Mechanisms of Ageing and Development 182 (2019) 111118

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Chromosomal instability and pro-inflammatory response in aging

Monika Barroso-Vilares[a,b], Elsa Logarinho[a,b,*]

[a] Ageing and Aneuploidy Laboratory, IBMC, Instituto de Biologia Molecular e Celular, Universidade do Porto, 4200-135, Porto, Portugal
[b] i3S, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4200-135, Porto, Portugal

ARTICLE INFO

Keywords:
Aging
Aneuploidy
Chromosomal instability
Senescence-associated secretory phenotype
cGAS-STING
Inflammaging

ABSTRACT

Aging refers to the progressive deterioration of tissue and organ function over time. Increasing evidence points to the accumulation of highly damaged cell cycle-arrested cells with age (cellular senescence) as major reason for the development of certain aging-associated diseases. Recent studies have independently shown that aneuploidy, an abnormal chromosome set, occurs in senescent cells, and that the accumulation of cytoplasmic DNA driven by faulty chromosome segregation during mitosis aids in the establishment of senescence and its associated secretory phenotype known as SASP. Here we review the emerging link between chromosomal instability (CIN) and senescence in the context of aging, with emphasis on the cGAS-STING pathway activation and its role in the development of the SASP. Based on current evidence, we propose that age-associated CIN in mitotically active cells contrib diseases, and we discuss the inhibition of CIN as a potential strategy to prevent th escent cells and thereby to delay aging.

Chromosomal instability and pro-inflammatory response in aging Monika Barroso-Vilares, Elsa Logarinho

1. Introduction

Chromosomal instability (CIN) refers to the process b experience increased rates of chromosome segregation d mitosis over several generations, and thus lead to heter pulations of cells with chromosomal layouts (karyotypes) that are no longer a multiple of the haploid complement (Geigl et al., 2008). The resulting state of having an unbalanced karyotype is termed aneuploidy and is generally detrimental at both organismal and cellular levels. Studies in different models of aneuploidy show that changes in chromosome content translate into altered RNA and protein levels, and thus negatively impact proliferation, metabolism, proteostasis and maintenance of genome integrity (reviewed by (Santaguida and Amon, 2015; Zhu et al., 2018)). Still, low levels of aneuploidy can be found in specific tissues such as brain and liver (Duncan et al., 2010; Knouse et al., 2014; Rehen et al., 2005), even though the negative connotation given to aneuploidy arises from its high prevalence in pathological conditions, including infertility (Harton and Tempest, 2012; Nagaoka et al., 2012), cancer (Weaver and Cleveland, 2006) and neurodegeneration (Siegel and Amon, 2012). The susceptibility to develop these diseases increases with age, suggesting thereby a causal link between chromosomal imbalances and age-associated diseases. For instance, maternal age dramatically increases the occurrence of aneuploidy in oocytes, which represents one of the leading causes of miscarriage and inherited birth defects (Nagaoka et al., 2012). In addition to the chromosomal imbalances were also detected in somatic cells t tissues, namely in blood lymphocytes (Stone and Sandberg, n fibroblasts (Mukherjee and Thomas, 1997) and myeloid herjee et al., 1996) of elderly individuals, as well as the aging rov et al., 2009; Mosch et al., 2007). Individuals with Down syndrome aged beyond 30 or 40 years develop a pathological condition that cannot be discerned from Alzheimer's disease (AD) (Potter, 1991), and several studies have sustained the link between aneuploidy and AD (Arendt et al., 2015; Dumanski et al., 2016; Iourov et al., 2009; Mendivil-Perez et al., 2019; Thomas et al., 2008; Yurov et al., 2014).

Aging is driven by several conditions that progressively disrupt the balance of key biological processes, hence perturbing tissue and organ homeostasis, with an overall deterioration of physiological functions over time (Lopez-Otin et al., 2013). It correlates with the accumulation of molecular damage, including genomic instability, proteotoxicity, telomere attrition and epigenetic remodelling. This in turn, translates into cellular and organismal features including metabolic stress, mitochondrial dysfunction, deregulated nutrient sensing, stem cell exhaustion, chronic low-grade inflammation and cellular senescence. Altogether, these interconnected hallmarks contribute to the rate of aging (Lopez-Otin et al., 2013).

The cellular senescence hallmark has long been thought to contribute to organismal aging (Campisi, 2013), although it remains unsolved whether it is a cause or consequence. Cellular senescence was originally defined by Hayflick and Moorhead as a permanent cell cycle

* Corresponding author.
E-mail addresses: monika.vilares@ibmc.up.pt (M. Barroso-Vilares), elsa.logarinho@ibmc.up.pt (E. Logarinho).

https://doi.org/10.1016/j.mad.2019.111118
Received 10 January 2019; Received in revised form 25 April 2019; Accepted 14 May 2019
Available online 15 May 2019

arrest stress response exhibited by primary cells at the end of their replicative lifespan (Hayflick and Moorhead, 1961), and later extended to include premature cellular senescence triggered in normal or transformed cells upon exposure to stressors such as chemotherapy, radiotherapy, oxidative damage or activated oncogenes (reviewed in (Hernandez-Segura et al., 2018)). Acute induction of cellular senescence is beneficial in tissue remodelling/homeostasis during embryogenesis (Munoz-Espin et al., 2013; Storer et al., 2013), wound healing (Demaria et al., 2014) and tumor suppression (Campisi, 2001; Serrano et al., 1997), whereas chronic persistence of cellular senescence leads to tissue dysfunction during aging and age-related diseases (Campisi, 2005; van Deursen, 2014). Senescence markers include senescence-associated β-galactosidase activity, the cell cycle inhibitors $p16^{INK4a}$ and $p21^{CIP1}$, and many secreted inflammatory factors (collectively referred as the senescence-associated secretory phenotype or SASP). These markers are not exclusive to senescent cells, and senescent cells do not always exhibit all markers. Interestingly, recent evidence suggests that differentiated (or postmitotic) cells, including neurons (Jurk et al., 2012; Oubaha et al., 2016), adipocytes (Minamino et al., 2009), osteocytes (Farr et al., 2016, 2017) and hepatocytes (da Silva et al., 2019; Ogrodnik et al., 2017), are also equipped with cellular machinery to engage programs of cellular senescence in response to stressors (Sapieha and Mallette, 2018), even though the repercussions of this postmitotic cellular senescence in tissue health and function are ill-defined. However, in this review, we will stick into the conceptual framework on cellular senescence built from proliferative/mitotic cells such as fibroblasts, epithelial and endothelial cells, and the rationale that these senescent cells can exert pro-aging effects in neighboring differentiated cells of parenchymal tissue through their pro-inflammatory secretome (paracrine/non-cell autonomous effect).

Intriguingly, some of the cellular hallmarks evidenced by proliferative cells of elderly donors overlap with aneuploidy-associated features, namely genomic and chromosomal instability (Nicholson et al., 2015; Passerini et al., 2016), proteotoxic stress (Oromendia et al., 2012; Santaguida et al., 2015; Stingele et al., 2012), epigenetic alterations (Mulla et al., 2017), metabolic stress (Torres et al., 2007; Williams et al., 2008) and cellular senescence (Santaguida et al., 2017). This suggests a positive feedback loop between aging and aneuploidy (Macedo et al., 2017), even though the underlying mechanisms by which cellular aging leads to aneuploidy and by which aneuploidy accelerates cellular aging have remained largely elusive. Recently, however, a set of independent studies emerged unveiling, on one hand, a molecular mechanism behind mitotic dysfunction in aging (Macedo et al., 2018), and on the other hand, a correlation between defective chromosome segregation and cellular senescence (Andriani et al., 2016; He et al., 2018; Macedo et al., 2018; Santaguida et al., 2017). This suggests that aneuploidization in proliferative cells with age might play an important role in the development of the senescent phenotype and thereby contribute to age-related diseases. This review summarizes the emerging role of CIN in senescence and highlights novel observations that place the conserved cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) as a central player in the development of pro-inflammatory SASP. In light of these findings, we discuss cytosolic DNA recognition in the context of aging and propose inhibition of age-associated CIN as a potential strategy to delay senescence.

2. Mitotic dysfunction with age underlies CIN-induced cellular senescence

Reports describing panels of fibroblast and lymphocyte cultures from young and old individuals revealed changes in the expression of genes associated with centromere and kinetochore function, as well as in the microtubule and spindle assembly apparatus (Geigl et al., 2004). Accurate chromosome segregation requires the organization of microtubules into a bipolar mitotic spindle, its proper attachment to sister kinetochores of all chromosomes, and a suitable length of time to allow these events to occur properly. Consequently, CIN will occur as a result of flaws in this process, including spindle assembly checkpoint (SAC) defects leading to anaphase onset in the presence of unattached kinetochores, or premature sister chromatids separation due to cohesion defects (Thompson et al., 2010). In addition, establishment of improper merotelic kinetochore-microtubule (k-MT) interactions, which are not detected by the SAC, also result in aneuploidy if left uncorrected prior to anaphase (Cimini et al., 2003; Nicholson and Cimini, 2011). Bearing in mind the mechanisms underlying aneuploidy, together with the fact that age correlates with increased aneuploidy and elicits gene expression changes in mitotic genes, this raises the question whether a dysfunction of the mitotic machinery occurs along aging.

