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Innate immunosensing of DNA in cellular senescence

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Senescence is a multistep cellular program featuring a stable cell cycle arrest, which occurs upon exposure to various stressors. Senescent cells exhibit metabolic activity and hypertrophy and produce a multitude of factors with both cell intrinsic as well as non-cell autonomous functions. These factors are collectively referred to as the senescence-associated secretory phenotype (SASP). Recently, the DNA sensor cyclic GMP AMP synthase (cGAS) and the adaptor stimulator of interferon genes (STING) have been reported to be critically involved in the regulation of senescence. This suggests that cGAS has an important function as a more general cell intrinsic stress sensor with implications for multiple senescence-associated diseases.

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Introduction

Recognition of DNA is an evolutionary conserved strategy utilized by various organisms to detect potential danger. In mammals, distinct receptor systems are tasked with the recognition of DNA, the most established being Toll-like receptor 9, absent in melanoma 2 (AIM2), and cyclic GMP-AMP synthase (cGAS). Of these, cGAS is the predominant cytosolic DNA sensor that regulates *de novo* transcriptional immune responses [1]. Interestingly, except for a certain length preference, cGAS senses dsDNA in a relatively non-specific manner achieved by interacting with the phosphate-sugar backbone of dsDNA [2]. Binding to dsDNA causes a conformational change in its catalytic center, which allows for the catalysis of the second messenger cyclic GMP-AMP (c[G(2′–5′)pA(3′–5′)p]). cGAMP in turn stimulates the endoplasmic reticulum-located transmembrane protein STING, which leads to the activation and nuclear translocation of the transcription factors interferon-regulatory factor 3 (IRF3) and nuclear factor κB (NF-κB). The concerted action of these and likely additional transactivators results in the induced expression of several antiviral effector proteins including the Type I interferons (IFN) and IFN-stimulated genes (ISG) as well as various cytokines and chemokines. These gene products play crucial roles not only during infection, but also in various stress adaptation processes such as DNA damage and senescence as discussed in this review. Here, we will highlight recent findings about the role of cGAS in senescence and discuss possible consequences of its activation for understanding senescence-associated phenomena and for designing new therapeutic avenues for targeting senescence.

