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The senescence-associated secretory phenotype and its regulation

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ABSTRACT

The senescence-associated secretory phenotype (SASP) defines the ability of senescent cells to express and secrete a variety of extracellular modulators that includes cytokines, chemokines, proteases, growth factors and bioactive lipids. The role of the SASP depends on the context. The SASP reinforces the senescent cell cycle arrest, stimulates the immune-mediated clearance of potentially tumorigenic cells, limits fibrosis and promotes wound healing and tissue regeneration. On the other hand, the SASP can mediate chronic inflammation and stimulate the growth and survival of tumor cells. The regulation of the SASP occurs at multiple levels including chromatin remodelling, activation of specific transcription factors such as C/EBP and NF-κB, control of mRNA translation and intracellular trafficking. Several SASP modulators have already been identified setting the stage for future research on their clinical applications.

1. Introduction

Senescence is a cell fate triggered by stressors or developmental signals and is characterized by a stable growth arrest, active metabolism, resistance to cell death and secretion of extracellular factors. The abundance of senescent cells increases with chronological aging in multiple tissues [1,2]. The number of senescent cells in very old primates was estimated in the range of 5–20% [2–4]. Since the human body contains 37 trillion cells, senescent cells in aging organisms easily outnumber professional secretory cells. For example, the pituitary gland has around 1 million-cells for their major secretory cell types [5]. Therefore, the senescence-associated secretory phenotype (SASP) can have a major effect in the physiology of old organisms and can be responsible for chronic inflammation and age-linked diseases including cancer [6,7]. In younger organisms, senescence have positive effects linked to tumor suppression [8–11], limiting fibrosis [8], promoting wound healing [12,13] and tissue regeneration [14].

Specialized secretory cell types secrete most extracellular mediators. However, senescence reactivates the expression of multiple pro-inflammatory genes in many different cell types. Here we review our current understanding of this remarkable gene reprogramming process that turns any cell type into a secretory cell.

2. A brief overview of the SASP

The SASP defines the secretion of diverse cytokines, chemokines, growth factors, proteases and lipids by senescent cells. The composition of this special secretome is variable and depends on the senescence trigger. The SASP acts as a double-edged sword: it has some beneficial effects such as allowing the recruitment of the immune system to premalignant lesions [9,15,16] and promoting the repair of damaged tissues [12,13,17]. However, the secretion of many pro-inflammatory factors such as IL-6, IL-8, membrane cofactor proteins (MCPs) and (macrophage inflammatory proteins (MIPs) [18] can lead to deleterious effects such as promoting proliferation [19,20], angiogenesis [21] and inflammation [18], both in autocrine and paracrine manners. The SASP has been linked to a persistent DNA damage signaling [22]. In tumor cells, cytotoxic chemotherapy can induce a SASP response sometimes without a full development of a senescent phenotype. This therapy-induced SASP has been linked to chemoresistance [23,24]. Multiple components of the SASP can transmit senescence to neighbouring non-senescent cells, a phenomenon known as paracrine senescence [25]. The SASP is initially regulated at the transcriptional level. Two main transcription factors allow the activation of the SASP in response to senescence inducers: C/EBP and NF-κB.

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3. C/EBP controls the SASP

The CCAT/Enhancer Binding Protein family comprises transcription factors that are part of the basic leucine zipper (bZIP) superfamily [26]. Six isoforms were characterized: C/EBPα, β, δ, ε, γ and ζ and they can either homodimerize or heterodimerize. It is important to note that C/EBPζ does not possess a functional DNA Binding Domain (DBD) which enacts it to function as a dominant negative of transcriptional activation when complexed with other members of the family [26]. C/EBPβ has been shown to regulate many cytokines and factors known to constitute the SASP such as IL-1β, IL-8, IL-6, GROα and NAP2. Furthermore, several studies have shown that this transcription factor is necessary for senescence and also sufficient to induce the process when over-expressed [10,11,27]. Indeed, it was shown that C/EBPβ is upregulated during oncogene-induced senescence and that it binds to the IL-6 promoter in this context [11].

Transformed cells harbouring *RAS* or *BRAF* oncogenes often express high levels of the *C/EBPβ* mRNA and protein. However, in these tumor cells C/EBPβ cannot exert an anti-proliferative effect because the 3′UTR of the C/EBPβ mRNA excludes translation from the perinuclear compartment where the protein is phosphorylated and activated [28]. Finally, the C/EBPγ isoform was shown to suppress senescence by forming heterodimers with C/EBPβ and suppressing the transcription of SASP genes [29].