A set of studies with CIN-prone mice models uncovered a link between compromised SAC function and premature onset of aging phenotypes. BubR1 hypomorphic mice experience increases in aneuploidy as a result of diminished mitotic checkpoint activity, concomitantly with an unexpected premature aging phenotype (Baker et al., 2004). At the time, naturally aged wild-type mice were found to have decreased BubR1 protein levels (Baker et al., 2004). Observations taken from Bub3/Rae1 haploinsufficient mice further supported that defective checkpoint activity leads to CIN while generating cell cycle-arrested (or senescent) cells along with progeroid features (Baker et al., 2006). Subsequent studies elegantly confirmed that the premature onset of aging phenotypes in mice with mitotic checkpoint gene defects was linked to cellular senescence. Both BubR1-overexpression (Baker et al., 2013) and targeted clearance of senescent ($p16^{INK4A}$-positive) cells (Baker et al., 2011) in BubR1 hypomorphic mice was able to delay tissue dysfunction and extend lifespan. In addition to mouse models, the link was also observed in the Mosaic Variegated Aneuploidy (MVA) syndrome, a pediatric condition in which patients harbor mutations within BubR1 that reduce steady state levels of the protein (Suijkerbuijk et al., 2010). Accordingly, individuals with MVA experience increased chromosome mis-segregation events alongside with progeroid features (Hanks et al., 2004; Matsuura et al., 2006).

Moreover, three independent studies further showed that challenging chromosome stability in otherwise karyotypically stable human cells elicits the senescence secretion signature (Andriani et al., 2016; He et al., 2018; Santaguida et al., 2017), that comprises a wide range of cytokines, chemokines, matrix metalloproteinases and growth factors (Acosta et al., 2013; Coppe et al., 2008; Hernandez-Segura et al., 2017). This pro-inflammatory secretome was found to trigger immune clearance of karyotypically abnormal cells (Santaguida et al., 2017). Importantly, live-cell imaging analysis of human dermal fibroblasts derived from neonatal to octogenarian individuals demonstrated loss of proliferative capacity and mitotic dysfunction with age, which was found to be dependent on the repression of the transcription factor Forkhead box M1 (FoxM1) that primarily drives the expression of the late cell cycle gene cluster (Macedo et al., 2018). FoxM1 downregulation during aging is likely mediated by the activation of stress pathways in response to cellular damage. For instance, engagement of the p53-p21-DREAM pathway upon genotoxic stress prevents early cell cycle gene expression required for FoxM1 transcriptional activity (Anders et al., 2011; Fischer et al., 2016). As a result of FoxM1 repression, including a global mitotic gene shutdown, fibroblasts from elderly donors experience chromosome segregation defects that were shown to ultimately trigger the development of a full-blown senescence phenotype (Macedo et al., 2018). Restoring FoxM1 activity improved mitotic fitness, concomitantly with a visible decrease in levels of aneuploidy and senescence in fibroblast cultures from aged donors (Macedo et al., 2018).

Taken together, this set of intriguing findings suggests that age-associated mitotic dysfunction underlies mild CIN, which in turn prompts the accumulation of aneuploid senescent cells. In addition to senescent cells induced by any other stresses (e.g., DNA damage, telomere attrition, oxidative stress), the aneuploidy-driven senescent cells will modulate and exert detrimental effects on the surrounding

microenvironment and neighbor cells, which may be further potentiated by their limited clearance along age. Still, the exact relationship between aneuploidy and senescence, and its contribution to phenotypes that characterize aging remain a matter of debate. Although some CIN mice exhibit progeroid features, others do not recapitulate those phenotypes (Simon et al., 2015). This suggests that CIN alone might not be sufficient to explain the observed age-related changes, which indicates that specific perturbations in the chromosome segregation machinery, or even the degree of instability that is being generated, could play a role in the observed differences. The studies available to date report that, while high-grade CIN is required to trigger senescence in otherwise "fit" immortalized cell lines (He et al., 2018; Santaguida et al., 2017), mild levels of chromosome mis-segregation in naturally aged primary cells are sufficient to elicit a transition (Macedo et al., 2018). This raises the question whether additional cellular damage, such as the one accrued with age, is needed for low-grade CIN to elicit a full senescent state, which comes in agreement with the idea that the senescent state can be highly heterogeneous and evolve (Hernandez-Segura et al., 2017). It would thus be interesting to address if mild CIN in a primary cellular model without pre-existing damage (hence, a "young" background) is able to elicit a senescence signature. Finally, although a mitotic dysfunction could be observed in elderly dividing cells, the exact mechanism(s) (e.g. defects in SAC, cohesion and/or k-MT dynamics) by which the gradual mitotic gene shutdown ultimately underlies aneuploidization with age is still an open question. To address this would be fundamental in light of all the emerging findings that link chromosome segregation defects with senescence.

3. Age-associated CIN triggers a pro-inflammatory response

Erosion of mitotic fidelity in both mice and human cells suggests that aneuploidy may foster aging-related changes by contributing to the development of senescence and its associated secretory phenotype (SASP). A major source of aneuploidy is the persistence of improper merotelic k-MT attachments, which manifest as lagging chromosomes in anaphase and generate micronuclei (MN) after being excluded from daughter cell nuclei (Cimini et al., 2001; Thompson and Compton, 2008). Several studies have shown that MN chromatin is highly susceptible to DNA damage, causing massive genomic rearrangement, an event termed chromothripsis (Ly et al., 2017; Stephens et al., 2011; Zhang et al., 2015). MN are faulty in the recruitment of DNA replication and repair machineries (Crasta et al., 2012) and experience defective import of key proteins required to assemble a proper nuclear envelope (Liu et al., 2018; Maass et al., 2018). As a result, dysfunctional MN membranes are more susceptible to disruption which, combined to DNA replication/repair deficiency, will dictate DNA damage within the chromosome(s) excluded from the main nucleus (Hatch et al., 2013). In addition to damage, loss of compartmentalization will release MN chromatin to the cytoplasm, which becomes exposed to the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) (Bakhoum et al., 2018; Harding et al., 2017; Mackenzie et al., 2017). In agreement with a mitotic dysfunction along aging (Macedo et al., 2018), MN frequencies are increased in aged cells (Guttenbach et al., 1994; Macedo et al., 2018; Thomas et al., 2008). This is particularly interesting as a set of recent findings show that cGAS activation mediated by cytoplasmic chromatin fragments (CCF) is essential for cellular senescence (Dou et al., 2017; Gluck et al., 2017; Yang et al., 2017).

cGAS represents the forefront of a conserved pathway meant to mediate innate immune recognition of and response to antimicrobial infection, including DNA viruses, retroviruses and bacteria (see (Paludan, 2015; Pandey et al., 2014; Sun et al., 2013)). Upon double-stranded DNA (dsDNA) binding, cGAS activation catalyzes the formation of the second-messenger 2′3′-cyclic-GMP-AMP (cGAMP) (Wu et al., 2013) that is recognized by the adaptor protein Stimulator of Interferon Genes (STING) (Gao et al., 2013). STING in turn mediates the transcriptional activation of inflammatory pathways, namely type I interferon signaling (Sun et al., 2013). In addition to microbial patterns, cGAS also senses self-DNA that is altered, misplaced or accumulated in the cytoplasm as a result of cellular stress. Accordingly, accumulation of cytoplasmic DNA due to defects in cytoplasmic DNases has been correlated with autoimmune disorders, such as the Aicardi-Goutières syndrome (Crow, 2015; Crow et al., 2006; Stetson et al., 2008), and more recently with cellular senescence (Takahashi et al., 2018). Cellular senescence is characterized by very specific alterations (Rodier and Campisi, 2011), including changes in nuclear envelope (NE) composition due to defective recruitment of lamin B1 (Freund et al., 2012; Shah et al., 2013; Shimi et al., 2011), as well as several other NE proteins (nuclear atypia)(Lenain et al., 2015). As a result, CCF bud off from nuclei of senescent cells (Dou et al., 2015; Ivanov et al., 2013) and, similarly to MN chromatin, become available to be recognized by cGAS. Indeed, several studies reported that senescent cells engage the cGAS-STING signaling cascade after recognition of those aberrant CCFs herniating from the defective NE (Dou et al., 2017; Gluck et al., 2017; Yang et al., 2017). Notably, abrogation of cGAS and/or STING function prevented the expression of senescence-associated inflammatory genes in response to damage-inducing insults, both *in vitro* and *in vivo*. Altogether, this established the cGAS-STING pathway as a crucial player to be taken into account during senescence and the SASP (Dou et al., 2017; Gluck et al., 2017; Yang et al., 2017).

In addition to nuclear atypia in both the main nucleus and MN, DNA fragments can also be released by stalled replication forks (replication stress), which are recognized by and activate cGAS-STING-mediated innate immune signaling (Coquel et al., 2018). In fact, this has been reported for the Hutchinson-Gilford progeria syndrome (HGPS), a premature aging disease caused by a mutant lamin A protein (progerin). Progerin induces replication fork stalling and nuclease-mediated degradation of stalled forks, which lead to genomic instability concomitantly with upregulation of the cGAS-STING pathway and activation of a STAT1-mediated interferon-like response (Kreienkamp et al., 2018). Similarly, induction of pro-inflammatory responses is also described for other syndromes of genomic instability and accelerated aging, such as the Ataxia telangiectasia (AT) and Fanconi anemia (FA). Absence of functional Ataxia-telangiectasia mutated (ATM) in AT (Hartlova et al., 2015), and SLX4 deficiency in FA (Bregnard et al., 2016), cause unrepaired DNA lesions that can be released into the cytoplasm. In both cases, activation of cGAS-STING signaling elicits an interferon response, which suggests that excessive cytoplasmic DNA may actively contribute to the premature aging phenotypes that characterize these syndromes. Most likely, the same will hold true for natural aging, as senescent cells with nuclear atypia, replication stress and CIN also occur in this context (Fig. 1a). Therefore, this raises the hypothesis of a yet to be established cGAS-STING-dependent link between chromosome imbalances and senescence during natural aging, which generates pro-inflammatory signals of paracrine senescence that perturb tissue homeostasis.