Characteristics of cellular senescence

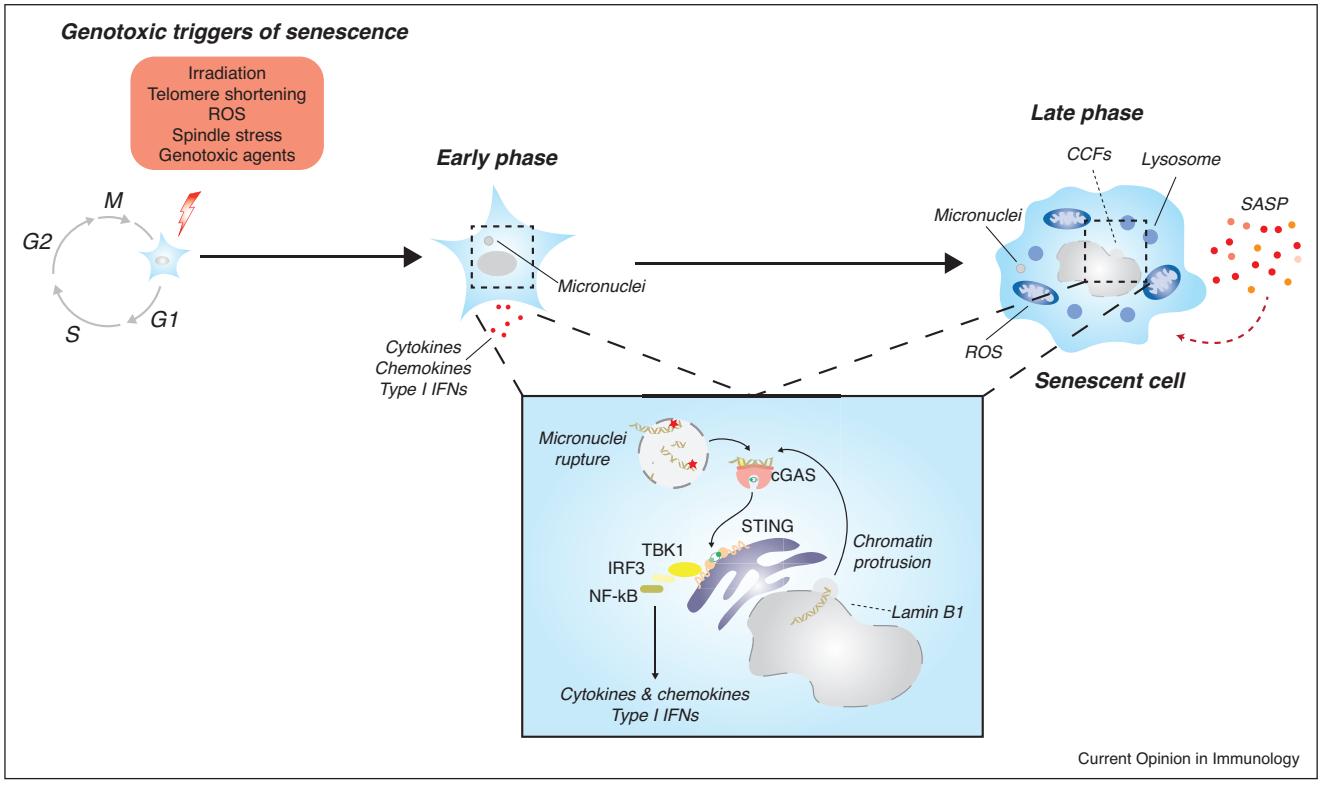
Originally, cellular senescence was identified as a permanent cell cycle arrest occurring in cultured human fibroblasts after a certain period of proliferation [3]. Today, senescence is viewed as a dynamic cellular effector program which can be triggered in response to various types of stressors both *in vitro* and *in vivo*. Among the most extensively studied senescence-inducing conditions are triggers of DNA damage (genotoxic agents, irradiation, oxidative stress) or replication stress (oncogene expression), but also mitochondrial dysfunction and the unfolded protein response have been shown to promote senescence. The two major pathways responsible for the establishment of senescence are the p53/p21 and p16/RB signaling pathways. The activation of either mechanism alone or in conjunction is critical for mediating the stable proliferation arrest. A key characteristic of senescent cells is the secretion of various cytokines (IL-6, IL-8, IL-1α), chemokines (e.g. CXCLs, CCLs), growth factors (e.g. GM-CSF, VEGF), and proteases, collectively termed the SASP, which enables non-cell autonomous functions [4]. Additional features of senescent cells include increased activity of senescence-associated β-galactosidase (often used as an indicator for the presence of senescent cells), large-scale chromatin reorganization, resistance to apoptosis, altered metabolic and autophagy activity, and morphological changes such as an enlarged cytoplasm or abnormally shaped nuclei.

The cGAS-STING pathway regulates the SASP

Developing a unifying model explaining the regulation of the SASP is hampered by its considerable heterogeneity depending on cell-specific, time-specific and stress-specific cues. Although secretory activity is a shared feature across various different types of senescence, most studies have focused on the SASP associated with genomic damage. Earlier work established that within this particular type of senescence, persistent DNA damage is

required for the initiation of an 'inflammatory' SASP, which is regulated independently of p53, p21 or $p16^{Ink4a}$, the master regulators of senescence [5]. Also mTOR has been implicated in the regulation of inflammatory SASP factors [6,7]. At a transcriptional level, the SASP is controlled by CCAAT/enhancer-binding protein β (C/EBP-β) and NF-κB transcription factors [8,9]. Moreover, modulators acting upstream and/or synergistically with NF-κB include p38MAPK and the transcription factor GATA4 [10,11]. These transactivators are commonly found downstream of various immune signaling cascades, thus raising the question of whether senescent cells regulate the SASP, or at least part of it, through (innate) immune sensing mechanisms. Indeed, we and others recently showed that cGAS and STING are important for the regulation of senescence and the SASP [12••,13••,14••,15••]. It appears that after exposure to genotoxic stimuli engagement of cGAS follows a biphasic pattern (Figure 1). First, immediately (e.g. 1–2 days *in vitro* after irradiation) after exposure to genotoxic agents, a rapid cGAS-dependent and STING-dependent response is induced that entails the secretion of type I IFNs and other cytokines. In certain contexts of genotoxic stress, this rapid cGAS-mediated secretory activity facilitates the transition of cells into a senescent state via autocrine and paracrine effects including type I IFN signaling, a known inducer of senescence (see below) [16,17]. Mechanistically, at this pre-senescent stage activation of cGAS is likely mediated through the recognition of self-DNA within ruptured mirconuclei [18••,19••]. After cells enter senescence as defined by conventional criteria ($p16^{Ink4a}$ expression, SA-β-Gal activity) the SASP evolves. While the SASP includes several families of soluble and insoluble factors, inflammatory, NF-κB-dependent cytokines and chemokines are primary targets of cGAS-STING activity in senescent cells. Interestingly, inside cells this senescent phase coincides with the downregulation of Lamin B1, and morphological changes to the nucleus. Notably, these alterations to the nuclear envelope can trigger chromatin protrusions from the nucleus, which result in the formation of cytosolic chromatin fragments (CCF) likely serving as the stimulus for cGAS activation in senescent cells [20]. Alternatively, and not mutually exclusive, aberrant self-DNA accumulation in senescent cells may be in part

