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REVIEW

Special Topic - AGING, DISEASE & REGENERATION

Regulation of cellular senescence by innate immunity

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Abstract During the COVID-19 pandemic, the interplay between the processes of immunity and senescence is drawing more and more intensive attention. SARS-CoV-2 infection induces senescence in lung cells, failure to clear infected cells and increased presence of inflammatory factors could lead to a cytokine storm and acute respiratory disease syndrome (ARDS), which together with aging and age-associated disease lead to 70% of COVID-19-related deaths. Studies on how senescence initiates upon viral infection and how to restrict excessive accumulation of senescent cells to avoid harmful inflammation are crucially important. Senescence can induce innate immune signaling, and innate immunity can engage cell senescence. Here, we mainly review the innate immune pathways, such as cGAS-STING, TLRs, NF-κB, and NLRP3 inflammasome, participating in the senescence process. In these pathways, IFN-I and inflammatory factors play key roles. At the end of the review, we propose the strategies by which we can improve the immune function and reduce inflammation based on these findings.

Keywords IFN-I, NF-κB, cGAS-STING, TLRs, NLRP3 inflammasome, Cell senescence

INTRODUCTION

Pathogen-associated molecular patterns (PAMPs) can be recognized by the pattern recognition receptors (PRRs) of the cell (Ablasser and Hur 2020; Aleynick *et al.* 2019; Lukhele *et al.* 2019), by which the innate immune system represents the first defense line of the organism. Undoubtedly, foreign or misplaced nucleic acids are a critically important signal received by the innate immune system (Akira *et al.* 2006). Once PAMPs are sensed by PRRs, an efficient signal transduction system is elicited, resulting in the induction of type I interferons (IFN-I) and proinflammatory cytokines (Zheng and Gao 2019). Although, there is little correlation between the processes of immunity and senescence. However, because of the COVID-19 pandemic, the interdisciplinary connection between these fields is highly emphasized.

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During exposure to stressful insults and certain physiological processes, cellular senescence occurs with a stable loss of growth potential and phenotypic alterations, especially the senescence-associated secretory phenotype (SASP) accompanied by a proinflammatory secretome (Calcinotto *et al.* 2019). In the early stages of senescence, chromatin and mtDNA fragments leaked to the cytosol to activate innate immune responses (Erdal *et al.* 2017; Fenech *et al.* 2011). After that, the IFN-I and inflammatory cytokines secreted by the host can engage in cell senescence in the late stage (Frisch and MacFawn 2020). In a word, innate immunity is affected by senescence and coordinates with it at the same time. Herein, we introduce the latest progress on innate immune pathways involved in cellular senescence. Subsequently, the association between immunity and senescence is illustrated. Finally, we discuss the potential therapeutic target based on innate immune responses for aging and age-associated diseases.

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CELL SENESCENCE

The senescence process is characterized by a generally irreversible cell-cycle arrest and other phenotypic alterations, like secretory features, macromolecular damage, and altered metabolism (Gorgoulis *et al.* 2019). Senescence exists at any life stage and is essential in embryogenesis, tissue homeostasis, and tumor suppression. Nevertheless, senescence may be the key ingredient of aging and age-associated diseases. Cellular senescence was first found in normal diploid cells undergoing an irreversible growth arrest after a fixed number of divisions by Hayflick and colleagues in 1961 (Hayflick and Moorhead 1961). After that, they noticed that this phenomenon was not observed in cells separated from malignant tumors, implying that senescence may be related to tumor suppression (Hayflick 1965).

Senescence is characterized by a permanent cell-cycle halt that results from exposure to damaging stimuli such as nutritional deprivation, genotoxic chemicals, hypoxia and dysfunction in the mitochondria, or abnormal proliferation such as oncogene activation. The p53 proteins and retinoblastoma (RB) family are important factors to enter senescent cell-cycle arrest in mammalian cells (Rodier and Campisi 2011). In senescent cells, ectopic expression of activated BRAF or RAS and persistent DNA damage upregulates the expression of CDK4/6 inhibitor p16INK4A and (CDKN2A) CDK2 inhibitor p21WAF1/Cip1 (CDKN1A) respectively (Sieben *et al.* 2018). Then RB family proteins activate persistently, repressing E2F transactivation and, ultimately, cell-cycle arrest, which can not be reversed by inhibiting p53 or RB family proteins (Beausejour *et al.* 2003; Sharpless and Sherr 2015). There are many reasons for this irreversibility, such as the influence of cytokines induced by senescent cells (Rodier and Campisi 2011), the heterochromatinization of E2F target genes (Salama *et al.* 2014), and the consistent generation of reactive oxygen species (ROS) (Takahashi *et al.* 2006). Besides, an additional protein, ARF, plays a crucial part in cell-cycle regulation, which is an alternate reading frame protein of p16 and can activate p53 as well (Sharpless and Sherr 2015).

The secretion of senescent cells is another prominent feature of senescence. Senescent cells typically produce numerous molecules, collectively called the senescent-associated secretory phenotype (SASP), including angiogenic factors, matrix metalloproteinases (MMPs), growth modulators, and various proinflammatory chemokines and cytokines (Coppe *et al.* 2010; Kuilman and Peeper 2009). Specifically, there are many signaling pathways participating in the production of SASP, mainly through enhancer remodeling and transcription factors activation, including mammalian target of rapamycin (mTOR), p38MAPK (Freund *et al.* 2011; Ito *et al.* 2017; Kuilman and Peeper 2009), NF-κB, GATA4, and C/EBPβ (Kang *et al.* 2015; Salama *et al.* 2014). Various signaling pathways contributing to SASP activation result from the different senescence inducers. Due to DNA damage, type I interferon response is triggered by cytoplasmic chromatin fragments (CCFs), and the inflammasome is activated by damage-associated molecular patterns (DAMPs) instead (Acosta *et al.* 2013; Davalos *et al.* 2013; Li and Chen 2018). Depending on the pathophysiological context, the senescence response can be useful or harmful. Early in our embryonic development, the SASP can help the morphogenesis of certain structures (Munoz-Espin *et al.* 2013) and initiate parturition (Menon *et al.* 2019). Besides, when tissue damage occurs, senescent cells can be found in the injured site transiently, where they function in wound healing and regeneration tissue repair, mainly by secretion of certain SASP factors (Ritschka *et al.* 2017; Sarig *et al.* 2019). One more critical function of SASP is in the process of immunity. Senescent cells can secrete SASP factors through autocrine and paracrine (Acosta *et al.* 2013; Coppe *et al.* 2010; Kuilman and Peeper 2009), which can activate immune responses, leading to the clearance of senescent cells (Krizhanovsky *et al.* 2008; Munoz-Espin and Serrano 2014). Considering the flip side, there are detrimental, pro-aging impacts of senescence because of the SASP. As reported, broad statistics from pharmacological interventions and transgenic rodent models consistently associate senescent cells with a high risk of various age-related pathologies, including tumorigenesis, cardiovascular diseases, and neurodegenerative disorders (Childs *et al.* 2017; Song *et al.* 2020). Chronic inflammation, mainly due to the SASP development, also termed "inflammaging" *in vivo*, is a main trigger for these illnesses (Franceschi and Campisi 2014). More and more senescent cells accumulate in various organs and tissues with age (Bussian *et al.* 2018; Childs *et al.* 2018), leading to compromised functional ability and more susceptibility to age-related disease.

cGAS-STING

Genomic instability is a major contributor to aging. Persistent DNA damage is reported to lead to aging by causing senescence, cell death, and tissue dysfunction. DNA-sensor cyclic GMP-AMP synthase (cGAS) can bind extrachromosomal DNA fragments leaked into the

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cytoplasm in senescent cells (Schmitz *et al.* 2023), which leads to its liquid-liquid phase separation (Liu *et al.* 2023; Zheng and Gao 2023), conformational change, and activation. The activated cGAS utilizes GMP and AMP to produce the second messenger, cyclic GMP-AMP (cGAMP). cGAMP then binds a stimulator of interferon genes (STING) in the endoplasmic reticulum, activating STING and translocating to the Golgi apparatus (Motwani *et al.* 2019). Followed by the translocation of STING, IκB kinase (IKK) and TANK-binding kinase 1 (TBK1) are recruited and phosphorylate the NF-κB inhibitor IκBα and interferon regulatory factor 3 (IRF3). Then, NF-κB stimulates proinflammatory molecules due to phosphorylated IκBα and IFN-I and relevant downstream genes produced upon the transportation of active IRF3 to the nucleus (Corrales *et al.* 2017; Ishikawa *et al.* 2009). The following sections will explain the details about IFN I and NF-κB. Other sensors for cytosolic double-stranded DNA (dsDNA) include AIM2 and IFI16. They are members of the PYHIN family and can be induced by the interferon (IFN). AIM2 can assemble inflammasome to secret IL-1β and IL-18, whereas IFI16 induces IFN-β production upon binding dsDNA (Duan *et al.* 2011).

In cellular senescence, the abnormal accumulation of DNA in the cytoplasm is caused by several scenarios. One is cytosolic chromatin fragments (CCFs), due to the nuclear Lamin B1 loss in senescent cells, a main cause of genomic instability (Dou *et al.* 2015; Graziano *et al.* 2018). As reported, Lamin B1 over-expression can suppress the SASP (Rodier *et al.* 2009). In addition, long-interspersed element-1 (LINE-1 or L1), a major human retro-transposable element, is derepressed in senescent cells through downregulation in RB and an upregulation of the FOXA1 transcription factor, also serves as a source of cytosolic DNA (De Cecco *et al.* 2019). Its activation leads to cDNA accumulation, because of its high reverse transcriptase activity. Normally, LINE-1 elements are degraded by cytoplasmic DNases TREX1 and DNase2, decreased in senescent cells due to loss of E2F activity (Takahashi *et al.* 2018). A recent study shows that various retrotransposable elements, such as LINEs, ERV, IAP, and SINE B1, increase significantly in the aged mouse kidney and brain, where aging signals occur first (Ghanam *et al.* 2019). Furthermore, dysfunctional mitochondria can release mtDNA fragments, which leads to the activation of cGAS-STING signaling. Except for the nucleus, the only organelle having a genome is the mitochondria in the cell. There are many ways mtDNA can be leaked into the cytosol. In senescent cells, clearance of damaged mitochondria by mitophagy is not in time (Chen *et al.* 2020). Besides, the TFAM protein localized to the mitochondria can associate with mtDNA, forming nucleoid-like structures and imposing restrictions on mtDNA (Bonekamp and Larsson 2018; Ngo *et al.* 2014; Zierhut and Funabiki 2020). TFAM translocates to the cytosol during mitochondrial stress, helping cGAS bind mtDNA (West *et al.* 2015). The mtDNA in the cytosol increases by three to four fold upon TFAM depletion. Moreover, mtDNA can enter the cytoplasm through pore formation by BCL-2 associated X protein (BAX) (McArthur *et al.* 2018) and voltage-dependent anion channel (VDAC) (Kim *et al.* 2019a). The accumulation of extranuclear DNA species, including CCFs, cDNA, and mtDNA in senescent cells, elicit cGAS-STING signaling to promote full-spectrum SASP expression. CCFs, cDNA, and mtDNA constitute the accumulation of extranuclear DNA species in senescent cells, by which cGAS-STING signaling initiates.