4. NF-κB controls the SASP

Many but not all pro-inflammatory genes expressed in senescent cells required the master transcription factor NF-κB [10,11,16,30,31]. However, non-canonical NF-κB activation can bypass senescence in melanoma [32] indicating a complex context-dependent function of this transcription factor. The activation of NF-κB during senescence has been linked to p38MAPK [33], GATA4 [34], the ROS-PKCdelta-PRKD1 pathway [35], mitochondria [31,36] and the multi-ligand scavenger receptor CD36 [37] (Fig. 1). P38 increases DNA binding and activity of NF-κB [33] while GATA4 induces the expression and secretion of IL1A, which is a well-known activator of NF-κB [34,38]. GATA4 accumulates in senescent cells due to a decrease in its degradation via autophagy [34]. IL1A is also regulated at the translational level by mTOR [39] and at a post-translational level by the inflammasome [25]. SASP activation through NF-κB is linked to the DNA damage response (DDR) [22] and in agreement, the methyl transferase MLL1 controls the SASP by inducing cell proliferation genes, replication stress and DNA damage [40]. The cytosolic DNA sensor cGAS, links DNA damage to activation of the SASP. cGAS catalyses the production of the second messenger cGMP which activates the adaptor protein STING, an activator of both IRF3 and NF-κB [41,42]. STING can be also activated via a non-canonical pathway triggered by DNA damage that does not depend on cGAS, involves p53 and the ubiquitin E3 ligase TRAF6 and preferentially activates NF-κB over IRF3 [43]. Since senescence involves DNA damage signaling [44], it is likely that this pathway is activated in senescent cells. Finally, CD36 is induced in multiple senescence contexts playing a critical role in the initiation of the SASP in response to ligands such as β-amyloid and oxidized LDL (oxLDL) [37,45] which could also play a role as senescence inducers [46,47].

The antidiabetic drug metformin inhibits NF-κB activation in senescent cells and selectively represses SASP genes that require this transcription factor [31,36]. Metformin inhibits the expression of most pro-inflammatory cytokines in cells that experienced oncogene-induced senescence (OIS) (Fig. 2). Metformin does not inhibit the growth arrest program of senescent cells [31,36] indicating that the SASP and the cell cycle arrest in senescence are independently controlled. Consistent with this idea, expression of the cyclin-dependent kinase inhibitors (CKI) p21, p16INK4A or RPS14 induces a SASP-free senescent cell cycle arrest [22,48–50]. Intriguingly, metformin acts in mitochondria to suppress the SASP and a similar effect was reported after eliminating mitochondria in senescent cells [51]. Hence, mitochondria are critical to regulate the senescence phenotype, but precise molecular mechanisms are unknown.

5. P53 controls the SASP: N-SASP and P-SASP

The SASP suppresses or promotes tumorigenicity depending on the status of p53. In the liver, senescent stellate cells secrete factors that promote macrophage differentiation towards tumor-inhibiting M1 state. In contrast, p53 null stellate cells secrete factors that promote M2 pro-tumorigenic macrophages [52]. In the colon, deletion of p53 changes the characteristics of the SASP, increasing the expression of TNFα and its ability to induce invasion and proliferation of tumor cells [53]. In metformin treated OIS cells, only a few secretion products are highly expressed. One of these genes is SEMA3F, a p53 target gene involved in antiangiogenesis [54,55]. Hence, the secretome of senescent cells is driven by NF-κB (the N-SASP) and inhibiting this transcription factor dramatically changes the pattern of secreted proteins allowing a relative enrichment of p53-dependent secretory factors (the P-SASP). Although p53 promotes the upregulation of some secreted factors, it is also considered a negative regulator of the SASP, since its absence promotes an enhanced SASP that is associated with pro-malignant functions [48]. p53 acts in part by suppressing p38MAPK signalling to NF-kB. Inactivation of p53 leads to a faster and stronger activation of p38MAPK by DNA damage, amplifying the SASP [33]. Treating senescent cells with the MDM2 inhibitor nutlin, increased p53 activity and reduced the expression of the pro-inflammatory cytokines IL-6 and IL-1A [56].