4. Different routes and outcomes of cGAS-STING activation

The recruitment of an inflammatory response relies on the execution of a series of events that, depending on the origin and time frame of the stimulus, will follow different routes that might lead to different outcomes. Pattern-recognition receptors (PRRs) are the first in place to survey the extracellular, endosomal and cytosolic compartments for free nucleic acids. While AIM2, cGAS, and TLR9 sense dsDNA, MDA5, OAS, RIG-I, TLR3, TLR7, and TLR8 are responsible for the detection of RNA. Nucleic acids can accumulate as a result of perturbations in cellular homeostasis. Those include defects in cytoplasmic nucleases (DNase2, TREX1 or RNaseH2), infections by pathogens (such as DNA viruses, retroviruses and bacteria), errors in chromosome segregation (CIN), DNA damage and defects in mitochondria, amongst others (reviewed in (Galluzzi et al., 2018; Margolis et al., 2017; Xiao and Fitzgerald, 2013)).

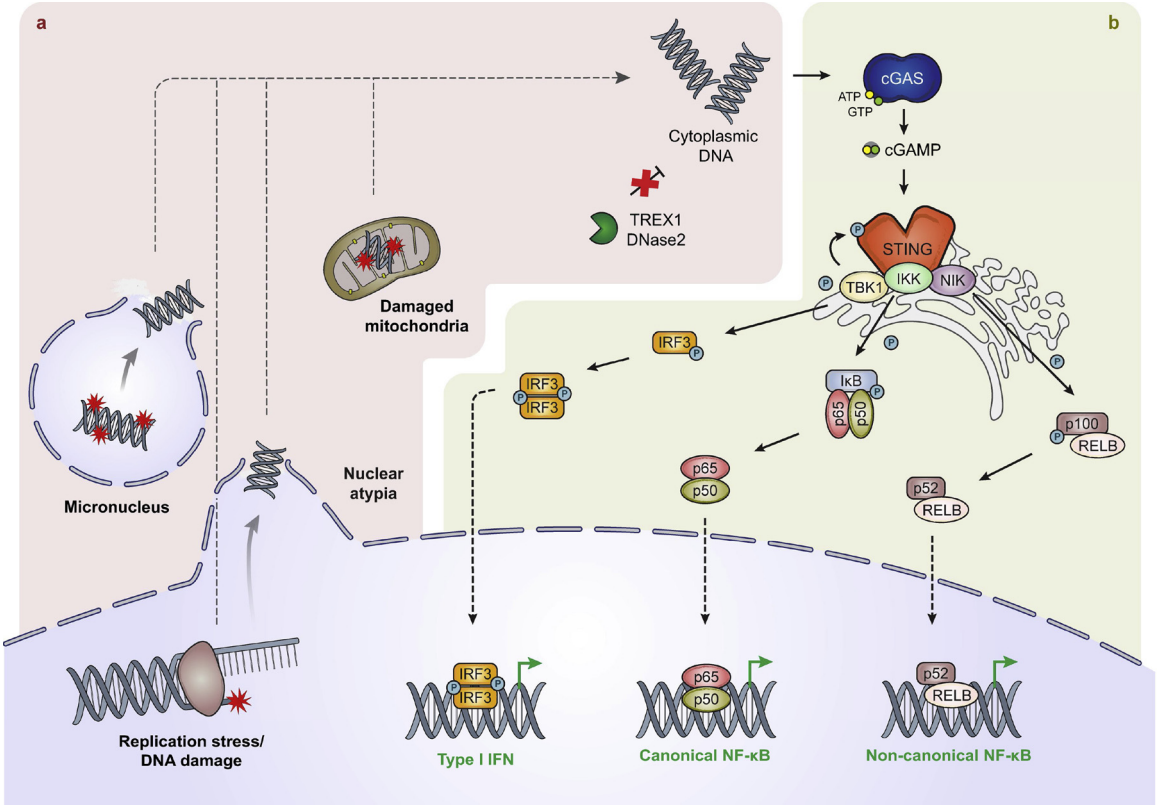

Fig. 1. Putative sources of immunostimulatory cytoplasmic chromatin and activation of the cGAS-STING pathway during aging.
(**a**) Faulty chromosome segregation due to mitotic dysfunction leads to the formation of rupture-prone micronuclei, which leak their DNA content into the cytoplasm. Elderly cells also experience replication stress and DNA damage, resulting in DNA fragments that bud off from nuclei due to defects in nuclear envelope composition (nuclear atypia). mtDNA leakage from damaged mitochondria and defective activity of cytoplasmic DNases, might further contribute to cytoplasmic DNA burden in aged cells; (**b**) Recognition of cytoplasmic chromatin by the anti-viral cGAS-STING pathway may activate three distinct kinases, namely TBK1, IKK or NIK, that trigger transcription of type I interferon-associated (IFN) genes, canonical NF-κB or non-canonical NF-κB targets, respectively. The senescence-associated secretory phenotype (SASP), which accompanies the permanent cell cycle arrest of senescent cells, has been attributed to chronic activation of NF-κB signaling, but other signaling pathways might be involved.

The specialized sensor cGAS catalyzes the synthesis of the dinucleotide cGAMP when in the presence of cytosolic dsDNA (Sun et al., 2013; Wu et al., 2013). Once engaged, cGAMP-mediated dimerization of STING can promote the activation of three distinct kinases, namely the TANK binding kinase 1 (TBK1), the multi-subunit IκB kinase complex (IKK), and the mitogen-activated protein kinase kinase kinase 14 (MAP3K14, or NIK) (Galluzzi et al., 2018) (Fig. 1b). Active TBK1 phosphorylates interferon regulatory factor 3 (IRF3), enabling its oligomerization and translocation into the nucleus, where it coordinates the expression of type I interferon-associated (IFN) genes (Fitzgerald et al., 2003; Sharma et al., 2003; Tanaka and Chen, 2012). Afterwards, IFNs are secreted where they bind the cell surface interferon receptors (IFNRs), which in turn induce the expression of interferon-stimulated genes (ISGs), including cGAS itself (Ma et al., 2015). In addition to IRF3, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is also a relevant regulator of ISG expression, in particular the canonical pathway, which is mediated by active IKK that promotes proteasomal degradation of the NF-κB inhibitor, IκBα. This enables the release and translocation of functional p50/p65 heterodimers into the nucleus to ultimately trigger the expression of canonical NF-κB targets (Beinke and Ley, 2004; Hayden and Ghosh, 2008). Finally, besides these two branches, engagement of cGAS-STING can also prompt NIK-dependent activation of the non-canonical NF-κB signaling cascade. In opposition to the canonical pathway, it relies on processing of the NF-κB precursor protein p100 to give rise to mature p52 and allow nuclear translocation of the noncanonical NF-κB complex p52/RELB (Senftleben et al., 2001; Xiao et al., 2001).

All the three pathways are meant to trigger the generation of a wealth of inflammatory molecules upon STING engagement, even though with distinct outcomes. Both the IRF3 and canonical NF-κB axes trigger the transcription of ISGs and additional pro-inflammatory molecules, including various cytokines and chemokines, that collectively aid in clearance of infected or damaged cells via cell death, senescence or the immune system (Santaguida et al., 2017). Conversely, in addition to its well-characterized function in B cell development, lymphoid organogenesis and osteoclast formation (Cildir et al., 2016; Sun, 2017), the non-canonical NF-κB signaling cascade triggered by chronic cGAS-STING engagement was recently shown to play a critical role in the development of metastatic behaviour in response to high levels of CIN (Bakhoum et al., 2018). Consequently, the end results of cGAS-STING activation are highly context-dependent, ranging from the establishment of an immune response and development of SASP to tumorigenesis. Thus, even though most cytoplasmic chromatin sources are likely present in the context of aging (Fig. 1), additional studies should investigate the downstream consequences of its recognition and the pathways being activated.

5. A role for cGAS-STING activation in aging and age-related diseases

Aging is associated with increased risk of blindness, neurodegeneration, cancer, and many other pathological conditions. While several mechanisms are ascribed to be relevant, chronic low-grade inflammation (or inflammaging) is likely to impact the risk of these age-related conditions. Such alteration primary viewed as non-cell autonomous through the secretion of bioactive molecules (SASP) by senescent cells

that accumulate along age (Franceschi and Campisi, 2014; Franceschi et al., 2018), has gathered evidence for cell-autonomous intrinsic processes that can initiate it, namely the cytosolic DNA-driven cGAS-STING pathway activation. Indeed, a correlative study that focused on STING R293Q genotyping in a cohort of 3397 aged subjects (65–103 years) revealed that the 293Q allele exerts a protective effect in regard to age-related diseases (*i.e.*, cardiovascular diseases, chronic lung diseases, cancer, type 2 diabetes, and cognitive impairment), most likely because its decreased signaling activity diminishes the process of inflammaging (Hamann et al., 2019). Remarkably, a set of additional recent studies has provided some mechanistic insights into how cGAS-STING activation may contribute to the development of aging diseases.