Emerging evidence suggests a connection between the cGAS-STING pathway and premature aging diseases. One of them is Hutchinson Guilford Progeria (HGPS), and the cause of this disease is truncation of Lamin A (progerin). Replicative stress induced by progerin can lead to genomic instability, further activating the cGAS-STING pathway to initiate IFN responses (Kreienkamp *et al.* 2018). Meanwhile, the cGAS-STING pathway participates in neurodegenerative disorders, such as Ataxia-Telangiectasia (A-T), Huntington's disease (HD), and Parkinson's disease (PD) (Paul *et al.* 2021). It is especially noteworthy that the YAP/TAZ-cGAS-STING signaling conduit finds a link between mechanosensing and innate immunity. YAP/TAZ activity and cellular mechano-signaling are decreased upon physiological aging, leading to unscheduled cGAS-STING activation (Sladitschek-Martens *et al.* 2022). Significantly, several effective drugs, such as aspirin and quinacrine, reduce the cGAS–STING signaling transduction. Mechanically, aspirin can directly bind and acetylate cGAS to keep cGAS inactive (Dai *et al.* 2019), while quinacrine disrupts the conformation of dsDNA to influence the cGAS activity indirectly (Lama *et al.* 2019). Research on new inhibitors is being actively carried out.

TOLL-LIKE RECEPTORS (TLRs)

Toll-like receptors (TLRs) are the first described PRRs in the innate immune system, which are crucial in inflammatory responses (Fitzgerald and Kagan 2020; Iwasaki and Medzhitov 2010). They were first identified in Drosophila (Schneider *et al.* 1994) and demonstrated to play important roles in innate immunity by later studies (Gay and Keith 1991). Among TLRs, TLR4 was first identified. After the discovery of

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TLR4, many PRRs and corresponding ligands were disclosed (Wright 1999). There are 13 different TLRs (TLRs 1–13) discovered in mammals until now (Kawai and Akira 2010), and 10 of these (TLRs 1–10) function in humans. Upon stimuli, TLRs recognize specific DAMPs and PAMPs to initiate signaling transduction (Anthoney *et al.* 2018; Satoh and Akira 2016). According to different adaptor proteins, there are two TLR signaling pathways, namely MyD88-dependent and MyD88-independent (Kawai and Akira 2007). Most TLRs depend on the MyD88-dependent pathway (von Bernuth *et al.* 2008). In this pathway, secretion of various pro-inflammatory factors, such as IL-6, IL-1, and TNF-α, are induced by MyD88 signaling, leading to inflammation (Gay *et al.* 2014; Kawai and Akira 2011). First, TLRs interact with the C-terminus of MyD88 through the intracellular Toll/interleukin-1 receptor (TIR) domain, and IL-1R-related kinase 4 (IRAK4) is recruited to the N terminus of MyD88 (De Nardo *et al.* 2018). Then, the central kinase domain of MyD88 undergoes autophosphorylation, which leads to the activation of IRAK1 and IRAK2. After that, transforming growth factor (TGF)-β-activated kinase 1 (TAK1) and two TAK-binding proteins (TAB1 and TAB4) form a complex with ubiquitin ligase TNF receptor associated factor 6 (TRAF6), by which IκB kinase (IKK) complex is activated through phosphorylation. Phosphorylation of IκB leads to its degradation through the ubiquitin-proteasome pathway (Hacker *et al.* 2006; Verstak *et al.* 2009), which releases the transcription factor NF-κB. The unleashing of NF-κB causes it to translocate from the cytoplasm to the nucleus and initiates the expression of inflammatory cytokines (Cohen and Strickson 2017; Kawai *et al.* 2004). Furthermore, TLR3 and TLR4 mediate the MyD88-independent pathway. TLR4 recruits and activates TIR-domain-containing adaptor inducing interferon-γ (TRIF) and TRIF-related adaptor molecule (TRAM), leading to the activation of IRF3 and NF-kB, eventually stimulating IFN-I production. TLR3 activation also needs adaptor TRIF, but the downstream signal molecules recruited are TBK1 and IKKε (Arancibia *et al.* 2007; Okun *et al.* 2009).

Numerous studies claim that TLRs are involved in aging and aging-related disorders, such as neurodegenerative diseases, cardiovascular diseases, and disc degeneration. The progress of neurodegeneration is caused by neuroinflammation. In this respect, TLRs are important in CNS disorders, especially TLR4 (Azam *et al.* 2019). The TLR4/NF-kB-signaling pathway can lead to many kinds of inflammatory cytokines, such as MMP-9 and COX-2, which may be a cause of secondary brain injury (Hua *et al.* 2007; Kerfoot *et al.* 2004; Lucas *et al.* 2006; Wang *et al.* 2000). In the clinic, loading nanoparticles with quercetin can prevent AD progression as a result of suppressing TLR4-involved pathway (Testa *et al.* 2014). Meanwhile, quercetin nanoparticles also downregulate inflammatory cytokine secretion by inhibiting the expression of TLR2 and TLR4 (Bhaskar *et al.* 2011). Based on these observations, TLR4 may be a potential target to develop novel strategies for neurodegenerative disorders. Many studies have shown that different TLRs are involved in the process of atherosclerosis through distinct mechanisms (Li *et al.* 2020; Wolf and Ley 2019). TLR7 can inhibit inflammation in atherosclerosis by secreting TNF-α and IL-10, so it is regarded as a prognosis marker in severe atherosclerosis patients (Karadimou *et al.* 2017). Besides, cell-free DNA (cf DNA) recognized by TLR9 can lead to the development of vascular inflammation, which induces the formation of initial atherosclerotic plaques (Fukuda *et al.* 2019). TLR5 upregulates the expression of proinflammatory factors by inducing the activation of NADPH oxidase 4 (Nox4), which is crucial for atherosclerotic intimal hyperplasia (Kim *et al.* 2016; Kim *et al.* 2019b). TLRs are also closely associated with disc degeneration and virus-induced aging. It is reported that TLR2 can induce senescence in intervertebral disc cells, and o-vanillin may be a suitable drug for these patients (Mannarino *et al.* 2021). Similarly, another study gives the novel hyaluronic acid granular hydrogel as a new strategy for osteoarthritis progression via suppressing TLR2-mediated cellular senescence (Zhang *et al.* 2023). Furthermore, TLR3 causes senescence in patients infected with COVID-19 and tremendously increases SASP production (Tripathi *et al.* 2021).

IFN-I

Interferons were first discovered in 1957 by Isaacs and Lindenmann (Isaacs and Lindenmann 1957). They are crucial molecules playing important roles in both innate and adaptive immunity. Through various pattern recognition receptors (PRRs), the process of innate immunity initiates, and the type I IFN genes are induced rapidly. These receptors recognize molecules from pathogens known as pathogen-associated molecular patterns (PAMPs), such as cytosolic DNA, double-stranded RNA (dsRNA), flagellin, bacterial lipoproteins, and bacterial lipopolysaccharides (Amarante-Mendes *et al.* 2018). In addition to PAMPs, damage-associated molecular patterns (DAMPs) presented by damaged cells can also be perceived by certain PRRs (Roh and

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Sohn 2018). Many other non-classical IFN-I stimuli were found recently, such as DNA damage, FAS/FASL activation (Qadir *et al.* 2020), and endogenous cytosolic chromatin fragments. These non-classical IFN-I stimuli link innate immunity and senescence together (Deng *et al.* 2014; Sistigu *et al.* 2014; Yu *et al.* 2015). Herein, we briefly review the signaling mechanisms of IFN-I induction induced by PRRs. First, endosomal Toll-like receptor (TLR3), as well as cytosolic receptors retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), recognize dsRNA. Cytosolic TLR9 and cGAS recognize DNA. Primarily, pattern recognition receptors converge signals upon IKK-family kinases, leading to the phosphorylation and activation of two downstream transcription factors, IRF3 and NF-κB. Upon activation, these factors directly induce the IFN-β gene and various antiviral target genes expression, including ISG15 (Villarroya-Beltri *et al.* 2017) and many antiviral genes containing MxA/B, IFIT- and IFITM-family genes (Ashley *et al.* 2019). After that, secreted IFN-β from upstream pathways activates another receptor called the IFNAR1/2 receptor. Then, Janus kinase phosphorylates STAT1 and STAT2, resulting in a canonical complex of STAT1/STAT2/IRF9 (ISGF3) formation. Certain genes, called interferon-stimulated genes (ISGs) expressing, contain ISGF3 response elements (ISRE), leading to a second wave of IFN-β production (Ng *et al.* 2016). Meanwhile, autocrine IFN-I causes cell-cycle arrest through p53 and Rb checkpoint pathways (Braumuller *et al.* 2013; Sangfelt *et al.* 1999). In addition, two ISGs can contribute to the cycle. While IFI16 can repress c-myc, IFI202a/b gene products can interfere with the transactivation of MYC and E2F proteins (Song *et al.* 2010). Besides, in many cases, apoptosis can serve as an efficient innate immune mechanism resulting from poly-ubiquitinated IRF3, named RLR-induced IRF-3-mediated apoptosis (RIPA) (Chattopadhyay *et al.* 2016).