One important SASP modulator is the tumor suppressor SOCS1. Although SOCS1 is sufficient to activate p53 and trigger senescence [57] it is also an inhibitor of NF-κB [58]. SOCS1 triggers a unique pattern of p53 target gene expression including several secretory products with potential tumor suppression activity (Fig. 2) [59]. SOCS1 also activates p53 to induce DDIT-3 (also known as C/EBPζ), a dominant negative inhibitor of C/EBP family of transcription factors [60]. SOCS1-induced senescence is devoid of the induction of classical SASP factors although it shows sustained DNA damage signalling [59].

6. Epigenetic control of the SASP

The reactivation of pro-inflammatory gene expression in multiple senescent non-immune cell types suggests that chromatin remodelling underlies this genetic reprogramming. Senescent cells exhibit large-scale changes in chromatin organization including loss of the repressive H3K27me3 modification that affects up to 65% of SASP genes [61]. These chromatin changes were linked to the downregulation of lamin B1 expression in senescent cells [61,62]. In addition, SASP genes show an enrichment for H4K16ac, the histone chaperone HIRA, the histone variant H3.3 [63] and a global remodelling of the enhancer landscape [64]. The latter includes the recruitment of BRD4 to superenhancers close to SASP genes [64].

DNA damage may trigger the chromatin changes required to prime SASP genes for activation. One mechanism involves the ATM-dependent protein degradation of the histone methyltranferases G9a and GLP [65]. Activation of ATM also triggers the removal of the histone variant macroH2A.1 from the chromatin of SASP genes [66]. This removal is related to the BRCA1-dependent ubiquitination of macroH2A.1 [67].

SASP genes display an enrichment for HMGB2 during oncogene-induced senescence (OIS) and the loss of this factor inhibits the SASP without altering the cell cycle arrest of senescent cells [68]. However, in contrast to this study, low expression of HMGB2 was reported to be an early event during replicative senescence entry that correlated with high expression of IL-6 and IL-8, increased nuclear size, changes in heterochromatin markers and chromatin folding [69]. Notably, upon entry into senescence, cells exhibited stronger intrachromosomal long-range interactions. In addition, HMGB2 did not associate to SASP genes