Age-related macular degeneration (AMD) is the major cause of blindness among elderly people, of which Geographic atrophy is an example. Retinal pigmented epithelium cell death that characterizes this form of blindness, was now shown to be mediated by cGAS-STING-dependent induction of a non-canonical inflammasome pathway able to activate caspases (Kerur et al., 2018). As a result of DICER1 deficiency and the consequent Alu-RNA accumulation, cytoplasmic escape of mitochondrial DNA (mtDNA) is triggered, which ultimately engages the cGAS signaling cascade (Kerur et al., 2018). This shows a yet unknown role of cGAS in responding to mobile-element transcripts accumulation with age. In addition to AMD, neurodegenerative conditions also associate with activation of innate immune response. Microglia represent the main innate immune defense of the central nervous system (Kim and de Vellis, 2005). Once active, microglia suffer morphological changes along with the secretion of bioactive factors, including pro-inflammatory molecules which are paramount for assembling an inflammasome signaling cascade (Hanisch and Kettenmann, 2007). During aging and neurodegeneration, it has been suggested that damaged and dysfunctional neurons fuel chronic reactivation of microglia, which themselves senesce with age. Persistent reactivation results in increased levels of pro-inflammation that negatively impact neighboring cells, thus generating a feedback loop (reviewed in (Heneka et al., 2018)). Interestingly, Mathur and co-workers found that functional STING is required for the antiviral drug ganciclovir to reduce inflammation in reactive microglia, in both cultured myeloid cells and a mouse model of multiple sclerosis (Mathur et al., 2017). Together with the observation that SASP-related cytokines are increased in the central nervous system of elderly mice (Youm et al., 2013) and patients with neurodegenerative diseases (Akiyama et al., 2000), this raises the hypothesis that cGAS-STING engagement might actively participate in the increased secretion of inflammatory molecules in these contexts. Curiously, the absence of functional mitophagy-associated proteins PINK1 and parkin (described for early onset Parkinson's disease or PD) in mice following exhaustive exercise leads to an inflammatory response that is completely abrogated in STING mutants (Sliter et al., 2018). Furthermore, the loss of dopaminergic neurons from the *substantia nigra pars compacta* and the motor defect experienced by aged parkin knock-out (KO) mice were also rescued by loss of STING, indicating that inflammation facilitates the observed phenotypes (Sliter et al., 2018). Consequently, clearance of damaged mitochondria appears crucial to prevent increased cytoplasmic and circulating mtDNA.

Inflammaging caused by progressive accumulation of chronic senescent cells, might also impact tissue homeostasis and increase the susceptibility to tumorigenesis. In the context of cancer, for which aging represents a major risk factor, cellular senescence and inflammation, are a clear example of antagonistic pleiotropy (Williams, 1957). Whereas at young age it acts to limit proliferation of cells upon DNA damage or oncogene activation (Campisi, 2001), and to orchestrate an inflammatory response through SASP which drives clearance by the immune system (Campisi, 2005; Cunha et al., 2018; Deng et al., 2014; Ding et al., 2018; Hoare et al., 2016; Kang et al., 2011; Kuilman et al., 2008; Li et al., 2016; Wang et al., 2017; Woo et al., 2014; Xue et al., 2007), at older age cellular senescence fuels carcinogenesis by inducing changes in pre-neoplastic and neoplastic cells and by reshaping the microenvironment (Abdul-Aziz et al., 2019; Bakhoum et al., 2018; Bavik et al., 2006; Canino et al., 2012; Capparelli et al., 2012; Coppe et al., 2008; Davalos et al., 2010; He et al., 2018; Kim et al., 2017; Krtolica et al., 2001; Liu and Hornsby, 2007; Taddei et al., 2014; Takahashi et al., 2018; Yoshimoto et al., 2013). Interestingly, non-steroidal anti-inflammatory drugs (NSAIDs) are among the most promising chemopreventive agents for different cancer types, with expected contribution to the control of neoplasia development in high-risk groups (Cuzick et al., 2009). However, the mechanism responsible for their anti-neoplastic activity remains elusive, with the classical targets of their anti-inflammatory actions, cyclooxygenase (COX) enzymes (Brown and DuBois, 2005), being questioned as major players of the anti-cancer effect (Gurpinar et al., 2013), but nevertheless limiting the use of NSAIDs in the treatment of a relatively healthy, at risk population due to the potential gastrointestinal and cardiovascular side effects. Even though the role of inflammation in cancer and carcinogenesis is complex, evidence suggests that the positive or negative outcome of senescence depends on both the severity and duration of the SASP-derived pro-inflammatory signals (Campisi, 2013). While an acute inflammation response within a short period of time can indeed be beneficial by safeguarding immune clearance of damaged senescent cells, a chronic inflammatory state and prolonged SASP will modulate the extracellular matrix with factors that enhance proliferation, migration and invasion (Ahn et al., 2014; Bakhoum et al., 2018; Coussens and Werb, 2002; Dou et al., 2017). Interestingly, loss of chromosomal stability (Weaver and Cleveland, 2006) and persistent cytoplasmic chromatin (Dou et al., 2017), which engage cGAS-STING activation, are widespread among cancer cell lines. Recent studies have now shown that the resulting secretome provides paracrine factors that foster the malignant behavior of these tumor cells, including invasion (Coppe et al., 2008; He et al., 2018; Kim et al., 2017) and metastasis (Bakhoum and Cantley, 2018). However, cancer cells can experience selective pressure to suppress interferon production to evade immune detection, for instance through activation of p38MAPK that disrupts the IRF3-mediated transcriptional response (Chen et al., 2017).

The antagonistic pleiotropy of senescence and associated pro-inflammatory signalling has turned modulation of the cGAS-STING pathway paradoxical. On one hand, activation of innate immune signalling (e.g. drugs that activate STING) is on the basis of early-stage clinical trials for cancer treatment (Fu et al., 2015), even though coming with the risk of possibly accelerating the progression of aging conditions. On the other hand, inhibition of cGAS-STING signalling could delay aging but with the risk of immune response impairment to infections. Intriguingly, a recent study revealed that replacement of the highly conserved serine residue (S358) on the adaptor protein STING allows bats to cope with the cytoplasmic DNA burden caused by viral infections and the high metabolic demands of flight, which likely contributes to their longer lifespan (Xie et al., 2018).

6. Modulation of CIN as an anti-aging strategy

Cumulative evidence reveals an accrual of senescent cells in different tissues and organs with age (Biran et al., 2017; Dimri et al., 1995; Janzen et al., 2006; Krishnamurthy et al., 2004; Liu et al., 2009; Melk et al., 2004; Molofsky et al., 2006; Ressler et al., 2006; Wang et al., 2009), a causal role for senescence in certain pathologies associated with aging. Indeed, the design of a transgene able to induce apoptosis of $p16^{INK4A}$-positive cells (or senolysis) in both BubR1-mutant progeroid and naturally aged mice showed that targeted removal of senescent cells works to extend healthspan (Baker et al., 2016, 2011). Although cellular senescence unlikely explains all aging phenotypes, senolysis delayed or even prevented the development of age-related conditions including acute myeloid leukemia (Abdul-Aziz et al., 2019), osteoarthritis (Jeon et al., 2017), atherosclerosis (Childs et al., 2016), cardiovascular complications (Roos et al., 2016), bone loss (Farr et al., 2017) and tau-mediated diseases (Bussian et al., 2018). Collectively, these

studies were fundamental to support a causal link between senescence and aging initially described based on detection of distinct senescence markers, while also suggesting that removal of senescent cells (or senolytic therapies) could be an appealing strategy to counteract aging. This idea gained strength with the discovery of pharmacological interventions based on BCL-2 familiy inhibition, which circumvent the apoptosis resistance of senescent cells and thus enable their selective killing (Chang et al., 2016; Tse et al., 2008; Yosef et al., 2016). Other compounds with senolytic activity have been identified including, amongst others, quercetin, piperlongumine and fisetin, as well as a forkhead box protein O4 (FOXO4)-interacting peptide, the histone deacetylase inhibitor Panobinostat, and heat shock protein 90 inhibitors (reviewed in (Childs et al., 2017; Niedernhofer and Robbins, 2018; Sun et al., 2018)). "unSASPing" senescence has also emerged as an alternative avenue within senotherapies. Metformin and rapamycin are amongst the compounds with known SASP-interfering activity (see (Childs et al., 2017)). The secretome of senescent cells has, however, a very heterogenous composition, which depends on the type and duration of the senescence-inducing stimuli, the cell type and ultimately the signalling cascades being activated. Consequently, despite the significant progress, senotherapeutics still face hurdles that must be overcome. The time-window at which therapy should be initiated and how to limit the off-target effects on beneficial senescence that is required during development, wound healing and tissue regeneration (Demaria et al., 2014; Munoz-Espin et al., 2013; Storer et al., 2013), are still issues under investigation. Furthermore, as senescence represents a "safety mechanism" that halts the proliferation of malignant cells, the manipulation of SASP may compromise the anti-tumor activity of this program. Upcoming studies will be elemental to strengthen the potential of therapeutically targeting senescence to promote healthspan.