There has been plenty of evidence pointing out that IFN-I plays a strong part in DNA damage signaling and senescence (Frisch and MacFawn 2020). The up-regulation of ISGs was first found in senescent fibroblasts in 1995, which can be inhibited by IFN-β-neutralizing antibodies (Tahara *et al.* 1995). Then, in 2003, through oligonucleotide microarrays, Michael Tainsky's laboratory found that among the genes upregulated in senescent cells and down-regulated in immortalized cells simultaneously, 46% were IFNs or ISGs (Kulaeva *et al.* 2003). In the same year, Tadatsugu Taniguchi's laboratory found that in response to DNA damage, IFN-I increased the expression of p53 and cooperated with stressful events to activate p53 (Takaoka *et al.* 2003). IFN-I can engage in p53 signals, and the important role p53 plays is initiating senescence from growth arrest, but p53 is not necessary for the secretion of SASP (Coppe *et al.* 2008), which is exactly the stage where IFN-I comes into play. Later reports showed that cell senescence could be induced by prolonged IFN-β treatment in fibroblasts, resulting in various DNA damage response (DDR) features containing phosphorylation of γ-H2AX foci (indicative of unrepaired double-strand DNA breaks), ATM, p53, CHK2, and increased ROS (Moiseeva *et al.* 2006). The senescence was dependent on ATM and ROS. Meanwhile, the laboratory of Serge Fuch (Yu *et al.* 2015) found that DSB induced by FokI nuclease fusion proteins resulted in IFN-β production and the induction of phospho-STAT1. Furthermore, this phenomenon depended on ATM, IRF3, and IKKα/β activation. More surprisingly, IRF3 was found to resident in chromatin repair foci, which provided a molecular basis.

A clinical study observed that there was an increase in DNA repair foci and high expression of IFN-β in fibroblasts isolated from Terc-deficient mice or progeria patients (Yu *et al.* 2015). Prominently, neutralizing antibodies targeting IFN-β can partially combat the effects of senescence, whether in the normal senescent and progeria fibroblasts. This laboratory also demonstrated that knockout of the IFNAR1 receptor partially survived the phenotypes resulting from the shorter telomeres in stem cells, with distorted intestinal crypt-and-villus structure. These results suggested that IFN-I signaling participated in stem cell senescence. In agreement with previous studies, IFN-I also upregulates DDR because knockout of IFNAR1 leads to decreased p53 activation and the senescence markers, p21WAF/CIP, and p16INK4a. Research suggests that $Terc^{-/-}$ mice are more susceptible to suffering a premature aging phenotype after incubating for some generations. Prominently, the IFNAR1 knockout relieved this phenotype and increased life span significantly (Yu *et al.* 2015). In conclusion, not only IFN-I contributes to DDR-induced senescence, but also DDR contributes to IFN-I. Besides, as membrane-bound IFNAR1 gradually decreases and IFN-I signaling is inhibited with age, melanoma progression commonly occurs (Araya and Goldszmid 2017; Fuchs 2013). It is conceivable that IFN-I and IFNAR1 are likely potential targets for increasing the health span of older adults.

NF-κB

Inflammaging is defined as a chronic, sterile, low-grade inflammation (Franceschi *et al.* 2000), which does not

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simply increase with age but has a highly positive correlation with a decline in health, age-related diseases, and mortality risk (Arai *et al.* 2015; Bruunsgaard 2006; Krabbe *et al.* 2004). Inflammaging results from a chronic gathering of senescent cells with age, which produce large amounts of SASP, including chemokines, proinflammatory cytokines, metalloproteases, soluble receptors, growth factors, and certain protease inhibitors (Coppe *et al.* 2010; Freund *et al.* 2010; Malaquin *et al.* 2016). The secretion of SASP varies in certain signaling pathways from cell to cell, but the central one is the same: the transcription factor NF-κB (Chien *et al.* 2011; Meyer *et al.* 2017; Salminen *et al.* 2012). It plays an important role in regulating inflammation response in the immunity process, and a later study discovered it to be crucial in SASP generation.

There are a wide variety of inducers leading to the activation of NF-κB, containing ionizing radiation, bacterial lipopolysaccharides, reactive oxygen species (ROS), abnormal DNA and RNA, and cytokines like interleukin 1-beta (IL-1β), and tumor necrosis factor-alpha (TNF-α) (Zhang *et al.* 2017). During the resting state, NF-κB localizes in the cytoplasm, forming a complex with inhibitors of NF-κB (IκBs), which maintains the inactive stage of NF-κB. In response to stimulation, IκB kinase (IKK) phosphorylates IκBs for degradation, resulting in the transport of NF-κB to the nucleus. After that, larger quantities of gene transcription are initiated, which contributes to cell proliferation, inflammation, and apoptosis (Oeckinghaus and Ghosh 2009), which is termed the "canonical pathway" of NF-κB because NF-κB essential modulator (NEMO) participates in the process, which is a part of the IKK complex (Hariharan *et al.* 2021). Except for cGAS-STING signals, the upstream canonical pathway includes dsRNA-dependent protein kinase (PKR) (Williams 1999) and myeloid differentiation primary response 88 (MyD88) (D'Acquisto *et al.* 2002). The PKR can also participate in the "noncanonical pathway" of NF-κB activation by TNF-α. This pathway can lead to a chronic and persistent inflammation response, contrasting with the canonical one (Dorrington and Fraser 2019). Besides, the serine-threonine protein kinases MAPKs activate NF-κB in a noncanonical way. During pathophysiological and stress, MAPKs activated by P38 mitogen mediate the production of IL-1β and TNF-α (Battagello *et al.* 2020). To achieve full activation, The Janus Kinase (JAK)-transcription factor (STAT) pathway needs to be activated by IL-6, a remarkable marker in senescent cells. Upon IL-6 sensed, STAT3 is phosphorylated and then translocated to the nucleus to decrease the production of IFN-γ and release inflammatory factors (Brasier 2010). Apart from the signaling above, cGAS-STING can also control innate immunity by transcribing acute-phase serum amyloids (A-SAAs) and Toll-like receptor 2 (TLR2) mediated by NF-κB in senescent cells. In this pathway, TLR2 recognizes A-SAAs, leading to the further activation of NF-κB with the secretion of proinflammatory SASP molecules, which serves as a positive feedback loop in senescence. As reported, overexpression of TLR2 causes cell cycle arrest, leading to SA-β-gal production, while TLR2 deficiency decreases the expression of p16, p21, and SASP (Hari *et al.* 2019).

Recently, studies have shown that NF-κB-mediated inflammation directly affects DNA damage response (Fang *et al.* 2014; Hinz *et al.* 2010; Kang *et al.* 2015). When DNA damage occurs, ATM and RAD3-related (ATR) and ataxia-telangiectasia mutated (ATM) are recruited to the DNA lesion by single-stranded DNA breaks and DSBs, respectively (d'Adda di Fagagna 2008). During the resting state, the p62 protein can target transcription factor GATA4 for degradation by autophagy. Upon stimuli, p62 is restrained by ATM or ATR, providing the basis for GATA4 to induce inflammation mediated by NF-κB. In addition, via translocation to cytoplasm, ATM can activate TRAF6 to initiate NF-κB signals further. Prominently, ATM can activate STING without cGAS, contributing to NF-κB activation (Dunphy *et al.* 2018). Additionally, activated ATM can degrade IκBα, further leading to the phosphorylation of RELA (p65), resulting in NF-κB activation. ATM has a dramatic effect on the process. To sum up, DNA damage has increasingly become a crucial regulator of inflammation, binding inflammation and aging together (Zhao *et al.* 2023).

The study on NF-κB pathways may provide new drug targets for aging and aging-related illnesses. For this problem, a well-studied antidiabetic drug, metformin, is wildly used to relieve inflammaging. Metformin can restrain NF-κB signaling and the production of proinflammatory factors downstream (Moiseeva *et al.* 2013). Meanwhile, it can activate autophagy to clear up senescent cells (Bharath *et al.* 2020). Recent studies showed that metformin can promote autophagy, improve mitochondria function in $CD4^+$ T cells isolated from old donors in vitro, and restrict the age-related proinflammatory profile of Th17. Furthermore, many reports focus on the roles of metformin in reducing autoimmunity and supporting healthy immune function.

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Besides, there are new therapies targeting IL-6 to suppress NF-κB pathways. Dexamethasone, a steroid hormone, can retain NF-κB in the cytosol by increasing IκB expression (Auphan *et al.* 1995) and inhibit the activity of NF-κB by interfering with IL-6 secretion (Buhl *et al.* 2019; Ge *et al.* 2018; Laberge *et al.* 2012). Tocilizumab and sarilumab, two antibodies targeting the IL-6 receptor, have been utilized in clinics as an ideal therapeutic method for severe patients (Wise 2020).

NLRP3

Acting as a signal complex, it is obvious that the inflammasomes play an important role in various inflammation-associated diseases. There are various inflammasomes, such as NLRP1, NLRP3, NLRC4, IPAF, and AIM2. Among them, the NLRP3 inflammasome garners particular attention for its capacity to identify numerous DAMPs and PAMPs and to resist the invasion of exotic microbes. The NLRP3 inflammasome contains three members: nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain containing receptor 3 (NLRP3), apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and pro-caspase-1 (Yang *et al.* 2019). NLRP3 monomers gather in oligomers, then recruit and bind with ASC upon danger stimuli. Afterward, pro-caspase-1 joins the signal complex via ASC (Yang *et al.* 2019; Zahid *et al.* 2019). The activation of NLRP3 inflammasome requires PAMPs and DAMPs. Derived from immune cells stimulated by damaged tissues, they are termed DAMPs, whereas sugar conjugates and glycans compose PAMPs. There have been many studies on PAMPs and DAMPs with the NLRP3 inflammasome recently. For instance, NLRP3 inflammasome can be activated by the cumulation of uric acid (UA) (Martinon *et al.* 2006) and the expression of cathepsin B (CTSB) (Tang *et al.* 2018). Furthermore, sensed by TLR4 localized on the cellular plasma membrane, lipopolysaccharides (LPS) from Gram-negative bacteria activate NF-κB to promote the activation of the NLRP3 inflammasome, sending the signals to caspase-1 (Yu *et al.* 2017). After that, caspase-1 cleaves pro-IL-18 and pro-IL-1β to generate IL-18 and IL-1β, and then the inflammatory response initiates to secrete plenty of proinflammatory factors (Yang *et al.* 2019).