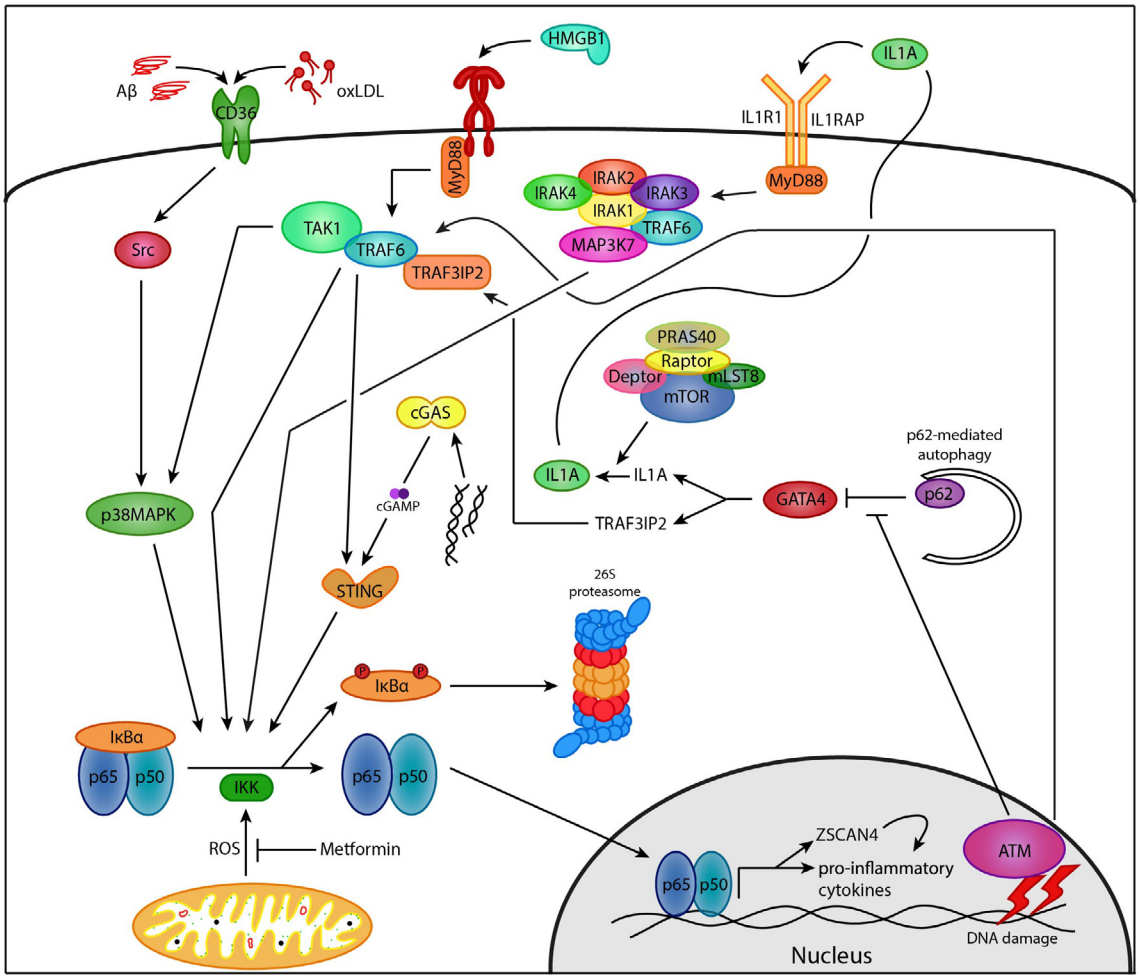

Fig. 1. Regulation of NF-κB in senescent cells. Multiple pathways converge to activate NF-κB in senescent cells. The initial triggers can originate inside the cells (cytosolic DNA, cytosolic chromatin fragments, DNA damage) or act on membrane receptors (Aβ peptides, oxLDL, IL1A, HMGB1). The signals converge into the IKK complex that phosphorylates and disables the inhibitor IκBα that sequesters NF-κB in the cytosol. After nuclear translocation, NF-κB induces the SASP genes but also ZSCAN4 which further amplify cytokine gene expression.

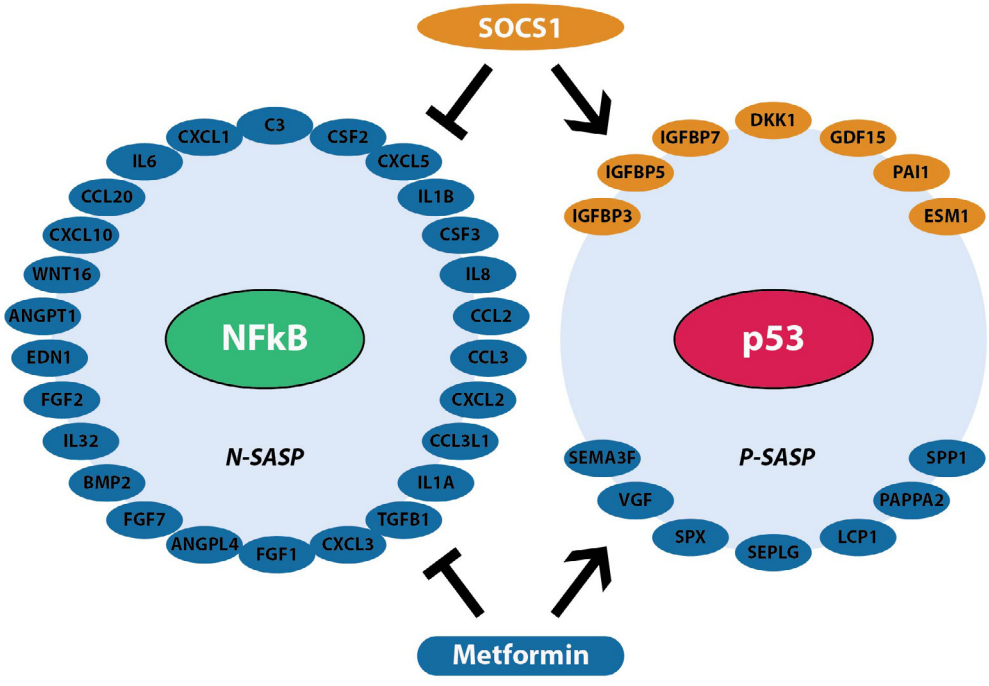

Fig. 2. Classification of the SASP according to the major transcription factors regulating its components. The N-SASP is driven by NF-κB and is inhibited by p53, SOCS1 and metformin. The P-SASP depends on p53 and its modulator SOCS1 and has been so far understudied. Data in the figure comes from microarray data sets GSE98216 (SOCS1) and GSE33612 (metformin).

in replicative senescence [69]. The reasons for these differences remain to be investigated. However, it is clear that HMGB2 loss is not the only factor implementing the senescence decision because its inactivation failed to recapitulate the senescence phenotype [69].