Fibroblasts derived from elderly individuals that are still proliferating exhibit a pro-inflammatory signature that, upon faulty chromosome segregation, evolves into a full-blown senescent state (permanent cell cycle arrest) (Macedo et al., 2018) (Fig. 2a). This is likely a result of the immunostimulatory cytoplasmic DNA released by rupture-prone MN (Harding et al., 2017; Mackenzie et al., 2017). In chromosomally unstable cells this was already shown to foster senescence and its associated secretome (SASP), presumably via the engagement of the cGAS-STING signaling cascade (He et al., 2018; Santaguida et al., 2017). This indicates that senescence triggered by chromosome mis-segregation will likely contribute to the chronic low-grade pro-inflammatory state observed with age and that thereby modulation of CIN could represent a novel strategy to delay senescence-associated changes with age in alternative to selective killing and SASP neutralizing approaches (Fig. 2b). Indeed, improved chromosome segregation upon overexpression of the checkpoint protein BubR1, in BubR1 hypomorphic mice, was able to delay tissue dysfunction and extend lifespan (Baker et al., 2013). Similarly, expression of a constitutively active form of the transcription factor FoxM1, which amongst others drives the expression of BubR1 (Fischer et al., 2016), improved mitotic fitness of elderly fibroblasts concomitantly with a rescue of aneuploidy and the senescence phenotype (*i.e.,* cell cycle inhibition, DNA damage and SASP)(Macedo et al., 2018). This is particularly interesting as several types of proliferative cells support both stem and differentiated cell pools' function through secretion of bioactive molecules (paracrine signaling) and thus represent important modulators of tissue homeostasis. Consequently, delayed emergence of a full-blown senescent state in proliferative cell types through improved chromosome segregation fidelity could likely counteract the SASP-mediated microenvironmental changes in tissues with age, and thereby exert a protective effect on stem and differentiated cell function which generally decline with aging (Chien and Karsenty, 2005; Geiger and Van Zant, 2002; Janzen et al., 2006; Molofsky et al., 2006). A very recent study supports this idea by showing that continuous removal of senescent astrocytes and microglia (proliferative cell pools in the brain), preserves cognitive function in a mouse model of tau-dependent neurodegenerative disease (Bussian et al., 2018). Both transgenic and pharmacologically induced senoclearance revealed the ability to prevent gliosis, neurofibrillary tangle formation, as well as the degeneration of cortical and hippocampal neurons (Bussian et al., 2018). These findings suggest that the proliferative capacity of astrocytes and microglia is crucial to maintain brain function. Furthermore, diet rejuvenation strategies also appear to play a role through a boost in cell proliferation (Melo Pereira et al., 2019). The periodic fasting-mimicking diet (FMD), consisting of cycles of very low caloric restriction intake for 4 days, repeated twice a month, with ad libitum feeding in between, when initiated in 16-month-old mice, reverses age-associated hematopoietic differentiation bias, increases hippocampal neurogenesis, decreases cancer incidence and inflammatory diseases, and extends median lifespan (Brandhorst et al., 2015). Some of the beneficial effects of FMD appear likely due to increased cell proliferation and number of stem cells (Brandhorst et al., 2015), and possibly improved tissue function by out dilution of damaged cells with youthful cells (Fig. 2b). Interestingly, when looking over the cell types primarily targeted by the existing rejuvenation strategies, one can find adult stem cells, vascular and connective tissue cells, and senescent cells, all related to proliferative capacity. For example, quiescent stem cells exhibit increased age-related features compared to actively proliferating stem cells, which raises the possibility that proliferation rewire in stem cell populations could itself reset aging features. Regarding the vascular and connective tissue cells, which are present throughout the organism, improvement of their proliferative capacity could have broad organismal effects. Finally, senescent cells (restricted to the definition built for proliferative/mitotic cells), beyond their elimination by senotherapies, it is also plausible that the proliferation boost induced by FMD or partial reprogramming could dilute senescent cells and/or trigger their clearance. Thus, safeguarding proliferation of cells with fidelity is a conceivable approach to delay the consequences of perturbed tissue homeostasis with age. Alleviating the burden of SASP factors through CIN modulation might also positively impact the changes in the immune system observed with age (immunosenescence), which have been attributed to persistent pro-inflammatory stimuli present in aged tissues (Fulop et al., 2017).

Although it is still elusive whether aneuploid senescent cells indeed accumulate *in vivo* with aging, a combination of resistance to and failure in the establishment of an efficient immune response are likely required for an accrual to occur, since pro-inflammation induced by karyotypically abnormal cells was shown to induce their clearance by natural killer cells (Santaguida et al., 2017). It has been proposed that accumulation of senescent cells with age results from the intrinsic decline of the immune system, the presence of immune-impairing molecules and a possible ability of senescent cells to evade immune responses (Childs et al., 2015; Fulop et al., 2017). In addition, mild levels of aneuploidy such as those that have been described for elderly cells might not be sufficient to efficiently recruit immune clearance, despite the clear evolution in senescence and the expression of pro-inflammatory molecules upon defective chromosome segregation (Macedo et al., 2018; Santaguida et al., 2017). The potential of CIN modulation to delay aging still faces critical questions that must be tackled. It remains to be determined whether the evolution in senescence upon aneuploidy occurring in elderly cells is cGAS-STING-dependent, and if MN formation upon chromosome mis-segregation is sufficient to trigger an immunostimulatory signal, or if further defects (e.g., nuclear atypia, replication stress, downregulation of cytoplasmic DNases) are required. Subsequent insights into downstream routes of STING engagement in aneuploid senescent cells will provide additional information, possibly aging-specific preferences that aid immune evasion of these cells, similarly to what was recently described for highly aneuploid malignant cells that experience chronic cytoplasmic DNA-mediated immune stimulation (Bakhoum et al., 2018; Dou et al., 2017). Nonetheless, modulation of CIN would encompass several already identified advantages of senolysis by preventing the generation of fully

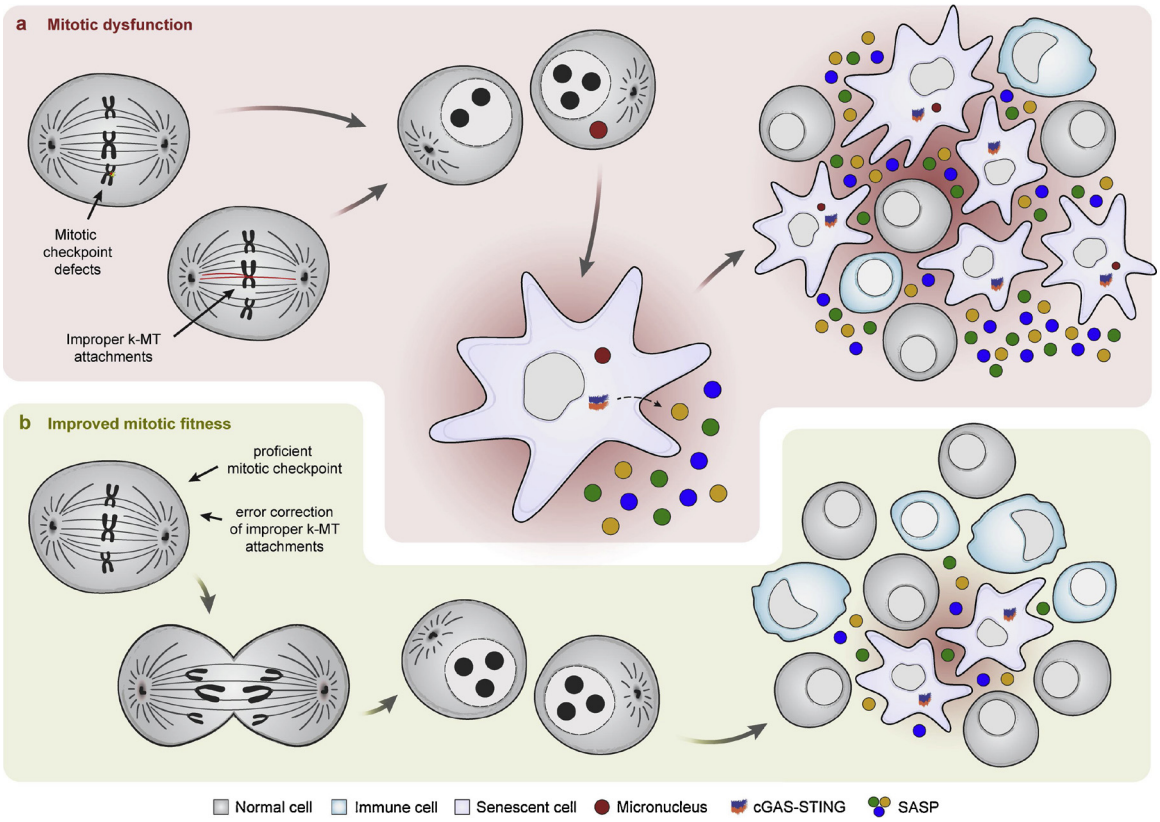

Fig. 2. Modulation of age-associated CIN as an anti-aging strategy.
(**a**) Mitotic dysfunction observed in aged cells causes chromosome mis-segregation and micronuclei formation, which is crucial for the transition into a permanent cell cycle arrest (full senescence), presumably due to cGAS-STING activation by cytosolic DNA released from micronuclei, leading to active secretion of pro-inflammatory molecules (SASP). In combination with the decreased efficiency of the immune system, which itself senesces (immunosenescence), accrual of aneuploid senescent cells leads to a chronic inflammatory state that perturbs tissue function contributing to the development of aging-associated phenotypes; (**b**) By improving mitotic fitness of proliferative elderly cells (inhibition of CIN through BubR1 and FoxM1 overexpression, for example), generation of aneuploid senescent cells is prevented, which is expected to alleviate the pro-inflammatory status of aged tissues and thus act to delay the onset of age-related conditions.

senescent cells and their detrimental paracrine signaling, while bypassing the off-target effects on beneficial senescent cells and the need to determine a critical time window for treatment onset, concerns that still hamper the safe applicability of senolytic therapies (reviewed in (Melo Pereira et al., 2019)). It will be crucial to go into the molecular mechanism(s) behind the loss of chromosome segregation fidelity with age, the manipulation of which might be explored to delay the onset of aging phenotypes by alleviating the burden of cellular senescence. The identified mitotic gene shutdown suggests that overall fitness during mitosis becomes compromised with age likely due to the accumulation of macromolecular damage (Macedo et al., 2018). Therefore, the reversal of this global shutdown, rather than the manipulation of individual components, might offer a multitude of benefits that go far beyond cells' improved chromosome segregation and delayed transition into a full senescent state. Importantly, the replenishment of elderly cell populations with fit and proliferative cells will act to dilute the negative effects of senescence triggered by other means which also accumulates over time.

7. Concluding remarks

Chromosomal instability was recently established as a source of immunostimulatory cytoplasmic chromatin able to activate the cGAS-STING pathway (Harding et al., 2017; Mackenzie et al., 2017), which in turn reveals important for the development of cellular senescence and its associated secretome (Dou et al., 2017; Gluck et al., 2017; Yang et al., 2017). With the observation that premature aging phenotypes evidenced by mouse models with CIN are rescued upon selective removal of senescent cells (Baker et al., 2011), it is tempting to speculate that cGAS-STING engagement mediated by CIN-positive senescent cells may fuel a chronic pro-inflammatory environment. The secreted factors will affect surrounding cells and compartments, perturbing tissue homeostasis and organ function that characterizes aging. A complex combination of evasion to and failure of immune clearance likely accounts for accrual of senescent cells, thus suggesting that preventing the emergence or promoting the clearance of these cells should be beneficial to delay aging-associated changes.