Mounting evidence shows that NLRP3 participates in the process of many age-related symptoms. Regarding aging-related fibrosis, the alveolar macrophages isolated from old mice with bleomycin (BLM)-induced lung injury have a higher activation of NLRP3 inflammasome and secret more IL-18 and IL-1β, compared to young mice (Stout-Delgado *et al.* 2016). Notably, chronic aging-related diseases, like nonalcoholic fatty liver disease, lead to metabolic disorders, causing hyperactivation of NLRP3 inflammasomes and severe liver fibrosis (Liu *et al.* 2022). Consequently, the NLRP3 inflammasome is one of the main causes of fibrosis development. Not only that, it also contributes to organ aging. In the ovary, the expression of NLRP3 increases with age in WT mice, which is not observed in the littermate control of NLRP3 KO mice. Knockout of NLRP3 can ameliorate the function of the ovary and increase pregnancy rates obviously (Navarro-Pando *et al.* 2021).

Controlling the activation of inflammatory response is crucial for delaying the natural aging process and staying healthy. NLRP3 may be an appropriate target to be inhibited, by which inflammation is suppressed (Zahid *et al.* 2019). Recently, in macrophages from old mice, deacetylation of NLRP3 via SIRT2 suppressed age-related inflammation resulting from NLRP3 activation (He *et al.* 2020). The expression of SIRT2 reduced with age, and the NLRP3 inflammasome was activated by mitochondrial dysfunction, destroying the regenerative ability of HSCs (Luo *et al.* 2019). In addition, MCC950, an inhibitor of NLRP3, can inhibit the mammalian targets of rapamycin (mTOR) pathway in aging mice, thereby increasing autophagy and reducing the inflammation response, finally improving liver dysfunction (Marin-Aguilar *et al.* 2020). More importantly, MCC950 can reduce liver, lung, and kidney fibrosis in aging mice. Besides, MCC950 can increase the fertilization ratio in female mice to the same level in $Nlrp3^{-/-}$ mice (Navarro-Pando *et al.* 2021). MCC950 has significant efficacy and specific features in age-related inflammation in mice, but it still has a long way to go for human clinical trials.

SUMMARY AND PERSPECTIVES

From the modern point of view, aging means symptoms of degenerative changes, leading to many chronic diseases, including neurological degeneration, fibrosis, cardiovascular disease, diabetes, and cancer (Cai *et al.* 2022). In contrast, cellular senescence serves as the main cause of aging. Upon stimuli, such as exposure to genotoxic agents and oncogene activation, cells enter a stage with irreversible growth arrest, accompanied by secretory features, oxidative damage of

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biomacromolecules, and metabolic changes. The SASP secreted by senescent cells recruits immune cells to recognize and clear up damaged cells, finally maintaining the balance of the immune system (Kohli *et al.* 2021). However, immune system dysfunction causes senescent cell accumulation, persistent tissue damage, and, more severely, chronic low-grade inflammation, termed inflammaging (Teissier *et al.* 2022). The key strategy to suppress senescence is improving the immune function and reducing the inflammation response. In this review, we introduce the signaling pathways involved in senescence. First, we briefly give the basic conception of senescence, including the initiation of senescence, the characteristics of different stages, and the classic pathways contributing to senescence. Second, we summarize the key innate immune pathways participating in senescence, including cGAS-STING pathways, TLRs pathways, IFN-I and downstream pathways, NF-κB pathways, and NLRP3 inflammasome pathways. In senescent cells, the occurrence and regulation of these pathways, different from normal responses, are elaborated in the following paragraphs. Each part is not independent and is linked to all the others. cGAS-STING pathways play important parts in connecting cellular damage and inflammation, the activation of which can lead to both IFN-I and inflammatory factors. Similarly, TLRs-mediated signal transduction pathways can both activate proinflammatory cytokine responses and upregulate IFN-I and ISGs expression, integrating innate immune responses. While IFN-I and ISGs can amplify the damage signals and trigger the clearance of senescent cells. Meanwhile, it can work in concert with NF-κB pathways also. Inflammatory factors secreted upon NF-κB activation serve as triggers for the downstream of IFN-I, like IL-6. Besides, NF-κB pathways can provide the first signal of the NLRP3 activation. At the end of each section, we discuss the potential strategies targeting the key molecules, including cGAS, STING, TLRs, IFN-I, IL-6, and NLRP3. Some of the drugs above have strong and stable effects in animal tests, but more research is needed to conduct human trials.

In this review, we summarize the crucial innate immune signaling pathways associated with cellular senescence and elaborate on the relationship between cellular senescence and innate immunity (Fig. 1). Senescence, IFN-I, and inflammation all have one thing in common: they are all double-edged swords with both advantages and disadvantages. On one hand, aging removes damaged cells, facilitates tissue recovery, and inhibits carcinogenesis. On the other hand, it can also cause premature aging and a series of aging-related diseases. IFN-I responses, on the one hand, can help the body resist pathogen invasion and help the immune clearance of target cells. On the other hand, it can also cause autoimmune diseases. Likewise, inflammation can secrete inflammatory factors to help the host kill pathogenic microorganisms, leading to apoptosis and cell death but disrupting immune homeostasis. At present, the study of cellular senescence is in the ascendant, and the relationship with immunity has gradually received attention because of the COVID-19 pandemic. According to current research, immunity is involved in cellular senescence, mainly in the later stage, playing a regulatory role (Frisch and MacFawn 2020). Whether IFN-I and inflammatory signaling pathways are involved in the early stages of aging warrants further study. Many studies have only found the link between immune molecules and senescence, but the mechanism has yet to be addressed. For example, cGAS-STING is involved in the process of aging regulated by YAP/TAZ, but the specific mechanism has not been discovered (Sladitschek-Martens *et al.* 2022). In addition, it is not known whether the senescence pathway is directly involved in immune regulation and whether p21, p16, and DNA damage-related molecules are directly involved. Overall, the crosstalk between senescence and innate immune signaling pathways remained to be explored.

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Compliance with Ethical Standards

Conflict of interest Jinxiu Hou, Yi Zheng, and Chengjiang Gao declare that they have no conflict of interest

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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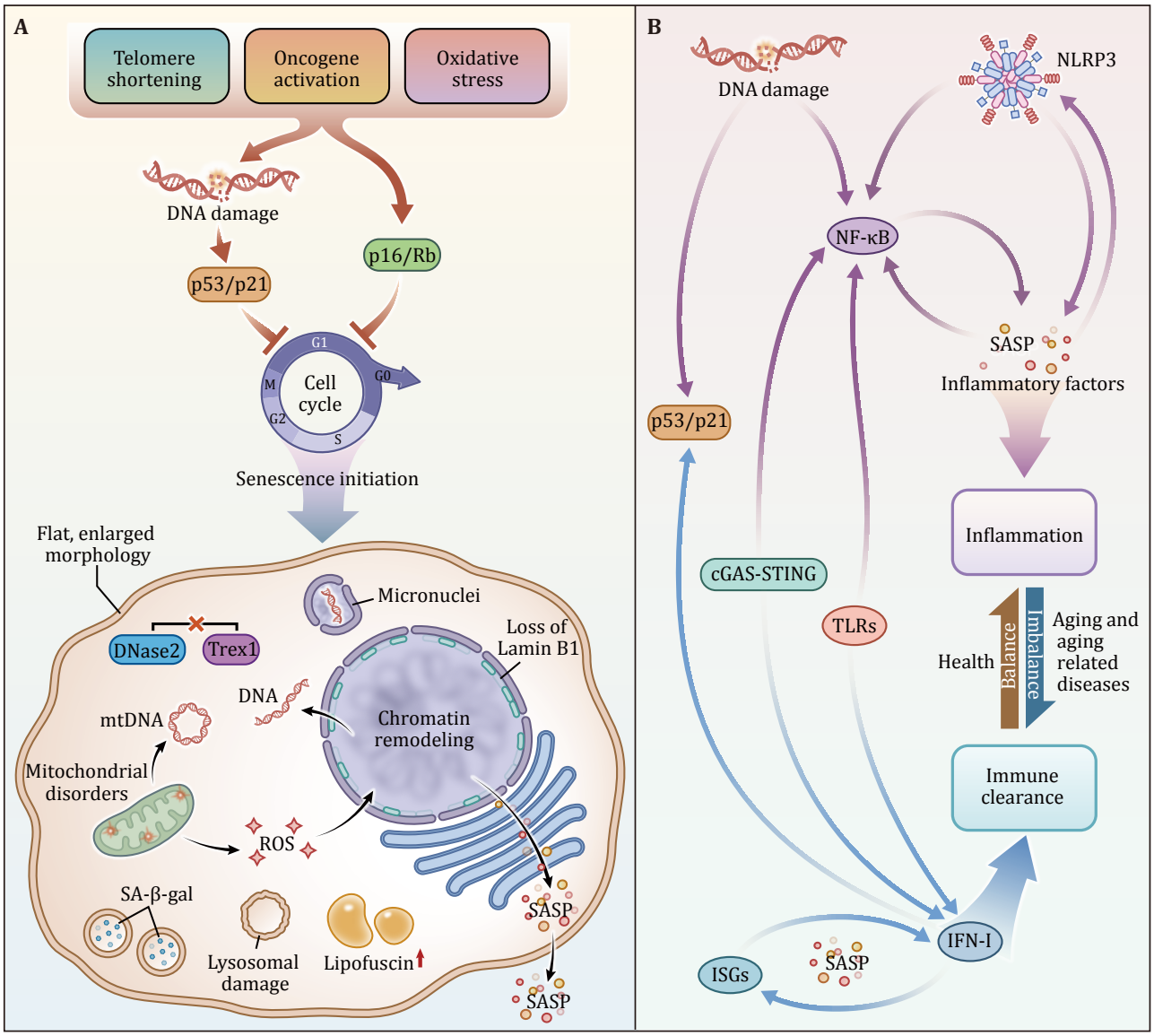


Fig. 1 The interaction between senescence and innate immune signaling pathways. **A** The mechanisms of cell senescence. During senescence, p53-p21 and p16-Rb pathways are firstly activated by numerous stressors, leading to irreversible cell-cycle arrest. Then, a series of changes, such as cytoplasmic DNA accumulation, mitochondrial disorders, and lysosomal damage, occur. Additionally, SA-β-gal activity, lipofuscin accumulation, and SASP production are induced and regarded as senescent markers. **B** cGAS-STING, TLRs, and NLRP3 inflammasome participate in the process of senescence and promote the SASP through the production of inflammatory factors, IFN-I, and downstream ISGs, respectively. In addition, NF-κB can be stimulated by DNA damage, and IFN-I can regulate the P53 signaling pathway, which is directly involved in the signaling pathway of senescence. The balance of inflammation and immunity is essential for the body to achieve healthy aging

References

Ablasser A, Hur S (2020) Regulation of cGAS- and RLR-mediated immunity to nucleic acids. Nat Immunol 21(1): 17–29

Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, Athineos D, Kang TW, Lasitschka F, Andrulis M, Pascual G, Morris KJ, Khan S, Jin H, Dharmalingam G, Snijders AP, Carroll T, Capper D, Pritchard C, Inman GJ, Longerich T, Sansom OJ, Benitah SA, Zender L, Gil J (2013) A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat Cell Biol 15(8): 978–990

Akira S, Uematsu S, Takeuchi O (2006) Pathogen recognition and innate immunity. Cell 124(4): 783–801

Aleynick M, Svensson-Arvelund J, Flowers CR, Marabelle A, Brody JD (2019) Pathogen molecular pattern receptor agonists: treating cancer by mimicking infection. Clin Cancer Res 25(21): 6283–6294

Amarante-Mendes GP, Adjemian S, Branco LM, Zanetti LC, Weinlich R, Bortoluci KR (2018) Pattern recognition receptors and the

 © The Author(s) 2023

host cell death molecular machinery. Front Immunol 9: 2379. https://doi.org/10.3389/fimmu.2018.02379

Anthoney N, Foldi I, Hidalgo A (2018) Toll and Toll-like receptor signalling in development. Development 145(9): dev156018. https://doi.org/10.1242/dev.156018

Arai Y, Martin-Ruiz CM, Takayama M, Abe Y, Takebayashi T, Koyasu S, Suematsu M, Hirose N, von Zglinicki T (2015) Inflammation, but not telomere length, predicts successful ageing at extreme old age: a longitudinal study of semi-supercentenarians. EBioMedicine 2(10): 1549–1558

Arancibia SA, Beltran CJ, Aguirre IM, Silva P, Peralta AL, Malinarich F, Hermoso MA (2007) Toll-like receptors are key participants in innate immune responses. Biol Res 40(2): 97–112

Araya RE, Goldszmid RS (2017) IFNAR1 degradation: a new mechanism for tumor immune evasion? Cancer Cell 31(2): 161-163

Ashley CL, Abendroth A, McSharry BP, Slobedman B (2019) Interferon-independent innate responses to cytomegalovirus. Front Immunol 10: 2751. https://doi.org/10.3389/fimmu.2019.02751

Auphan N, DiDonato JA, Rosette C, Helmberg A, Karin M (1995) Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. Science 270(5234): 286–290

Azam S, Jakaria M, Kim IS, Kim J, Haque ME, Choi DK (2019) Regulation of Toll-like receptor (TLR) signaling pathway by polyphenols in the treatment of age-linked neurodegenerative diseases: focus on TLR4 signaling. Front Immunol 10: 1000. https://doi.org/10.3389/fimmu.2019.01000

Battagello DS, Dragunas G, Klein MO, Ayub ALP, Velloso FJ, Correa RG (2020) Unpuzzling COVID-19: tissue-related signaling pathways associated with SARS-CoV-2 infection and transmission. Clin Sci (Lond) 134(16): 2137–2160

Beausejour CM, Krtolica A, Galimi F, Narita M, Lowe SW, Yaswen P, Campisi J (2003) Reversal of human cellular senescence: roles of the p53 and p16 pathways. EMBO J 22(16): 4212–4222

Bharath LP, Agrawal M, McCambridge G, Nicholas DA, Hasturk H, Liu J, Jiang K, Liu R, Guo Z, Deeney J, Apovian CM, Snyder-Cappione J, Hawk GS, Fleeman RM, Pihl RMF, Thompson K, Belkina AC, Cui L, Proctor EA, Kern PA, Nikolajczyk BS (2020) Metformin Enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation. Cell Metab 32(1): 44–55

Bhaskar S, Shalini V, Helen A (2011) Quercetin regulates oxidized LDL induced inflammatory changes in human PBMCs by modulating the TLR-NF-kappaB signaling pathway. Immunobiology 216(3): 367–373

Bonekamp NA, Larsson NG (2018) SnapShot: mitochondrial nucleoid. Cell 172(1–2): 388–388.e1

Brasier AR (2010) The nuclear factor-kappaB-interleukin-6 signalling pathway mediating vascular inflammation. Cardiovasc Res 86(2): 211–218

Braumuller H, Wieder T, Brenner E, Assmann S, Hahn M, Alkhaled M, Schilbach K, Essmann F, Kneilling M, Griessinger C, Ranta F, Ullrich S, Mocikat R, Braungart K, Mehra T, Fehrenbacher B, Berdel J, Niessner H, Meier F, van den Broek M, Haring HU, Handgretinger R, Quintanilla-Martinez L, Fend F, Pesic M, Bauer J, Zender L, Schaller M, Schulze-Osthoff K, Rocken M (2013) T-helper-1-cell cytokines drive cancer into senescence. Nature 494(7437): 361–365

Bruunsgaard H (2006) The clinical impact of systemic low-level inflammation in elderly populations. With special reference to cardiovascular disease, dementia and mortality. Dan Med Bull 53(3): 285–309

Buhl JL, Selt F, Hielscher T, Guiho R, Ecker J, Sahm F, Ridinger J, Riehl D, Usta D, Ismer B, Sommerkamp AC, Martinez-Barbera JP, Wefers AK, Remke M, Picard D, Pusch S, Gronych J, Oehme I, van Tilburg CM, Kool M, Kuhn D, Capper D, von Deimling A, Schuhmann MU, Herold-Mende C, Korshunov A, Brummer T, Pfister SM, Jones DTW, Witt O, Milde T (2019) The senescence-associated secretory phenotype mediates oncogene-induced senescence in pediatric pilocytic astrocytoma. Clin Cancer Res 25(6): 1851–1866

Bussian TJ, Aziz A, Meyer CF, Swenson BL, van Deursen JM, Baker DJ (2018) Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. Nature 562(7728): 578–582

Cai Y, Song W, Li J, Jing Y, Liang C, Zhang L, Zhang X, Zhang W, Liu B, An Y, Li J, Tang B, Pei S, Wu X, Liu Y, Zhuang CL, Ying Y, Dou X, Chen Y, Xiao FH, Li D, Yang R, Zhao Y, Wang Y, Wang L, Li Y, Ma S, Wang S, Song X, Ren J, Zhang L, Wang J, Zhang W, Xie Z, Qu J, Wang J, Xiao Y, Tian Y, Wang G, Hu P, Ye J, Sun Y, Mao Z, Kong QP, Liu Q, Zou W, Tian XL, Xiao ZX, Liu Y, Liu JP, Song M, Han JJ, Liu GH (2022) The landscape of aging. Sci China Life Sci 65(12): 2354–2454

Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A (2019) Cellular senescence: aging, cancer, and injury. Physiol Rev 99(2): 1047–1078

Chattopadhyay S, Kuzmanovic T, Zhang Y, Wetzel JL, Sen GC (2016) Ubiquitination of the transcription factor IRF-3 activates RIPA, the apoptotic pathway that protects mice from viral pathogenesis. Immunity 44(5): 1151–1161

Chen G, Kroemer G, Kepp O (2020) Mitophagy: an emerging role in aging and age-associated diseases. Front Cell Dev Biol 8: 200. https://doi.org/10.3389/fcell.2020.00200

Chien Y, Scuoppo C, Wang X, Fang X, Balgley B, Bolden JE, Premsrirut P, Luo W, Chicas A, Lee CS, Kogan SC, Lowe SW (2011) Control of the senescence-associated secretory phenotype by NF-kappaB promotes senescence and enhances chemosensitivity. Genes Dev 25(20): 2125–2136

Childs BG, Gluscevic M, Baker DJ, Laberge RM, Marquess D, Dananberg J, van Deursen JM (2017) Senescent cells: an emerging target for diseases of ageing. Nat Rev Drug Discov 16(10): 718–735

Childs BG, Li H, van Deursen JM (2018) Senescent cells: a therapeutic target for cardiovascular disease. J Clin Invest 128(4): 1217–1228

Cohen P, Strickson S (2017) The role of hybrid ubiquitin chains in the MyD88 and other innate immune signalling pathways. Cell Death Differ 24(7): 1153–1159

Coppe JP, Desprez PY, Krtolica A, Campisi J (2010) The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol 5: 99–118

Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6(12): 2853–2868

Corrales L, Matson V, Flood B, Spranger S, Gajewski TF (2017) Innate immune signaling and regulation in cancer immunotherapy. Cell Res 27(1): 96–108

D'Acquisto F, May MJ, Ghosh S (2002) Inhibition of nuclear factor kappa B (NF-B): an emerging theme in anti-inflammatory therapies. Mol Interv 2(1): 22–35

d'Adda di Fagagna F (2008) Living on a break: cellular senescence as a DNA-damage response. Nat Rev Cancer 8(7): 512–522

Dai J, Huang YJ, He X, Zhao M, Wang X, Liu ZS, Xue W, Cai H, Zhan XY, Huang SY, He K, Wang H, Wang N, Sang Z, Li T, Han QY, Mao J, Diao X, Song N, Chen Y, Li WH, Man JH, Li AL, Zhou T, Liu ZG, Zhang XM, Li T (2019) Acetylation blocks cGAS activity and

© The Author(s) 2023

inhibits self-DNA-induced autoimmunity. Cell 176(6): 1447–1460

Davalos AR, Kawahara M, Malhotra GK, Schaum N, Huang J, Ved U, Beausejour CM, Coppe JP, Rodier F, Campisi J (2013) p53-dependent release of Alarmin HMGB1 is a central mediator of senescent phenotypes. J Cell Biol 201(4): 613–629

De Cecco M, Ito T, Petrashen AP, Elias AE, Skvir NJ, Criscione SW, Caligiana A, Brocculi G, Adney EM, Boeke JD, Le O, Beausejour C, Ambati J, Ambati K, Simon M, Seluanov A, Gorbunova V, Slagboom PE, Helfand SL, Neretti N, Sedivy JM (2019) L1 drives IFN in senescent cells and promotes age-associated inflammation. Nature 566(7742): 73–78

De Nardo D, Balka KR, Cardona Gloria Y, Rao VR, Latz E, Masters SL (2018) Interleukin-1 receptor-associated kinase 4 (IRAK4) plays a dual role in myddosome formation and Toll-like receptor signaling. J Biol Chem 293(39): 15195–15207

Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, Li XD, Mauceri H, Beckett M, Darga T, Huang X, Gajewski TF, Chen ZJ, Fu YX, Weichselbaum RR (2014) STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. Immunity 41(5): 843–852