Chromosomes are organized into topologically associated domains (TADs) whose organization is linked to the regulation of gene expression. This organization has been revealed using chromosome conformation capture methods and is affected by the repressor CTCF, cohesin and cohesion-associated proteins [70]. HMGB2 binds to positions of chromatin insulation and its loss in replicative senescent cells is associated to changes in TAD boundaries and altered expression of genes within those TADs [69]. Taken together, these studies support a role of HMGB2 in reorganizing chromatin in replicative senescence cells and raise questions about the mechanism responsible for controlling the same process in OIS.

7. Secreted proteases as modulators of the SASP

It is well known that SASP factors not only include pro-inflammatory cytokines, but also a myriad of proteins and enzymes implicated in reorganization of the extracellular matrix (ECM). Among those enzymes are Matrix Metalloproteinases (MMPs), Serine/cysteine Proteinase Inhibitors (SERPINs), Tissue Inhibitor of Metalloproteinases (TIMPs) and Cathepsins (CTSs) [71]. MMPs (1/2/3/7/8/9/13) not only help to reorganize the ECM, but also play an important role in modulating immune and inflammatory responses through the processing of chemokines and subsequent generation of antagonists with anti-inflammatory properties [72]. Therefore, secretion of these proteases by senescent cells might decrease their immune clearance and contribute to deleterious/pro-tumorigenic features of the SASP due to subsequent reduced immune surveillance. Likewise, it was shown in a xenograft model that senescent fibroblasts increased growth of co-transplanted breast cancer cells in an MMP-dependent manner [73]. The SASP can recruit other inflammatory cells such as neutrophils and mast cells, which secrete extracellular proteases that can activate precursors of the IL-1 family [74–76]. This process generates a local feed-forward amplification of the SASP. The final outcome of the interplay between extracellular proteases and cytokines may depend on the context and further studies are required to identify factors that tilt the balance towards positive or negative interactions (Fig. 3).

8. HMGB1 and the DAMPs

The SASP includes Damage-associated molecular patterns (DAMPs), also called Alarmins [77]. As opposed to PAMPs (Pathogen-associated molecular patterns), DAMPs are endogenous molecules of nuclear or cytoplasmic origin that can be secreted upon stress induction [77]. DAMPs can induce paracrine senescence and mediate pro-inflammatory response in an autocrine or paracrine manner [78]. Consequently, they can stimulate immune cells recruitment, wound healing and tissue repair [79]. The HMGB1 protein (High mobility group protein B1) is the most studied example, but DAMPs also include histones, S100s proteins, heat shock proteins, mitochondrial and nuclear DNA, RNA, nucleotides [77] and oxidized lipids [80]. In senescence, secretion of HMGB1 is an early event, occurring 24–48 h post-irradiation [78]. HMGB1 shuttles between the nucleus and the cytoplasm and its subsequent secretion have been shown to depend on CRM1-dependent nuclear export, followed by loading in secretory lysosomes [81]. This process can be regulated by multiple post-translational modifications, such as acetylation [81] and oxidation [82]. Deacetylation of HMGB1 by the NAD-dependent deacetylase SIRT1, an enzyme implicated in senescence and ageing [83], also blocks its nuclear-to-cytoplasmic shuttling and secretion [84]. HMGB1 controls mitochondrial fitness through regulation of HSPB1 and mitophagy [85], suggesting that secretion of HMGB1 in senescent cells may contribute to their mitochondrial dysfunction. Extracellular HMGB1 was shown to induce a sterile inflammation through TLR receptors binding and induction of IL-6. *In vivo*, old mice showed decreased nuclear HMGB1 in comparison to young mice, and also increased HMGB1 in their serum [78]. Loss of nuclear and gain of extracellular HMGB1 both contribute to the senescence phenotype, notably by increasing genomic instability and telomere dysfunction [86] and extracellularly by TLR/NF-κB stimulation of SASP respectively [78]. Consequently, overexpression or knockdown of HMGB1 can induce senescence in a p53-dependent manner [78]. Overall, secretion of DAMPs including HMGB1 has been linked to chronic inflammation and several age-related diseases such as atherosclerosis and arthritis [87], thereby underscoring their relevance in the senescence field as unique SASP factors.