Senolytic strategies have already paved way by showing that selective removal of senescent cells, concomitantly with a reduction of the associated SASP, is beneficial in the context of aging by attenuating or even preventing the onset of certain pathological conditions. Thus, interventions at the level of cGAS-STING activity to either reduce the burden of pro-inflammatory molecules (SASP) or potentiate immune system-mediated clearance of senescent cells could be an option to be taken into consideration. However, cGAS-STING signaling remains still elusive in the context of aging. It will be fundamental to determine which implications this signaling cascade has in the establishment of the senescent state in the context of aging, including the elucidation of the downstream pathways that become activated upon STING engagement. Several cGAS antagonists have been successfully tested *in vitro* (An et al., 2015; Hall et al., 2017; Vincent et al., 2017) and STING agonists are also emerging (Ramanjulu et al., 2018), or have even progressed into clinical trials (Corrales et al., 2015; Sali et al., 2015). However, similarly to what is being the current discussion in the cancer field (see (Bose, 2017; Ng et al., 2018)), modulation of this pathway in the aging context might reveal a double-edged sword. On one hand, one

would envision that using targeted stimulation of cGAS or STING would improve the immune system efficacy to ultimately aid clearance of the detrimental senescent cells. However, on the other hand, being aging the end result of a low-grade chronic inflammatory state, encouraging the production of pro-inflammatory molecules by cGAS/STING stimulation could further fuel the disruption of tissue function. Thus, cGAS-STING modulation would have to be fine-tuned to avoid excessive pro-inflammation (pro-aging), while not weakening immunity to infections and tumorigenesis. One plausible alternative would be to go further upstream in the order of events, i.e. CIN – micronuclei – cytosolic DNA – cGAS/STING activation – SASP, so that mitotic competence is rewired in a way that CIN, and consequently any SASP-driven irreversible tissue deterioration, are prevented. Noteworthy, in the BubR1 hypomorphic mouse, the INK-ATTAC transgene-mediated senolysis in late life blunted further tissue deterioration but did not reverse dysfunction. Also, agents targeted against SASP proteases, besides effective in preventing aberrant extracellular matrix degradation caused by senescent cells, may also impair protease-mediated activation of other SASP components (McQuibban et al., 2002). Hence, modulation of age-associated CIN reveals a particularly appealing strategy, as it would replenish tissues with "fitter" cells and dilute out damaged cells generated even by other means than CIN, while circumventing the off-target effects of senolytics and the yet unpredictable impact of cGAS/STING modulation. Still, the molecular mechanism(s) underlying loss of chromosome segregation fidelity (hence, aneuploidy) during aging and how aneuploidy ultimately contributes to the changes observed with age remain largely unknown. Collective addressment of these questions will be elemental to establish an aneuploid senescent cell signature, which may in the future be explored as a more specific senolytic approach. Moreover, it will be interesting to determine whether beneficial effects of current rejuvenation strategies, i.e., blood factors, diet regimens, senolytics and cellular reprogramming, could after all arise from improved proliferative capacity in specific target cells.

Funding

E.L. holds an FCT Investigator Postdoctoral Grant (IF/00916/2014) and M.V. holds an FCT Fellowship SFRH/BD/133478/2017 from FCT/MCTES (Fundação para a Ciência e a Tecnologia/Ministério da Ciência, Tecnologia e Ensino Superior). The following project grants supported this work: National Funds through FCT under the project PTDC/BEX-BCM/2090/2014; European Regional Development Fund (FEDER) through the COMPETE 2020 - Operational Program for Competitiveness and Internationalization (POCI), Portugal 2020, and National funds through FCT in the framework of the project POCI-01-0145-FEDER-031120 (PTDC/BIA-CEL/31,120/2017); NORTE-01-0145-FEDER-000029 funded by North Regional Operational Program (NORTE2020) under PORTUGAL 2020 Partnership Agreement through FEDER; and POCI-01-0145-FEDER-007274 i3S framework project co-funded by COMPETE 2020/PORTUGAL 2020 through FEDER and by FCT.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

We apologize to those colleagues whose work we could not cite owing to space limitations. The review mostly highlights recent publications on the topic. The authors acknowledge all members of Ageing and Aneuploidy lab for insightful proofreading of the manuscript.

References

Abdul-Aziz, A.M., Sun, Y., Hellmich, C., Marlein, C.R., Mistry, J., Forde, E., Piddock, R.E., Shafat, M.S., Morfakis, A., Mehta, T., Di Palma, F., Macaulay, I., Ingham, C.J., Haestier, A., Collins, A., Campisi, J., Bowles, K.M., Rushworth, S.A., 2019. Acute myeloid leukemia induces protumoral p16INK4a-driven senescence in the bone marrow microenvironment. Blood 133, 446–456.

Acosta, J.C., Banito, A., Wuestefeld, T., Georgilis, A., Janich, P., Morton, J.P., Athineos, D., Kang, T.W., Lasitschka, F., Andrulis, M., Pascual, G., Morris, K.J., Khan, S., Jin, H., Dharmalingam, G., Snijders, A.P., Carroll, T., Capper, D., Pritchard, C., Inman, G.J., Longerich, T., Sansom, O.J., Benitah, S.A., Zender, L., Gil, J., 2013. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat. Cell Biol. 15, 978–990.

Ahn, J., Xia, T., Konno, H., Konno, K., Ruiz, P., Barber, G.N., 2014. Inflammation-driven carcinogenesis is mediated through STING. Nat. Commun. 5, 5166.

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G.M., Cooper, N.R., Eikelenboom, P., Emmerling, M., Fiebich, B.L., Finch, C.E., Frautschy, S., Griffin, W.S., Hampel, H., Hull, M., Landreth, G., Lue, L., Mrak, R., Mackenzie, I.R., McGeer, P.L., O'Banion, M.K., Pachter, J., Pasinetti, G., Plata-Salaman, C., Rogers, J., Rydel, R., Shen, Y., Streit, W., Strohmeyer, R., Tooyoma, I., Van Muiswinkel, F.L., Veerhuis, R., Walker, D., Webster, S., Wegrzyniak, B., Wenk, G., Wyss-Coray, T., 2000. Inflammation and Alzheimer's disease. Neurobiol. Aging 21, 383–421.

An, J., Woodward, J.J., Sasaki, T., Minie, M., Elkon, K.B., 2015. Cutting edge: antimalarial drugs inhibit IFN-beta production through blockade of cyclic GMP-AMP synthase-DNA interaction. J. Immunol. 194, 4089–4093.

Anders, L., Ke, N., Hydbring, P., Choi, Y.J., Widlund, H.R., Chick, J.M., Zhai, H., Vidal, M., Gygi, S.P., Braun, P., Sicinski, P., 2011. A systematic screen for CDK4/6 substrates links FOXM1 phosphorylation to senescence suppression in cancer cells. Cancer Cell 20, 620–634.

Andriani, G.A., Almeida, V.P., Faggioli, F., Mauro, M., Tsai, W.L., Santambrogio, L., Maslov, A., Gadina, M., Campisi, J., Vijg, J., Montagna, C., 2016. Whole chromosome instability induces senescence and promotes SASP. Sci. Rep. 6, 35218.

Arendt, T., Bruckner, M.K., Losche, A., 2015. Regional mosaic genomic heterogeneity in the elderly and in Alzheimer's disease as a correlate of neuronal vulnerability. Acta Neuropathol. 130, 501–510.

Baker, D.J., Jeganathan, K.B., Cameron, J.D., Thompson, M., Juneja, S., Kopecka, A., Kumar, R., Jenkins, R.B., de Groen, P.C., Roche, P., van Deursen, J.M., 2004. BubR1 insufficiency causes early onset of aging-associated phenotypes and infertility in mice. Nat. Genet. 36, 744–749.

Baker, D.J., Jeganathan, K.B., Malureanu, L., Perez-Terzic, C., Terzic, A., van Deursen, J.M., 2006. Early aging-associated phenotypes in Bub3/Rae1 haploinsufficient mice. J. Cell Biol. 172, 529–540.

Baker, D.J., Wijshake, T., Tchkonia, T., LeBrasseur, N.K., Childs, B.G., van de Sluis, B., Kirkland, J.L., van Deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236.

Baker, D.J., Dawlaty, M.M., Wijshake, T., Jeganathan, K.B., Malureanu, L., van Ree, J.H., Crespo-Diaz, R., Reyes, S., Seaburg, L., Shapiro, V., Behfar, A., Terzic, A., van de Sluis, B., van Deursen, J.M., 2013. Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. Nat. Cell Biol. 15, 96–102.

Baker, D.J., Childs, B.G., Durik, M., Wijers, M.E., Sieben, C.J., Zhong, J., Saltness, R.A., Jeganathan, K.B., Verzosa, G.C., Pezeshki, A., Khazaie, K., Miller, J.D., van Deursen, J.M., 2016. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530, 184–189.

Bakhoum, S.F., Cantley, L.C., 2018. The multifaceted role of chromosomal instability in Cancer and its microenvironment. Cell 174, 1347–1360.

Bakhoum, S.F., Ngo, B., Laughney, A.M., Cavallo, J.A., Murphy, C.J., Ly, P., Shah, P., Sriram, R.K., Watkins, T.B.K., Taunk, N.K., Duran, M., Pauli, C., Shaw, C., Chadalavada, K., Rajasekhar, V.K., Genovese, G., Venkatesan, S., Birkbak, N.J., McGranahan, N., Lundquist, M., LaPlant, Q., Healey, J.H., Elemento, O., Chung, C.H., Lee, N.Y., Imielenski, M., Nanjangud, G., Pe'er, D., Cleveland, D.W., Powell, S.N., Lammerding, J., Swanton, C., Cantley, L.C., 2018. Chromosomal instability drives metastasis through a cytosolic DNA response. Nature 553, 467–472.

