (CAR-T) technique have been utilized for the specific targeting and removal of cancer cells under both in vitro and in vivo conditions. In particular, the NKG2D-based CAR-T cells have been exploited to eradicate cancer cells, e.g., glioblastoma cells in cultures and also in mice (Yang et al., 2019). Baumeister et al. (2019) observed that the autologous NKG2D-based CAR-T therapy was safe in humans and it increased the secretion of cytokines in a phase I trial of myeloid leukemia and multiple myeloma patients. Xiao et al. (2019) demonstrated that the NKG2D CAR-technology increased the cytolytic activity of NK cells against tumor cells in cell cultures. The NKG2D-modified NK cells also delayed the growth of injected colorectal cancer cells in mice. Moreover, the injection of NKG2D-CAR-NK cells reduced the growth of metastatic colon cancer in the liver of human patients. Parikh et al. (2019) demonstrated that a combination therapy where injected NKG2D-ζ-NK cells targeted and eliminated the MDSCs expressing NKG2D ligands improved the anti-tumor therapy of CAR-T cells in mouse model. Although the CAR-NK/T models could be used in anti-aging therapy against senescent cells, there are several major obstacles still to be overcome, i.e., senescent cells are scattered throughout different tissues and the aging process increases immunosuppression which reduces the efficacy of adoptive cell transfer therapies.

Instead of killing senescent cells, the concept of feed-forward regulation provides some novel insights into the therapeutic prevention of cellular senescence and the generation of immunosuppression into aged tissues. AMP-activated protein kinase (AMPK) controls several functions involved in the development of the senescent phenotype. For instance, the activation of AMPK inhibits mTOR signaling which suppresses autophagy (Jeon, 2016). Moreover, the activation of AMPK signaling inhibits NF-κB signaling (Salminen et al., 2011a) which is the major inducer of inflammatory responses through the activation of SAPS (Chien et al., 2011; Salminen et al., 2012). In addition, AMPK signaling suppresses the function of immunosuppressive MDSCs (Salminen et al., 2019b) which might attenuate the activation of the co-operative immunosuppressive network. There are many studies indicating that the activation of AMPK inhibits the cellular senescence and alleviates many inflammatory diseases (Han et al., 2016; Cheng et al., 2017; Zhan et al., 2018). Metformin, an antidiabetic AMPK activator, delayed endothelial senescence in both human aortic endothelial cells and in ApoE−/− mice (Karnewar et al., 2018). It has been reported that metformin can attenuate several hallmarks of aging and thus improve human healthspan and even lifespan (Kulkarni et al., 2020). Currently, there are several AMPK activators under development, more specific than metformin (Steinberg and Carling, 2019). Moreover, there are several drug discovery projects aiming to reduce immunosuppression and thus delay tumor growth. Interestingly, several phytochemical compounds acting through the activation of AMPK signaling or the inhibition of STAT3 and NF-κB signaling, are able to inhibit the immunosuppressive activity of MDSCs and subsequently relieve immunosuppression both in growing tumors and in age-related chronic inflammatory disorders (Salminen et al., 2018). Given that the JAK-STAT3 pathway has a crucial role in the activation of immunosuppressive network, there are drug discovery programmes seeking novel and specific JAK inhibitors (Jakinibs) and STAT3 inhibitors (Stattics) (Villarino et al., 2017; Bharadwaj et al., 2020). Thus, when striving to develop anti-aging therapies, it seems more reasonable to adopt approaches aiming to prevent cellular senescence and immunosuppression rather than attempting to kill the growing number of senescent cells associated with the aging process.

9. Conclusions

Currently, the primary cause of the aging process is unknown although it seems that the increased cellular senescence associated with a chronic low-grade inflammation promotes the aging process. It is
known that persistent inflammation evokes a counteracting immunosuppression in many pathological conditions. It seems that anti-inflammatory and immunosenescence represent compensatory immunosuppression which appear during the aging process. The aging-related immunosuppression involves the activation of immunosuppressive phenotypes of several myeloid and lymphoid cells, e.g. MDCs, Tregs, Mreg/M2 macrophages, which not only counteract inflammasome but also suppress the functions of NK cells and cytotoxic CD8+ T cells, thus disturbing the surveillance and clearance of senescent cells. Subsequently, the accumulation of pro-inflammatory senescent cells further enhances inflammation and immunosuppression. This feed-forward process with aging maintains inflammasome and insidiously aggravates the age-related tissue degeneration. Moreover, senescent cells not only express the inhibitors of their immune recognition but also release the extracellular ligands of NKG2D and in that way, disturb their surveillance and clearance by immune cells. There are several drug discovery approaches to target and cleanse senescent cells from aging tissues, i.e. to target immunosuppressive cells or to inhibit their conversion towards the immunosuppressive phenotype. The feed-forward regulation between cellular senescence and immunosuppression provides novel therapeutic targets to alleviate the aging process and age-related diseases.

Declaration of Competing Interest
The authors report no declarations of interest.

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