Dorrington MG, Fraser IDC (2019) NF-kappaB signaling in macrophages: dynamics, crosstalk, and signal integration. Front Immunol 10: 705. https://doi.org/10.3389/fimmu.2019.00705

Dou Z, Xu C, Donahue G, Shimi T, Pan JA, Zhu J, Ivanov A, Capell BC, Drake AM, Shah PP, Catanzaro JM, Ricketts MD, Lamark T, Adam SA, Marmorstein R, Zong WX, Johansen T, Goldman RD, Adams PD, Berger SL (2015) Autophagy mediates degradation of nuclear lamina. Nature 527(7576): 105–109

Duan X, Ponomareva L, Veeranki S, Panchanathan R, Dickerson E, Choubey D (2011) Differential roles for the interferon-inducible IFI16 and AIM2 innate immune sensors for cytosolic DNA in cellular senescence of human fibroblasts. Mol Cancer Res 9(5): 589–602

Dunphy G, Flannery SM, Almine JF, Connolly DJ, Paulus C, Jonsson KL, Jakobsen MR, Nevels MM, Bowie AG, Unterholzner L (2018) Non-canonical activation of the DNA sensing adaptor STING by ATM and IFI16 mediates NF-kappaB signaling after nuclear dna damage. Mol Cell 71(5): 745-760 e745

Erdal E, Haider S, Rehwinkel J, Harris AL, McHugh PJ (2017) A prosurvival DNA damage-induced cytoplasmic interferon response is mediated by end resection factors and is limited by Trex1. Genes Dev 31(4): 353–369

Fang L, Choudhary S, Zhao Y, Edeh CB, Yang C, Boldogh I, Brasier AR (2014) ATM regulates NF-kappaB-dependent immediate-early genes via RelA Ser 276 phosphorylation coupled to CDK9 promoter recruitment. Nucleic Acids Res 42(13): 8416–8432

Fenech M, Kirsch-Volders M, Natarajan AT, Surralles J, Crott JW, Parry J, Norppa H, Eastmond DA, Tucker JD, Thomas P (2011) Molecular mechanisms of micronucleus, nucleoplasmic bridge and nuclear bud formation in mammalian and human cells. Mutagenesis 26(1): 125–132

Fitzgerald KA, Kagan JC (2020) Toll-like receptors and the control of immunity. Cell 180(6): 1044–1066

Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 908: 244–254

Franceschi C, Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 69(Suppl 1): S4–9

Freund A, Orjalo AV, Desprez PY, Campisi J (2010) Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med 16(5): 238–246

Freund A, Patil CK, Campisi J (2011) p38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. EMBO J 30(8): 1536–1548

Frisch SM, MacFawn IP (2020) Type I interferons and related pathways in cell senescence. Aging Cell 19(10): e13234. https://doi.org/10.1111/acel.13234

Fuchs SY (2013) Hope and fear for interferon: the receptor-centric outlook on the future of interferon therapy. J Interferon Cytokine Res 33(4): 211–225

Fukuda D, Nishimoto S, Aini K, Tanaka A, Nishiguchi T, Kim-Kaneyama JR, Lei XF, Masuda K, Naruto T, Tanaka K, Higashikuni Y, Hirata Y, Yagi S, Kusunose K, Yamada H, Soeki T, Imoto I, Akasaka T, Shimabukuro M, Sata M (2019) Toll-like receptor 9 plays a pivotal role in angiotensin II-induced atherosclerosis. J Am Heart Assoc 8(7): e010860. https://doi.org/10.1161/JAHA.118.010860

Gay NJ, Keith FJ (1991) Drosophila Toll and IL-1 receptor. Nature 351(6325): 355–356

Gay NJ, Symmons MF, Gangloff M, Bryant CE (2014) Assembly and localization of Toll-like receptor signalling complexes. Nat Rev Immunol 14(8): 546–558

Ge H, Ke J, Xu N, Li H, Gong J, Li X, Song Y, Zhu H, Bai C (2018) Dexamethasone alleviates pemetrexed-induced senescence in non-small-cell lung cancer. Food Chem Toxicol 119: 86–97

Ghanam AR, Cao J, Ouyang X, Song X (2019) New insights into chronological mobility of retrotransposons *in vivo*. Oxid Med Cell Longev 2019: 2818415. https://doi.org/10.1155/2019/2818415

Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, Campisi J, Collado M, Evangelou K, Ferbeyre G, Gil J, Hara E, Krizhanovsky V, Jurk D, Maier AB, Narita M, Niedernhofer L, Passos JF, Robbins PD, Schmitt CA, Sedivy J, Vougas K, von Zglinicki T, Zhou D, Serrano M, Demaria M (2019) Cellular senescence: defining a path forward. Cell 179(4): 813–827

Graziano S, Kreienkamp R, Coll-Bonfill N, Gonzalo S (2018) Causes and consequences of genomic instability in laminopathies: Replication stress and interferon response. Nucleus 9(1): 258–275

Hacker H, Redecke V, Blagoev B, Kratchmarova I, Hsu LC, Wang GG, Kamps MP, Raz E, Wagner H, Hacker G, Mann M, Karin M (2006) Specificity in Toll-like receptor signalling through distinct effector functions of TRAF3 and TRAF6. Nature 439(7073): 204–207

Hari P, Millar FR, Tarrats N, Birch J, Quintanilla A, Rink CJ, Fernandez-Duran I, Muir M, Finch AJ, Brunton VG, Passos JF, Morton JP, Boulter L, Acosta JC (2019) The innate immune sensor Toll-like receptor 2 controls the senescence-associated secretory phenotype. Sci Adv 5(6): eaaw0254. https://doi.org/10.1126/sciadv.aaw0254

Hariharan A, Hakeem AR, Radhakrishnan S, Reddy MS, Rela M (2021) The role and therapeutic potential of NF-kappa-B pathway in severe COVID-19 patients. Inflammopharmacology 29(1): 91–100

Hayflick L (1965) The limited *in vitro* lifetime of human diploid cell strains. Exp Cell Res 37: 614–636

Hayflick L, Moorhead PS (1961) The serial cultivation of human diploid cell strains. Exp Cell Res 25: 585–621

He M, Chiang HH, Luo H, Zheng Z, Qiao Q, Wang L, Tan M, Ohkubo R, Mu WC, Zhao S, Wu H, Chen D (2020) An acetylation switch of the NLRP3 inflammasome regulates aging-associated chronic inflammation and insulin resistance. Cell Metab 31(3): 580–591.e5

Hinz M, Stilmann M, Arslan SC, Khanna KK, Dittmar G, Scheidereit C (2010) A cytoplasmic ATM-TRAF6-cIAP1 module links nuclear

 © The Author(s) 2023

DNA damage signaling to ubiquitin-mediated NF-kappaB activation. Mol Cell 40(1): 63–74

Hua F, Ma J, Ha T, Xia Y, Kelley J, Williams DL, Kao RL, Browder IW, Schweitzer JB, Kalbfleisch JH, Li C (2007) Activation of Toll-like receptor 4 signaling contributes to hippocampal neuronal death following global cerebral ischemia/reperfusion. J Neuroimmunol 190(1-2): 101–111

Isaacs A, Lindenmann J (1957) Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 147(927): 258–267

Ishikawa H, Ma Z, Barber GN (2009) STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature 461(7265): 788–792

Ito Y, Hoare M, Narita M (2017) Spatial and temporal control of senescence. Trends Cell Biol 27(11): 820–832

Iwasaki A, Medzhitov R (2010) Regulation of adaptive immunity by the innate immune system. Science 327(5963): 291–295

Kang C, Xu Q, Martin TD, Li MZ, Demaria M, Aron L, Lu T, Yankner BA, Campisi J, Elledge SJ (2015) The DNA damage response induces inflammation and senescence by inhibiting autophagy of GATA4. Science 349(6255): aaa5612. https://doi.org/10.1126/science.aaa5612

Karadimou G, Folkersen L, Berg M, Perisic L, Discacciati A, Roy J, Hansson GK, Persson J, Paulsson-Berne G (2017) Low TLR7 gene expression in atherosclerotic plaques is associated with major adverse cardio- and cerebrovascular events. Cardiovasc Res 113(1): 30–39

Kawai T, Akira S (2007) Antiviral signaling through pattern recognition receptors. J Biochem 141(2): 137–145

Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol 11(5): 373–384

Kawai T, Akira S (2011) Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity 34(5): 637–650

Kawai T, Sato S, Ishii KJ, Coban C, Hemmi H, Yamamoto M, Terai K, Matsuda M, Inoue J, Uematsu S, Takeuchi O, Akira S (2004) Interferon-alpha induction through Toll-like receptors involves a direct interaction of IRF7 with MyD88 and TRAF6. Nat Immunol 5(10): 1061–1068

Kerfoot SM, Long EM, Hickey MJ, Andonegui G, Lapointe BM, Zanardo RC, Bonder C, James WG, Robbins SM, Kubes P (2004) TLR4 contributes to disease-inducing mechanisms resulting in central nervous system autoimmune disease. J Immunol 173(11): 7070–7077

Kim J, Gupta R, Blanco LP, Yang S, Shteinfer-Kuzmine A, Wang K, Zhu J, Yoon HE, Wang X, Kerkhofs M, Kang H, Brown AL, Park SJ, Xu X, Zandee van Rilland E, Kim MK, Cohen JI, Kaplan MJ, Shoshan-Barmatz V, Chung JH (2019a) VDAC oligomers form mitochondrial pores to release mtDNA fragments and promote lupus-like disease. Science 366(6472): 1531–1536

Kim J, Seo M, Kim SK, Bae YS (2016) Flagellin-induced NADPH oxidase 4 activation is involved in atherosclerosis. Sci Rep 6: 25437. https://doi.org/10.1038/srep25437

Kim J, Yoo JY, Suh JM, Park S, Kang D, Jo H, Bae YS (2019b) The flagellin-TLR5-Nox4 axis promotes the migration of smooth muscle cells in atherosclerosis. Exp Mol Med 51(7): 1–13

Kohli J, Veenstra I, Demaria M (2021) The struggle of a good friend getting old: cellular senescence in viral responses and therapy. EMBO Rep 22(4): e52243. https://doi.org/10.15252/embr.202052243

Krabbe KS, Pedersen M, Bruunsgaard H (2004) Inflammatory mediators in the elderly. Exp Gerontol 39(5): 687–699