Bavik, C., Coleman, I., Dean, J.P., Knudsen, B., Plymate, S., Nelson, P.S., 2006. The gene expression program of prostate fibroblast senescence modulates neoplastic epithelial cell proliferation through paracrine mechanisms. Cancer Res. 66, 794–802.

Beinke, S., Ley, S.C., 2004. Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. Biochem. J. 382, 393–409.

Biran, A., Zada, L., Abou Karam, P., Vadai, E., Roitman, L., Ovadya, Y., Porat, Z., Krizhanovsky, V., 2017. Quantitative identification of senescent cells in aging and disease. Aging Cell 16, 661–671.

Bose, D., 2017. cGAS/STING pathway in Cancer: jekyll and hyde story of Cancer immune response. Int. J. Mol. Sci. 18, 2456.

Brandhorst, S., Choi, I.Y., Wei, M., Cheng, C.W., Sedrakyan, S., Navarrete, G., Dubeau, L., Yap, L.P., Park, R., Vinciguerra, M., Di Biase, S., Mirzaei, H., Mirisola, M.G., Childress, P., Ji, L., Groshen, S., Penna, F., Odetti, P., Perin, L., Conti, P.S., Ikeno, Y., Kennedy, B.K., Cohen, P., Morgan, T.E., Dorff, T.B., Longo, V.D., 2015. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metabab. 22, 86–99.

Bregnard, C., Guerra, J., Dejardin, S., Passalacqua, F., Benkirane, M., Laguette, N., 2016. Upregulated LINE-1 activity in the fanconi Anemia Cancer susceptibility syndrome leads to spontaneous pro-inflammatory cytokine production. EBioMedicine 8, 184–194.

Brown, J.R., DuBois, R.N., 2005. COX-2: a molecular target for colorectal cancer prevention. J. Clin. Oncol. 23, 2840–2855.

Bussian, T.J., Aziz, A., Meyer, C.F., Swenson, B.L., van Deursen, J.M., Baker, D.J., 2018. Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. Nature 562, 578–582.

Campisi, J., 2001. Cellular senescence as a tumor-suppressor mechanism. Trends Cell Biol. 11, S27–31.

Campisi, J., 2005. Senescent cells, tumor suppression, and organismal aging: good