Figure 1



Activation of cGAS-STING signaling during senescence.
Exposure to distinct DNA damage-associated stressors activates an early phase of cGAS-STING activity in which cGAS detects endogenous DNA in rupturing micronuclei. This early phase is accompanied by low levels of type I IFNs and inflammatory cytokines. Later during the establishment of senescence, cGAS sustains a predominantly inflammatory SASP through the additional recognition of cytosolic chromatin fragments occurring in senescent cells. Through autocrine and paracrine mechanisms, the cGAS-STING-dependent response reinforces the senescent cell cycle arrest.

caused by the downregulation of cellular nucleases including TREX1 and DNase II, which can further promote the activation of cGAS [15••].

Of note, the SASP is an overall signaling output of several cellular processes running in parallel and influencing each other. Whereas IL1α, itself a prominent SASP component, promotes a positive feedforward activation loop via NF-κB, TGF-β family ligands may dampen inflammatory cytokines and type I IFNs [21,22]. Moreover, the SASP is highly dynamic and undergoes profound changes over time. In oncogene-induced senescence, an early profibrogenic SASP is followed by a SASP dominated by inflammatory components [22]. Major differences in the SASP composition have been described in the context of mitochondrial-induced senescence in which AMPK controls a SASP that lacks major inflammatory factors including IL1α, IL1β, IL6, and IL8 [23]. In light of this, it is interesting to note that DNA derived from mitochondria can be sensed by cGAS [24]. Whether this sensing contributes to the composition of the mitochondrial SASP remains to be investigated.

Effects of the SASP

The acquisition of a senescence-associated secretory phenotype is of major functional relevance, since it explains how senescent cells can exert such pleiotropic effects both within their local environment and at more distant sites within tissues or even systemically. First, some SASP components act by stabilizing the proliferation arrest of senescent cells via autocrine controlled positive feedback loops and can moreover propagate the senescence response in a paracrine manner. Remarkably, transplanting a small amount of senescent cells into young mice causes the accumulation of senescent cells and inflammation in various organs [25••]. The cGAS-STING pathway is important in controlling this non-cell autonomous reinforcement of senescence [13••]. Defects in cGAS or STING or interference with the expression or function of distinct inflammatory SASP components (IL1α, IL6, TGF-β family members, IL8) compromise senescence both *in vitro* and *in vivo* [8,26,27]. In response to distinct stressors *in vitro*, cGAS and STING differentially regulate conventional senescence markers, including cell cycle arrest genes (*CDKN1A*, *CDKN2A*). For example, several senescence markers are affected by absence of cGAS in prolonged MEFs cultures, whereas less so upon enforced expression of oncogenes. It is possible that the contribution of cGAS and STING to senescence markers distinct from the SASP depends on the relative influence of paracrine senescence in these contexts. Second, it is via the SASP that senescent cells exert non-cell autonomous functions. From a host perspective, one of the most important beneficial effects of the SASP is the initiation of an immune cell-mediated self-destruction program. The clearance of 'DNA-damaged' senescent cells constitutes a crucial tumor suppressive function of the SASP and is carried out by NK cells, macrophages, or T cells [28,29]. While SASP-associated chemokines, in particular CCL2, are in charge of recruiting immune cells, senescent cells also facilitate the clearing process through the expression of activating NK cell ligands, including NKG2D [30,31]. Of note, in a mouse model of NRAS-mediated senescence, cGAS and STING are involved in the immune-mediated senescent cell clearing process [12••,13••]. Specifically, mice lacking cGAS or STING are defective in the elimination of NRAS positive cells and, in the case of STING knockout mice, display reduced potential to recruit immune cells leading to an increased susceptibility to developing liver tumors. Similarly, DNA damage-associated senescence of hepatic stellate cells is controlled *in vivo* by STING and absence of STING promotes the development of hepatocellular carcinoma [15••]. Thus, an important conceptual advance emerging from these studies appears to be that the cGAS-STING controlled SASP is an important regulator of the cell extrinsic antitumor functions of senescent cells both through reinforcing an autocrine and paracrine permanent cell cycle arrest and through promoting an anti-senescence immune response *in vivo*.