Kreienkamp R, Graziano S, Coll-Bonfill N, Bedia-Diaz G, Cybulla E, Vindigni A, Dorsett D, Kubben N, Batista LFZ, Gonzalo S (2018) A cell-intrinsic interferon-like response links replication stress to cellular aging caused by progerin. Cell Rep 22(8): 2006–2015

Krizhanovsky V, Xue W, Zender L, Yon M, Hernando E, Lowe SW (2008) Implications of cellular senescence in tissue damage response, tumor suppression, and stem cell biology. Cold Spring Harb Symp Quant Biol 73: 513–522

Kuilman T, Peeper DS (2009) Senescence-messaging secretome: SMS-ing cellular stress. Nat Rev Cancer 9(2): 81–94

Kulaeva OI, Draghici S, Tang L, Kraniak JM, Land SJ, Tainsky MA (2003) Epigenetic silencing of multiple interferon pathway genes after cellular immortalization. Oncogene 22(26): 4118–4127

Laberge RM, Zhou L, Sarantos MR, Rodier F, Freund A, de Keizer PL, Liu S, Demaria M, Cong YS, Kapahi P, Desprez PY, Hughes RE, Campisi J (2012) Glucocorticoids suppress selected components of the senescence-associated secretory phenotype. Aging Cell 11(4): 569–578

Lama L, Adura C, Xie W, Tomita D, Kamei T, Kuryavyi V, Gogakos T, Steinberg JI, Miller M, Ramos-Espiritu L, Asano Y, Hashizume S, Aida J, Imaeda T, Okamoto R, Jennings AJ, Michino M, Kuroita T, Stamford A, Gao P, Meinke P, Glickman JF, Patel DJ, Tuschl T (2019) Development of human cGAS-specific small-molecule inhibitors for repression of dsDNA-triggered interferon expression. Nat Commun 10(1): 2261. https://doi.org/10.1038/s41467-019-08620-4

Li B, Xia Y, Hu B (2020) Infection and atherosclerosis: TLR-dependent pathways. Cell Mol Life Sci 77(14): 2751–2769

Li T, Chen ZJ (2018) The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. J Exp Med 215(5): 1287–1299

Liu H, Yan Z, Zhu D, Xu H, Liu F, Chen T, Zhang H, Zheng Y, Liu B, Zhang L, Zhao W, Gao C (2023) CD-NTase family member MB21D2 promotes cGAS-mediated antiviral and antitumor immunity. Cell Death Differ 30(4): 992–1004

Liu Y, Xu X, Lei W, Hou Y, Zhang Y, Tang R, Yang Z, Tian Y, Zhu Y, Wang C, Deng C, Zhang S, Yang Y (2022) The NLRP3 inflammasome in fibrosis and aging: The known unknowns. Ageing Res Rev 79: 101638. https://doi.org/10.1016/j.arr.2022.101638

Lucas SM, Rothwell NJ, Gibson RM (2006) The role of inflammation in CNS injury and disease. Br J Pharmacol 147(Suppl 1): S232–240

Lukhele S, Boukhaled GM, Brooks DG (2019) Type I interferon signaling, regulation and gene stimulation in chronic virus infection. Semin Immunol 43: 101277. https://doi.org/10.1016/j.smim.2019.05.001

Luo H, Mu WC, Karki R, Chiang HH, Mohrin M, Shin JJ, Ohkubo R, Ito K, Kanneganti TD, Chen D (2019) Mitochondrial stress-initiated aberrant activation of the NLRP3 inflammasome regulates the functional deterioration of hematopoietic stem cell aging. Cell Rep 26(4): 945–954.e4

Malaquin N, Martinez A, Rodier F (2016) Keeping the senescence secretome under control: molecular reins on the senescence-associated secretory phenotype. Exp Gerontol 82: 39–49

Mannarino M, Cherif H, Li L, Sheng K, Rabau O, Jarzem P, Weber MH, Ouellet JA, Haglund L (2021) Toll-like receptor 2 induced senescence in intervertebral disc cells of patients with back pain can be attenuated by o-vanillin. Arthritis Res Ther 23(1): 117. https://doi.org/10.1186/s13075-021-02504-z

Marin-Aguilar F, Castejon-Vega B, Alcocer-Gomez E, Lendines-Cordero D, Cooper MA, de la Cruz P, Andujar-Pulido E, Perez-Alegre M, Muntane J, Perez-Pulido AJ, Ryffel B, Robertson AAB, Ruiz-Cabello J, Bullon P, Cordero MD (2020) NLRP3 inflammasome inhibition by MCC950 in aged mice improves health via enhanced autophagy and pparalpha activity. J

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Gerontol A Biol Sci Med Sci 75(8): 1457–1464
Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J (2006) Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 440(7081): 237–241
McArthur K, Whitehead LW, Heddleston JM, Li L, Padman BS, Oorschot V, Geoghegan ND, Chappaz S, Davidson S, San Chin H, Lane RM, Dramicanin M, Saunders TL, Sugiana C, Lessene R, Osellame LD, Chew TL, Dewson G, Lazarou M, Ramm G, Lessene G, Ryan MT, Rogers KL, van Delft MF, Kile BT (2018) BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. Science 359(6378): eaao6047. https://doi.org/10.1126/science.aao6047
Menon R, Richardson LS, Lappas M (2019) Fetal membrane architecture, aging and inflammation in pregnancy and parturition. Placenta 79: 40–45
Meyer P, Maity P, Burkovski A, Schwab J, Mussel C, Singh K, Ferreira FF, Krug L, Maier HJ, Wlaschek M, Wirth T, Kestler HA, Scharffetter-Kochanek K (2017) A model of the onset of the senescence associated secretory phenotype after DNA damage induced senescence. PLoS Comput Biol 13(12): e1005741. https://doi.org/10.1371/journal.pcbi.1005741
Moiseeva O, Deschenes-Simard X, St-Germain E, Igelmann S, Huot G, Cadar AE, Bourdeau V, Pollak MN, Ferbeyre G (2013) Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-kappaB activation. Aging Cell 12(3): 489–498
Moiseeva O, Mallette FA, Mukhopadhyay UK, Moores A, Ferbeyre G (2006) DNA damage signaling and p53-dependent senescence after prolonged beta-interferon stimulation. Mol Biol Cell 17(4): 1583–1592
Motwani M, Pesiridis S, Fitzgerald KA (2019) DNA sensing by the cGAS-STING pathway in health and disease. Nat Rev Genet 20(11): 657–674
Munoz-Espin D, Canamero M, Maraver A, Gomez-Lopez G, Contreras J, Murillo-Cuesta S, Rodriguez-Baeza A, Varela-Nieto I, Ruberte J, Collado M, Serrano M (2013) Programmed cell senescence during mammalian embryonic development. Cell 155(5): 1104–1118
Munoz-Espin D, Serrano M (2014) Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol 15(7): 482–496
Navarro-Pando JM, Alcocer-Gomez E, Castejon-Vega B, Navarro-Villaran E, Condes-Hervas M, Mundi-Roldan M, Muntane J, Perez-Pulido AJ, Bullon P, Wang C, Hoffman HM, Sanz A, Mbalaviele G, Ryffel B, Cordero MD (2021) Inhibition of the NLRP3 inflammasome prevents ovarian aging. Sci Adv 7(1): eabc7409. https://doi.org/10.1126/sciadv.abc7409
Ng CT, Mendoza JL, Garcia KC, Oldstone MB (2016) Alpha and beta type 1 interferon signaling: passage for diverse biologic outcomes. Cell 164(3): 349–352
Ngo HB, Lovely GA, Phillips R, Chan DC (2014) Distinct structural features of TFAM drive mitochondrial DNA packaging versus transcriptional activation. Nat Commun 5: 3077. https://doi.org/10.1038/ncomms4077
Oeckinghaus A, Ghosh S (2009) The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol 1(4): a000034. https://doi.org/10.1101/cshperspect.a000034
Okun E, Griffioen KJ, Lathia JD, Tang SC, Mattson MP, Arumugam TV (2009) Toll-like receptors in neurodegeneration. Brain Res Rev 59(2): 278–292
Paul BD, Snyder SH, Bohr VA (2021) Signaling by cGAS-STING in neurodegeneration, neuroinflammation, and aging. Trends Neurosci 44(2): 83–96
Qadir AS, Stults AM, Murmann AE, Peter ME (2020) The mechanism of how CD95/Fas activates the Type I IFN/STAT1 axis, driving cancer stemness in breast cancer. Sci Rep 10(1): 1310. https://doi.org/10.1038/s41598-020-58211-3
Ritschka B, Storer M, Mas A, Heinzmann F, Ortells MC, Morton JP, Sansom OJ, Zender L, Keyes WM (2017) The senescence-associated secretory phenotype induces cellular plasticity and tissue regeneration. Genes Dev 31(2): 172–183
Rodier F, Campisi J (2011) Four faces of cellular senescence. J Cell Biol 192(4): 547–556
Rodier F, Coppe JP, Patil CK, Hoeijmakers WA, Munoz DP, Raza SR, Freund A, Campeau E, Davalos AR, Campisi J (2009) Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat Cell Biol 11(8): 973–979
Roh JS, Sohn DH (2018) Damage-associated molecular patterns in inflammatory diseases. Immune Netw 18(4): e27. https://doi.org/10.4110/in.2018.18.e27
Salama R, Sadaie M, Hoare M, Narita M (2014) Cellular senescence and its effector programs. Genes Dev 28(2): 99–114
Salminen A, Kauppinen A, Kaarniranta K (2012) Emerging role of NF-kappaB signaling in the induction of senescence-associated secretory phenotype (SASP). Cell Signal 24(4): 835–845
Sangfelt O, Erickson S, Castro J, Heiden T, Gustafsson A, Einhorn S, Grander D (1999) Molecular mechanisms underlying interferon-alpha-induced G0/G1 arrest: CKI-mediated regulation of G1 Cdk-complexes and activation of pocket proteins. Oncogene 18(18): 2798–2810
Sarig R, Rimmer R, Bassat E, Zhang L, Umansky KB, Lendengolts D, Perlmoter G, Yaniv K, Tzahor E (2019) Transient p53-mediated regenerative senescence in the injured heart. Circulation 139(21): 2491–2494
Satoh T, Akira S (2016) Toll-like receptor signaling and its inducible proteins. Microbiol Spectr 4(6). https://doi.org/10.1128/microbiolspec.MCHD-0040-2016
Schmitz CRR, Maurmann RM, Guma F, Bauer ME, Barbe-Tuana FM (2023) cGAS-STING pathway as a potential trigger of immunosenescence and inflammaging. Front Immunol 14: 1132653. https://doi.org/10.3389/fimmu.2023.1132653
Schneider DS, Jin Y, Morisato D, Anderson KV (1994) A processed form of the Spatzle protein defines dorsal-ventral polarity in the *Drosophila* embryo. Development 120(5): 1243–1250
Sharpless NE, Sherr CJ (2015) Forging a signature of *in vivo* senescence. Nat Rev Cancer 15(7): 397–408
Sieben CJ, Sturmlechner I, van de Sluis B, van Deursen JM (2018) Two-step senescence-focused cancer therapies. Trends Cell Biol 28(9): 723–737
Sistigu A, Yamazaki T, Vacchelli E, Chaba K, Enot DP, Adam J, Vitale I, Goubar A, Baracco EE, Remedios C, Fend L, Hannani D, Aymeric L, Ma Y, Niso-Santano M, Kepp O, Schultze JL, Tuting T, Belardelli F, Bracci L, La Sorsa V, Ziccheddu G, Sestili P, Urbani F, Delorenzi M, Lacroix-Triki M, Quidville V, Conforti R, Spano JP, Pusztai L, Poirier-Colame V, Delaloge S, Penault-Llorca F, Ladoire S, Arnould L, Cyrta J, Dessoliers MC, Eggermont A, Bianchi ME, Pittet M, Engblom C, Pfirschke C, Preville X, Uze G, Schreiber RD, Chow MT, Smyth MJ, Proietti E, Andre F, Kroemer G, Zitvogel L (2014) Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. Nat Med 20(11): 1301–1309
Sladitschek-Martens HL, Guarnieri A, Brumana G, Zanconato F, Battilana G, Xiccato RL, Panciera T, Forcato M, Bicciato S, Guzzardo V, Fassan M, Ulliana L, Gandin A, Tripodo C, Foiani M, Brusatin G, Cordenonsi M, Piccolo S (2022) YAP/TAZ activity in stromal cells prevents ageing by controlling cGAS-STING. Nature 607(7920): 790–798
Song LL, Ponomareva L, Shen H, Duan X, Alimirah F, Choubey D (2010) Interferon-inducible IFI16, a negative regulator of cell growth, down-regulates expression of human telomerase