9. Lipids in the SASP

Senescent cells also have the ability to secrete bio-active lipids, including eicosanoids derived enzymatically from arachidonic acid [88]. The production of eicosanoids is mediated by two major enzymes: Prostaglandin-endoperoxide synthase (PTGS), better known as cyclooxygenase (COX), that is responsible for formation of prostanoids, and arachidonate 5-lipoxygenase (ALOX5), that converts arachidonic acid into leukotrienes. These lipid compounds act as autocrine or paracrine factors that mediate a diversity of physiological functions, such as inflammation, vasodilation, immune responses and smooth muscle contraction [88].

Several studies have focused on the role of cyclooxygenases in senescence. COX2 is overexpressed in replicative and stress-induced senescence [11,31,89,90], and at least one selective COX2 inhibitor prevents senescence [91]. However, not all COX2 inhibitors can block senescence, suggesting that COX2 regulates the process by a non-catalytic mechanism [92]. Interestingly, COX2 expression is also increased in old cells [93–95] and post-natal transgenic expression of COX2 induces aging-related phenotypes in mice [96]. The major product of COX2 activity is prostaglandin E2 (PGE2) whose levels are increased in both replicative and premature senescence [97]. Also, senescent fibroblasts express very low levels of prostaglandin-D-synthase, explaining why PGE2 is the most important prostaglandin in senescence [98]. Furthermore, PGE2 treatment induces senescence in human fibroblasts [99–101] and in CD8 T cells [102]. Several studies have identified that COX2-mediated prostaglandin E2 (PGE2) production promotes a tumor-promoting environment in melanoma, breast, colorectal and hepatocellular carcinoma [103,104]. PGE2 expression is also increased in fibroblasts from patients of chronic obstructive pulmonary disease, which has been associated with lung fibroblasts senescence [105].

Leukotrienes and ROS are generated from arachidonic acid by 5-lipoxygenase, which has been reported to be a senescence-mediator through the p53 pathway [89]. Leukotriene C4 is a major mediator of oxidative DNA damage acting in an intracrine manner via nuclear translocation of the ROS producing enzyme NOX4 [106], which is required for RAS-induced senescence [107]. Leukotriene D4 can also induce cellular senescence dependent on cysteinyl leukotriene receptor 1 (cysLTR1) in osteoblasts [108], a receptor that also has a role in chondrocyte senescence [109].

10. SASP factors as intracrine signalling molecules

Several SASP components not only get secreted in the extracellular milieu, but also accumulate at very high levels in cells undergoing cellular senescence. Among these components, IL-6, PGE2, leukotriene C4, SERPINB2 (PAI-2) and SERPINB4 have been shown to be essential for senescence induction and maintenance acting via intracrine signaling, rather than outside of the cell [48,100,106,110,111]. Concerning PAI-2, it has been shown to be a direct target of p53 and to co-immunoprecipitate with p21, leading to its stabilization. Indeed, knockdown of p21 reverts PAI-2-induced senescence, whereas knockdown of p53 fails to revert the phenotype [110]. As for SERPINB4, it