Apart from tumor suppression, the SASP has been shown to establish a microenvironment that supports tissue regeneration upon injury [32,33], has non-redundant functions during embryonic development [34,35], and also promotes cellular reprogramming [36]. Obviously, given its diverse effects, different components of the SASP play predominant roles in these distinct contexts and it is conceivable that distinct SASP categories originate from different upstream signaling cascades.

Work over the past years have also revealed several harmful aspects of senescence. Senescent cells can contribute to the destruction of normal tissue organization and the deterioration of organ function, effects that are relevant not only for the pathogenesis of diseases, but also for normal aging and progeroid syndromes [37]. The first direct proof of a detrimental role of senescent cells in progeria and aging was provided by studies in which genetic ablation of senescent cells ($p16^{Ink4A}$) improved health and increased median lifespan [38,39••]. Of note, many of the negative aspects of senescent cells in aging and disease are mediated non-autonomously through the SASP. For example, SASP factors inhibit stem cell function, induce fibrosis, and can also exert pro-tumorigenic effects [40]. More generally, it is thought that the SASP is a causal contributor to the chronic inflammatory state associated with aging, a notion that coined the term 'inflammaging'. The observation that the transplantation of a small amount of senescent cells can trigger tissue degeneration in young, healthy animals along with triggering inflammatory cytokines further underscores the indirect SASP-mediated negative consequences of senescence [25••]. The causes of senescence accumulation

during aging are naturally manifold and many diverse triggers may ultimately cooperate in promoting age-related inflammation and disease. An important question will be whether specific contexts of 'maladaptive' senescence states are more dependent on a specific innate sensing pathway, for example DNA-damage associated aging phenotypes and the cGAS-STING pathway, and whether interfering with such a dominate mechanism can provide significant health benefits to the host.

Therapeutic interventions targeting the SASP

Senescence has emerged as a therapeutic target of high interest. First, the potent tumor suppressive effects of senescence have been the subject of decades of research and pro-senescence strategies are being pursued in the context of different cancer therapies. Second, anti-senescence therapies may be relevant for a wide range of distinct age-related pathologies. Administration of compounds that have senolytic activity ameliorate age-related tissue deterioration in distinct models of normal or premature aging and also shows efficacy in other disorders of aged humans such as atherosclerosis or osteoarthritis [25••,41,42]. The relatively broad effects of clearing senescent cells may be attributed to improvements of overall regenerative capacity and stress resistance in old organisms. In addition and as discussed above, a major pathogenic factor of senescent cells is suspected to be the production of an inflammatory SASP. In fact, the positive outcomes of senescent cell clearance often correlate with a global and local reduction of inflammatory markers including IL6, IL1α, and TNFα. Thus, an alternative mechanism of action of senolytics could be the neutralization of the adverse inflammatory effects of senescent cells. In support of such a strategy, inhibiting NF-κB in mice genetically or pharmaceutically or administering JAK inhibitor to aged mice reduced signs of age-related inflammation and frailty [43,44]. However, it remains possible that part of the beneficial effects achieved through immunosuppressive agents may also rely on the inflammatory capacity of non-senescent cells, most notably immune cells such as macrophages. But even though broadly antagonizing chronic inflammation does not qualify as a true senomorphic regimen and may also not be desirable for long-term usage given obvious safety concerns, targeting specific inflammatory pathways that are activated in damaged senescent cells in certain disease contexts may be beneficial in extending healthspan.

Conclusion

Recent work discussed above highlights the role of the cGAS-STING pathway in the context of senescence. Both cGAS and STING are critical mediators that promote senescence induced by genotoxic agents *in vitro* and *in vivo*. The establishment of senescence requires a coordinated process of gene expression that is regulated at multiple levels and that is highly variable both in terms of its upstream mechanism as well as in terms of its downstream effector responses. An important future goal will be to better characterize the roles of cGAS and STING in distinct contexts of senescence *in vitro* and *in vivo* — in particular in settings with little if any DNA damage — and to more precisely determine its effector outcomes. Along with this, it appears that cGAS KO MEFs show a more prominent phenotype relative to STING KO MEFs when considering the proliferation arrest *in vitro*. It will be interesting to better understand whether *in vivo* cGAS and STING are equally important for restricting cell growth and propagating senescence, or whether yet-to-be identified STING-independent function of cGAS may exist. Clearly, pharmacological manipulation of cGAS and STING holds great promise in autoinflammatory disease [45••]. The importance of cGAS and STING in the context of senescence-associated pathologies will also need to be addressed in order to explore whether modulating the cGAS-STING pathway might provide an avenue for therapeutic intervention in these diseases.

Conflict of interest statement

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