 © The Author(s) 2023

reverse transcriptase (hTERT) gene. PLoS One 5(1): e8569. https://doi.org/10.1371/journal.pone.0008569

Song S, Lam EW, Tchkonia T, Kirkland JL, Sun Y (2020) Senescent cells: emerging targets for human aging and age-related diseases. Trends Biochem Sci 45(7): 578–592

Stout-Delgado HW, Cho SJ, Chu SG, Mitzel DN, Villalba J, El-Chemaly S, Ryter SW, Choi AM, Rosas IO (2016) Age-dependent susceptibility to pulmonary fibrosis is associated with NLRP3 inflammasome activation. Am J Respir Cell Mol Biol 55(2): 252–263

Tahara H, Kamada K, Sato E, Tsuyama N, Kim JK, Hara E, Oda K, Ide T (1995) Increase in expression levels of interferon-inducible genes in senescent human diploid fibroblasts and in SV40-transformed human fibroblasts with extended lifespan. Oncogene 11(6): 1125–1132

Takahashi A, Loo TM, Okada R, Kamachi F, Watanabe Y, Wakita M, Watanabe S, Kawamoto S, Miyata K, Barber GN, Ohtani N, Hara E (2018) Downregulation of cytoplasmic DNases is implicated in cytoplasmic DNA accumulation and SASP in senescent cells. Nat Commun 9(1): 1249. https://doi.org/10.1038/s41467-018-03555-8

Takahashi A, Ohtani N, Yamakoshi K, Iida S, Tahara H, Nakayama K, Nakayama KI, Ide T, Saya H, Hara E (2006) Mitogenic signalling and the p16INK4a-Rb pathway cooperate to enforce irreversible cellular senescence. Nat Cell Biol 8(11): 1291–1297

Takaoka A, Hayakawa S, Yanai H, Stoiber D, Negishi H, Kikuchi H, Sasaki S, Imai K, Shibue T, Honda K, Taniguchi T (2003) Integration of interferon-alpha/beta signalling to p53 responses in tumour suppression and antiviral defence. Nature 424(6948): 516–523

Tang TT, Lv LL, Pan MM, Wen Y, Wang B, Li ZL, Wu M, Wang FM, Crowley SD, Liu BC (2018) Hydroxychloroquine attenuates renal ischemia/reperfusion injury by inhibiting cathepsin mediated NLRP3 inflammasome activation. Cell Death Dis 9(3): 351. https://doi.org/10.1038/s41419-018-0378-3

Teissier T, Boulanger E, Cox LS (2022) Interconnections between inflammageing and immunosenescence during ageing. Cells 11(3): 359. https://doi.org/10.3390/cells11030359

Testa G, Gamba P, Badilli U, Gargiulo S, Maina M, Guina T, Calfapietra S, Biasi F, Cavalli R, Poli G, Leonarduzzi G (2014) Loading into nanoparticles improves quercetin's efficacy in preventing neuroinflammation induced by oxysterols. PLoS One 9(5): e96795. https://doi.org/10.1371/journal.pone.0096795

Tripathi U, Nchioua R, Prata L, Zhu Y, Gerdes EOW, Giorgadze N, Pirtskhalava T, Parker E, Xue A, Espindola-Netto JM, Stenger S, Robbins PD, Niedernhofer LJ, Dickinson SL, Allison DB, Kirchhoff F, Sparrer KMJ, Tchkonia T, Kirkland JL (2021) SARS-CoV-2 causes senescence in human cells and exacerbates the senescence-associated secretory phenotype through TLR-3. Aging (Albany NY) 13(18): 21838–21854

Verstak B, Nagpal K, Bottomley SP, Golenbock DT, Hertzog PJ, Mansell A (2009) MyD88 adapter-like (Mal)/TIRAP interaction with TRAF6 is critical for TLR2- and TLR4-mediated NF-kappaB proinflammatory responses. J Biol Chem 284(36): 24192–24203

Villarroya-Beltri C, Guerra S, Sanchez-Madrid F (2017) ISGylation — a key to lock the cell gates for preventing the spread of threats. J Cell Sci 130(18): 2961–2969

von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, Chrabieh M, Mustapha IB, Ghandil P, Camcioglu Y, Vasconcelos J, Sirvent N, Guedes M, Vitor AB, Herrero-Mata MJ, Arostegui JI, Rodrigo C, Alsina L, Ruiz-Ortiz E, Juan M, Fortuny C, Yague J, Anton J, Pascal M, Chang HH, Janniere L, Rose Y, Garty BZ, Chapel H, Issekutz A, Marodi L, Rodriguez-Gallego C, Banchereau J, Abel L, Li X, Chaussabel D, Puel A, Casanova JL (2008) Pyogenic bacterial infections in humans with MyD88 deficiency. Science 321(5889): 691–696

Wang X, Jung J, Asahi M, Chwang W, Russo L, Moskowitz MA, Dixon CE, Fini ME, Lo EH (2000) Effects of matrix metalloproteinase-9 gene knock-out on morphological and motor outcomes after traumatic brain injury. J Neurosci 20(18): 7037–7042

West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, Bestwick M, Duguay BA, Raimundo N, MacDuff DA, Kaech SM, Smiley JR, Means RE, Iwasaki A, Shadel GS (2015) Mitochondrial DNA stress primes the antiviral innate immune response. Nature 520(7548): 553–557

Williams BR (1999) PKR; a sentinel kinase for cellular stress. Oncogene 18(45): 6112–6120

Wise J (2020) Covid-19: Critically ill patients treated with arthritis drug tocilizumab show improved outcomes, researchers report. BMJ 371: m4530. https://doi.org/10.1136/bmj.m4530

Wolf D, Ley K (2019) Immunity and inflammation in atherosclerosis. Circ Res 124(2): 315–327

Wright SD (1999) Toll, a new piece in the puzzle of innate immunity. J Exp Med 189(4): 605–609

Yang Y, Wang H, Kouadir M, Song H, Shi F (2019) Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. Cell Death Dis 10(2): 128. https://doi.org/10.1038/s41419-019-1413-8

Yu Q, Katlinskaya YV, Carbone CJ, Zhao B, Katlinski KV, Zheng H, Guha M, Li N, Chen Q, Yang T, Lengner CJ, Greenberg RA, Johnson FB, Fuchs SY (2015) DNA-damage-induced type I interferon promotes senescence and inhibits stem cell function. Cell Rep 11(5): 785–797

Yu X, Lan P, Hou X, Han Q, Lu N, Li T, Jiao C, Zhang J, Zhang C, Tian Z (2017) HBV inhibits LPS-induced NLRP3 inflammasome activation and IL-1beta production via suppressing the NF-kappaB pathway and ROS production. J Hepatol 66(4): 693–702

Zahid A, Li B, Kombe AJK, Jin T, Tao J (2019) Pharmacological Inhibitors of the NLRP3 Inflammasome. Front Immunol 10: 2538. https://doi.org/10.3389/fimmu.2019.02538

Zhang C, Cheng Z, Zhou Y, Yu Z, Mai H, Xu C, Zhang J, Wang J (2023) The novel hyaluronic acid granular hydrogel attenuates osteoarthritis progression by inhibiting the TLR-2/NF-kappaB signaling pathway through suppressing cellular senescence. Bioeng Transl Med 8(3): e10475. https://doi.org/10.1002/btm2.10475

Zhang Q, Lenardo MJ, Baltimore D (2017) 30 years of NF-kappaB: a blossoming of relevance to human pathobiology. Cell 168(1–2): 37–57

Zhao Y, Simon M, Seluanov A, Gorbunova V (2023) DNA damage and repair in age-related inflammation. Nat Rev Immunol 23(2): 75–89

Zheng Y, Gao C (2019) E3 ubiquitin ligases, the powerful modulator of innate antiviral immunity. Cell Immunol 340: 103915. https://doi.org/10.1016/j.cellimm.2019.04.003

Zheng Y, Gao C (2023) Phase separation: the robust modulator of innate antiviral signaling and SARS-CoV-2 infection. Pathogens 12(2): 243. https://doi.org/10.3390/pathogens12020243

Zierhut C, Funabiki H (2020) Regulation and consequences of cGAS activation by self-DNA. Trends Cell Biol 30(8): 594–605

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