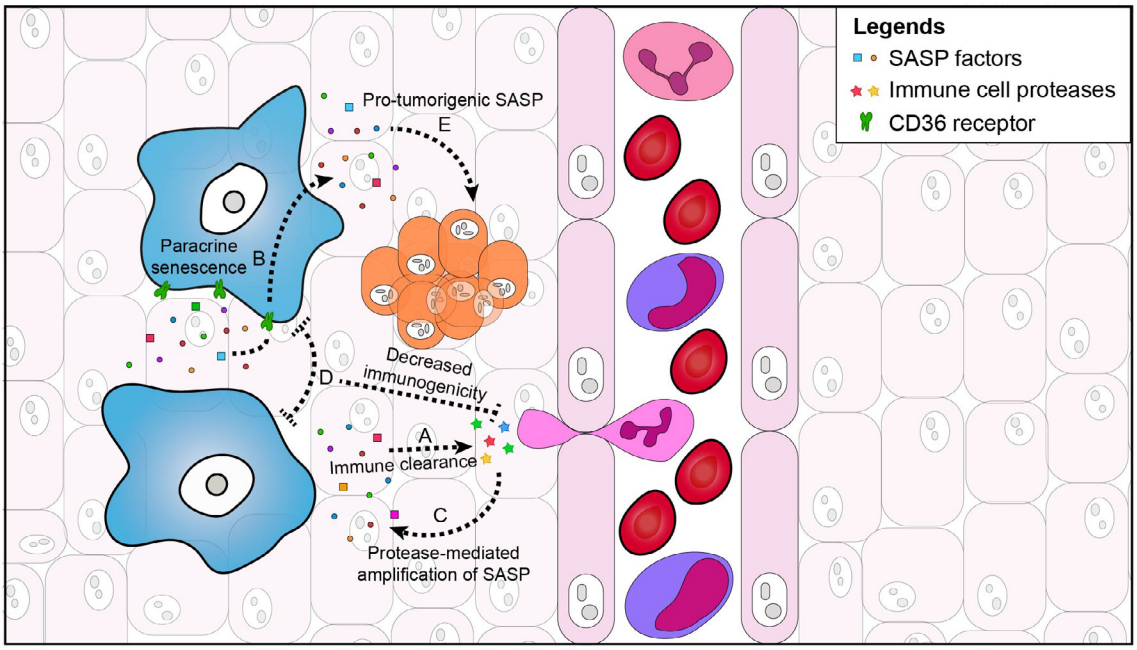

Fig. 3. Model proposed for positive and negative modulation of SASP through secreted proteases. (A) Secretion of pro-inflammatory cytokines by senescent cells (blue) leads to recruitment of immune cells (purple and pink) for further clearance. (B) CD36 is bound by SASP components from cells in the vicinity, leading to establishment of paracrine senescence and SASP. (C) In a context of acute inflammation, following extravasation of immune cells, the latter secrete proteases with the potential of amplifying the SASP through processing of secreted precursors from IL to 1 family. (D) The inter-senescent cells paracrine effect of SASP leads to MMPs-mediated degradation of pro-inflammatory cytokines. (E) In the context of carcinogenesis (orange), subsequent reduction of pro-inflammatory cytokines in the extracellular compartment leads to decreased recruitment of immune cells and increased tumor growth. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

has recently been shown to act on IMMP2L-mediated mitochondrial reprogramming to favor senescence over apoptosis upon oxidative stress [111]. Even though these proteins get secreted as part of the SASP, B subtype of SERPINs also accumulate inside cells due to lack of signal peptide [112]. Importantly, whereas several SASP factors are usually amplified in cancers (e.g. CXCL1/2/5, CCL2/3, etc.), according to cBioPortal, PAI-2 and SERPINB4 are both deleted in several cancers, especially in pancreatic cancer where it can be deleted in up to 24% of samples, confirming their tumor suppressor function.

11. Therapy-induced senescence and tumor-promoting properties of the SASP

Studies to better understand the molecular mechanisms regulating the SASP are becoming more and more clinically relevant. Cancer chemotherapy induces DNA damage both in tumor cells and in the surrounding stromal cells, such as fibroblasts, which subsequently enter senescence. The secreted products of the senescent stroma can then confer resistance to cancer chemotherapy [23]. It was recently reported that therapy-induced DNA damage in fibroblasts induced senescence and stimulated expression of multiple SASP factors such as AREG, SPINK1, MMP3, and expression of the transcription factor ZSCAN4 [113]. This transcription factor is induced in a DNA-damage dependent manner, through the ATM-TRAF6-TAK1-NF-κB axis in the surrounding stroma of tumors from NSCLC and breast cancer patients having received chemotherapy [113]. ZSCAN4 expression is associated to poor survival and cell culture models suggest a role for ZSCAN4 in a loop of amplification of the SASP [113]. It is known that the SASP can stimulate tumorigenesis and drug resistance by inducing a pro-inflammatory microenvironment [114]. A combination of TAK1 inhibition with chemotherapy blocks drug resistance by suppressing the SASP of senescent stromal cells in prostate and breast cancer xenografts, inducing tumor regression [113]. Altogether, this opens a promising field of research on how SASP modulation can benefit cancer patients undergoing DNA-damaging chemotherapy.

12. The SASP in senescence induced by lamin A defects

Cellular senescence is also triggered by defects in nuclear lamina assembly. In the Hutchinson-Gilford progeria syndrome, a disease characterized by a premature aging, a truncated form of lamin A, called progerin, has a defective turnover [115] and thus accumulates, causing a disturbed nuclear lamina, DNA damage and consequently cellular senescence [116]. Loss of the enzyme ZMPSTE24, which processes prelamin A into mature lamin A also leads to accumulation of prelamin A and senescence [117]. The SASP in this specific senescence model can trigger paracrine senescence through the monocyte chemoattractant protein-1 (MCP-1) and its binding to its receptor CCR2 on target cells [118]. Both progerin overexpression and ZMPSTE24 depletion in human mesenchymal stem cells induce an ATM/ATR-dependent DNA damage response that mediates the stabilisation of the transcription factor GATA4 that was shown to be necessary for NF-κB-dependent induction of MCP-1 and its subsequent secretion [118].

13. SASP, reprogramming and cellular plasticity

The SASP plays a role in embryonic development [119–121] and the reprogramming of cells towards a stem-like phenotype [122,123]. However, the SASP can either stimulate or inhibit reprogramming depending on the context. In a mouse model of induced pluripotent stem cells (iPSCs) elimination of senescent cells with the senolytic ABT-263, pharmacological inhibition of NF-κB or inhibition of IL-6 using an anti-IL-6 antibody, inhibited reprogramming and stem cell generation [122]. This senescence-driven reprogramming of cells was shown to be dependent on tissue injury. Consequently, bleomycin-treated cells have increased DNA damage [122] and secrete pro-inflammatory cytokines among which IL-6 is a major driver of cell reprogramming [122]. On the other hand, during aging, NF-κB hyperactivation leads to

upregulation of the reprogramming repressor DOT1L, which downregulates genes associated to pluripotency, thereby impairing iPSCs production [124]. Moreover, *in vivo* inhibition of DOT1L increases lifespan and ameliorates age-associated features in progeroid mice. Therefore, the precise action of SASP on reprogramming of cells is still poorly understood. Interestingly, it was recently shown that transient exposure to SASP leads to increased regenerative capacity *in vivo* and upregulation of stem cell markers, whereas prolonged exposure to the SASP leads to paracrine senescence and impairment of regenerative capacities [123]. This might reflect the dynamic properties of the SASP which at least is divided in two phases: Notch-high, followed by Notch-low phase [125]. The first is associated to a TGF-β-dependent SASP with immunosuppressive, fibrogenic and tissue regeneration properties, whereas the latter is associated to a NF-κB and C/EBPβ-dependent SASP with pro-inflammatory, fibrolytic and immune clearance properties. However, in situations where clearance is not achieved, further evolution of the SASP is likely a situation that can stimulate preneoplastic lesions to bypass senescence and acquire stem cell properties, thereby potentiating their transformation [126]. Finally, it is also likely that the heterogeneity of SASP composition across different cell types [127] could impact on the establishment of a micro-environment favourable for cell reprogramming.

14. Conclusions

The SASP is regulated at multiple levels. First, chromatin remodelling and changes in chromatin folding prime pro-inflammatory genes for activation. Although many histone modifications and non-histone chromosomal proteins have been linked to senescence, it is not yet understood how these processes are initiated. Second, specific transcription factors cooperate to dynamically establish the composition of the SASP. NF-κB, p53, C/EBP and GATA4 have been identified as key SASP regulators but it is likely that additional players will be identified. Third, the translation of several SASP factors is regulated by TOR signaling in senescent cells [39]. Fourth, the trans Golgi network, its components: PRKD1, ARF1 and PI4KIII**β** and the carrier membrane protein SCAMP4 are upregulated in senescent cells and required for the secretion of several SASP factors [128,129]. Finally, genes involved in intracellular trafficking undergo alternative splicing in senescent cells and PTBP1, a regulator of alternative splicing, is required for the pro-inflammatory SASP in senescent cells [130]. Further understanding of the molecular mechanism that control the SASP will help to design therapies for its modulation.

Pharmacological agents that decrease the SASP include the anti-diabetic drug metformin [31,131], glucocorticoids [132], JAK inhibitors [133], TAK1 inhibitors [113], rapamycin [39], nutlin [56] and trabectedin, an alkaloid isolated from the Caribbean tunicate *Ecteinascidia turbinate* [134]. The effects of these drugs have not been systematically studied in all situations associated to senescence. Also, when these drugs are effective, there is little data to support that they acted by suppressing the SASP. On another matter, the ability of senescent cells to act as factories for secretion of biological mediators could eventually be engineered for medical applications.

Declaration of interest

The author declares that there is no conflict of interest.

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