citizens, bad neighbors. Cell 120, 513–522.
Campisi, J., 2013. Aging, cellular senescence, and cancer. Annu. Rev. Physiol. 75, 685–705.
Canino, C., Mori, F., Cambria, A., Diamantini, A., Germoni, S., Alessandrini, G., Borsellino, G., Galati, R., Battistini, L., Blandino, R., Facciolo, F., Citro, G., Strano, S., Muti, P., Blandino, G., Cioce, M., 2012. SASP mediates chemoresistance and tumor-initiating-activity of mesothelioma cells. Oncogene 31, 3148–3163.
Capparelli, C., Guido, C., Whitaker-Menezes, D., Bonuccelli, G., Balliet, R., Pestell, T.G., Goldberg, A.F., Pestell, R.G., Howell, A., Sneddon, S., Birbe, R., Tsirigos, A., Martinez-Outschoorn, U., Sotgia, F., Lisanti, M.P., 2012. Autophagy and senescence in cancer-associated fibroblasts metabolically supports tumor growth and metastasis via glycolysis and ketone production. Cell Cycle 11, 2285–2302.
Chang, J., Wang, Y., Shao, L., Laberge, R.M., Demaria, M., Campisi, J., Janakiraman, K., Sharpless, N.E., Ding, S., Feng, W., Luo, Y., Wang, X., Aykin-Burns, N., Krager, K., Ponnappan, U., Hauer-Jensen, M., Meng, A., Zhou, D., 2016. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat. Med. 22, 78–83.
Chen, Y., Wang, L., Jin, J., Luan, Y., Chen, C., Li, Y., Chu, H., Wang, X., Liao, G., Yu, Y., Teng, H., Wang, Y., Pan, W., Fang, L., Liao, L., Jiang, Z., Ge, X., Li, B., Wang, P., 2017. p38 inhibition provides anti-DNA virus immunity by regulation of USP21 phosphorylation and STING activation. J. Exp. Med. 214, 991–1010.
Chien, K.R., Karsenty, G., 2005. Longevity and lineages: toward the integrative biology of degenerative diseases in heart, muscle, and bone. Cell 120, 533–544.
Childs, B.G., Durik, M., Baker, D.J., van Deursen, J.M., 2015. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat. Med. 21, 1424–1435.
Childs, B.G., Baker, D.J., Wijshake, T., Conover, C.A., Campisi, J., van Deursen, J.M., 2016. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science 354, 472–477.
Childs, B.G., Gluscevic, M., Baker, D.J., Laberge, R.M., Marquess, D., Dananberg, J., van Deursen, J.M., 2017. Senescent cells: an emerging target for diseases of ageing. Nat. Rev. Drug Discov. 16, 718–735.
Cildir, G., Low, K.C., Tergaonkar, V., 2016. Noncanonical NF-kappaB signaling in health and disease. Trends Mol. Med. 22, 414–429.
Cimini, D., Howell, B., Maddox, P., Khodjakov, A., Degrassi, F., Salmon, E.D., 2001. Merotelic kinetochore orientation is a major mechanism of aneuploidy in mitotic mammalian tissue cells. J. Cell Biol. 153, 517–527.
Cimini, D., Moree, B., Canman, J.C., Salmon, E.D., 2003. Merotelic kinetochore orientation occurs frequently during early mitosis in mammalian tissue cells and error correction is achieved by two different mechanisms. J. Cell. Sci. 116, 4213–4225.
Coppe, J.P., Patil, C.K., Rodier, F., Sun, Y., Munoz, D.P., Goldstein, J., Nelson, P.S., Desprez, P.Y., Campisi, J., 2008. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 6, 2853–2868.
Coquel, F., Silva, M.J., Techer, H., Zadorozhny, K., Sharma, S., Nieminuszczy, J., Mettling, C., Dardillac, E., Barthe, A., Schmitz, A.L., Promonet, A., Cribier, A., Sarrazin, A., Niedzwiedz, W., Lopez, B., Costanzo, V., Krejci, L., Chabes, A., Benkirane, M., Lin, Y.L., Pasero, P., 2018. SAMHD1 acts at stalled replication forks to prevent interferon induction. Nature 557, 57–61.
Corrales, L., Glickman, L.H., McWhirter, S.M., Kanne, D.B., Sivick, K.E., Katibah, G.E., Woo, S.R., Lemmens, E., Banda, T., Leong, J.J., Metchette, K., Dubensky Jr, T.W., Gajewski, T.F., 2015. Direct activation of STING in the tumor microenvironment leads to potent and systemic tumor regression and immunity. Cell Rep. 11, 1018–1030.
Coussens, L.M., Werb, Z., 2002. Inflammation and cancer. Nature 420, 860–867.
Crasta, K., Ganem, N.J., Dagher, R., Lantermann, A.B., Ivanova, E.V., Pan, Y., Nezi, L., Protopopov, A., Chowdhury, D., Pellman, D., 2012. DNA breaks and chromosome pulverization from errors in mitosis. Nature 482, 53–58.
Crow, Y.J., 2015. Type I interferonopathies: mendelian type I interferon up-regulation. Curr. Opin. Immunol. 32, 7–12.
Crow, Y.J., Hayward, B.E., Parmar, R., Robins, P., Leitch, A., Ali, M., Black, D.N., van Bokhoven, H., Brunner, H.G., Hamel, B.C., Corry, P.C., Cowan, F.M., Frints, S.G., Klepper, J., Livingston, J.H., Lynch, S.A., Massey, R.F., Meritet, J.F., Michaud, J.L., Ponsot, G., Voit, T., Lebon, P., Bonthron, D.T., Jackson, A.P., Barnes, D.E., Lindahl, T., 2006. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. Nat. Genet. 38, 917–920.
Cunha, L.D., Yang, M., Carter, R., Guy, C., Harris, L., Crawford, J.C., Quarato, G., Boada-Romero, E., Kalkavan, H., Johnson, M.D.L., Natarajan, S., Turnis, M.E., Finkelstein, D., Opferman, J.T., Gawad, C., Green, D.R., 2018. LC3-Associated Phagocytosis in Myeloid Cells Promotes Tumor Immune Tolerance. Cell 175 (429-441), e416.
Cuzick, J., Otto, F., Baron, J.A., Brown, P.H., Burn, J., Greenwald, P., Jankowski, J., La Vecchia, C., Meyskens, F., Senn, H.J., Thun, M., 2009. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol. 10, 501–507.
da Silva, P.F.L., Ogrodnik, M., Kucheryavenko, O., Glibert, J., Miwa, S., Cameron, K., Ishaq, A., Saretzki, G., Nagaraja-Grellscheid, S., Nelson, G., von Zglinicki, T., 2019. The bystander effect contributes to the accumulation of senescent cells in vivo. Aging Cell 18, e12848.
Davalos, A.R., Coppe, J.P., Campisi, J., Desprez, P.Y., 2010. Senescent cells as a source of inflammatory factors for tumor progression. Cancer Metastasis Rev. 29, 273–283.
Demaria, M., Ohtani, N., Youssef, S.A., Rodier, F., Toussaint, W., Mitchell, J.R., Laberge, R.M., Vijg, J., Van Steeg, H., Dolle, M.E., Hoeijmakers, J.H., de Bruin, A., Hara, E., Campisi, J., 2014. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev. Cell 31, 722–733.
Deng, L., Liang, H., Xu, M., Yang, X., Burnette, B., Arina, A., Li, X.D., Mauceri, H., Beckett, M., Darga, T., Huang, X., Gajewski, T.F., Chen, Z.J., Fu, Y.X., Weichselbaum, R.R., 2014. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity 41, 843–852.
Dimri, G.P., Lee, X., Basile, G., Acosta, M., Scott, G., Roskelley, C., Medrano, E.E., Linskens, M., Rubelj, I., Pereira-Smith, O., 1995. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc. Natl. Acad. Sci. 92, 9363–9367.
Ding, L., Kim, H.J., Wang, Q., Kearns, M., Jiang, T., Ohlson, C.E., Li, B.B., Xie, S., Liu, J.F., Stover, E.H., Howitt, B.E., Bronson, R.T., Lazo, S., Roberts, T.M., Freeman, G.J., Konstantinopoulos, P.A., Matulonis, U.A., Zhao, J.J., 2018. PARP inhibition elicits STING-Dependent antitumor immunity in Brca1-Deficient ovarian Cancer. Cell Rep. 25, 2972–2980 e2975.
Dou, Z., Xu, C., Donahue, G., Shimi, T., Pan, J.A., Zhu, J., Ivanov, A., Capell, B.C., Drake, A.M., Shah, P.P., Catanzaro, J.M., Ricketts, M.D., Lamark, T., Adam, S.A., Marmorstein, R., Zong, W.X., Johansen, T., Goldman, R.D., Adams, P.D., Berger, S.L., 2015. Autophagy mediates degradation of nuclear lamina. Nature 527, 105–109.
Dou, Z., Ghosh, K., Vizioli, M.G., Zhu, J., Sen, P., Wangensteen, K.J., Simithy, J., Lan, Y., Lin, Y., Zhou, Z., Capell, B.C., Xu, C., Xu, M., Kieckhaefer, J.E., Jiang, T., Shoshkes-Carmel, M., Tanim, K., Barber, G.N., Seykora, J.T., Millar, S.E., Kaestner, K.H., Garcia, B.A., Adams, P.D., Berger, S.L., 2017. Cytoplasmic chromatin triggers inflammation in senescence and cancer. Nature 550, 402–406.
Dumanski, J.P., Lambert, J.C., Rasi, C., Giedraitis, V., Davies, H., Grenier-Boley, B., Lindgren, C.M., Campion, D., Dufouil, C., European Alzheimer's Disease Initiative, I, Pasquier, F., Amouyel, P., Lannfelt, L., Ingelsson, M., Kilander, L., Lind, L., Forsberg, L.A., 2016. Mosaic loss of chromosome Y in blood is associated with alzheimer disease. Am. J. Hum. Genet. 98, 1208–1219.
Duncan, A.W., Taylor, M.H., Hickey, R.D., Hanlon Newell, A.E., Lenzi, M.L., Olson, S.B., Finegold, M.J., Grompe, M., 2010. The ploidy conveyor of mature hepatocytes as a source of genetic variation. Nature 467, 707–710.
Farr, J.N., Fraser, D.G., Wang, H., Jaehn, K., Ogrodnik, M.B., Weivoda, M.M., Drake, M.T., Tchkonia, T., LeBrasseur, N.K., Kirkland, J.L., Bonewald, L.F., Pignolo, R.J., Monroe, D.G., Khosla, S., 2016. Identification of senescent cells in the bone microenvironment. J. Bone Miner. Res. 31, 1920–1929.
Farr, J.N., Xu, M., Weivoda, M.M., Monroe, D.G., Fraser, D.G., Onken, J.L., Negley, B.A., Sfeir, J.G., Ogrodnik, M.B., Hachfeld, C.M., LeBrasseur, N.K., Drake, M.T., Pignolo, R.J., Pirtskhalava, T., Tchkonia, T., Oursler, M.J., Kirkland, J.L., Khosla, S., 2017. Targeting cellular senescence prevents age-related bone loss in mice. Nat. Med. 23, 1072–1079.
Fischer, M., Grossmann, P., Padi, M., DeCaprio, J.A., 2016. Integration of TP53, DREAM, MMB-FOXM1 and RB-E2F target gene analyses identifies cell cycle gene regulatory networks. Nucleic Acids Res. 44, 6070–6086.
Fitzgerald, K.A., McWhirter, S.M., Faia, K.L., Rowe, D.C., Latz, E., Golenbock, D.T., Coyle, A.J., Liao, S.M., Maniatis, T., 2003. IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. Nat. Immunol. 4, 491–496.
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.
Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat. Rev. Endocrinol. 14, 576–590.
Freund, A., Laberge, R.M., Demaria, M., Campisi, J., 2012. Lamin B1 loss is a senescence-associated biomarker. Mol. Biol. Cell 23, 2066–2075.
Fu, J., Kanne, D.B., Leong, M., Glickman, L.H., McWhirter, S.M., Lemmens, E., Mechette, K., Leong, J.J., Lauer, P., Liu, W., Sivick, K.E., Zeng, Q., Soares, K.C., Zheng, L., Portnoy, D.A., Woodward, J.J., Pardoll, D.M., Dubensky Jr, T.W., Kim, Y., 2015. STING agonist formulated cancer vaccines can cure established tumors resistant to PD-1 blockade. Sci. Transl. Med. 7, 283ra252.
Fulop, T., Larbi, A., Dupuis, G., Le Page, A., Frost, E.H., Cohen, A.A., Witkowski, J.M., Franceschi, C., 2017. Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front. Immunol. 8, 1960.
Galluzzi, L., Vanpouille-Box, C., Bakhoum, S.F., Demaria, S., 2018. SnapShot: CGAS-STING signaling. Cell 173 (276-276), e271.
Gao, D., Wu, J., Wu, Y.T., Du, F., Aroh, C., Yan, N., Sun, L., Chen, Z.J., 2013. Cyclic GMP-AMP synthase is an innate immune sensor of HIV and other retroviruses. Science 341, 903–906.
Geiger, H., Van Zant, G., 2002. The aging of lympho-hematopoietic stem cells. Nat. Immunol. 3, 329–333.
Geigl, J.B., Langer, S., Barwisch, S., Pfleghaar, K., Lederer, G., Speicher, M.R., 2004. Analysis of gene expression patterns and chromosomal changes associated with aging. Cancer Res. 64, 8550–8557.
Geigl, J.B., Obenauf, A.C., Schwarzbraun, T., Speicher, M.R., 2008. Defining' chromosomal instability'. Trends Genet. 24, 64–69.
Gluck, S., Guey, B., Gulen, M.F., Wolter, K., Kang, T.W., Schmacke, N.A., Bridgeman, A., Rehwinkel, J., Zender, L., Ablasser, A., 2017. Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence. Nat. Cell Biol. 19, 1061–1070.
Gurpinar, E., Grizzle, W.E., Piazza, G.A., 2013. COX-independent mechanisms of Cancer chemoprevention by anti-inflammatory drugs. Front. Oncol. 3, 181.
Guttenbach, M., Schakowski, R., Schmid, M., 1994. Aneuploidy and ageing: sex chromosome exclusion into micronuclei. Hum. Genet. 94, 295–298.
Hall, J., Brault, A., Vincent, F., Weng, S., Wang, H., Dumlao, D., Aulabaugh, A., Aivazian, D., Castro, D., Chen, M., Culp, J., Dower, K., Gardner, J., Hawrylik, S., Golenbock, D., Hepworth, D., Horn, M., Jones, L., Jones, P., Latz, E., Li, J., Lin, L.L., Lin, W., Lin, D., Lovering, F., Niljanskul, N., Nistler, R., Pierce, B., Plotnikova, O., Schmitt, D., Shanker, S., Smith, J., Snyder, W., Subashi, T., Trujillo, J., Tyminski, E., Wang, G., Wong, J., Lefker, B., Dakin, L., Leach, K., 2017. Discovery of PF-06928215 as a high affinity inhibitor of cGAS enabled by a novel fluorescence polarization assay. PLoS

One 12, e0184843.
Hamann, L., Ruiz-Moreno, J.S., Szwed, M., Mossakowska, M., Lundvall, L., Schumann, R.R., Opitz, B., Puzianowska-Kuznicka, M., 2019. STING SNP R293Q is associated with a decreased risk of aging-related diseases. Gerontology 65, 145–154.
Hanisch, U.K., Kettenmann, H., 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat. Neurosci. 10, 1387–1394.
Hanks, S., Coleman, K., Reid, S., Plaja, A., Firth, H., Fitzpatrick, D., Kidd, A., Mehes, K., Nash, R., Robin, N., Shannon, N., Tolmie, J., Swansbury, J., Irrthum, A., Douglas, J., Rahman, N., 2004. Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. Nat. Genet. 36, 1159–1161.
Harding, S.M., Benci, J.L., Irianto, J., Discher, D.E., Minn, A.J., Greenberg, R.A., 2017. Mitotic progression following DNA damage enables pattern recognition within micronuclei. Nature 548, 466–470.
Hartlova, A., Erttmann, S.F., Raffi, F.A., Schmalz, A.M., Resch, U., Anugula, S., Lienenklaus, S., Nilsson, L.M., Kroger, A., Nilsson, J.A., Ek, T., Weiss, S., Gekara, N.O., 2015. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. Immunity 42, 332–343.
Harton, G.L., Tempest, H.G., 2012. Chromosomal disorders and male infertility. Asian J. Androl. 14, 32–39.
Hatch, E.M., Fischer, A.H., Deerinck, T.J., Hetzer, M.W., 2013. Catastrophic nuclear envelope collapse in cancer cell micronuclei. Cell 154, 47–60.
Hayden, M.S., Ghosh, S., 2008. Shared principles in NF-kappaB signaling. Cell 132, 344–362.
Hayflick, L., Moorhead, P.S., 1961. The serial cultivation of human diploid cell strains. Exp. Cell Res. 25, 585–621.
He, Q., Au, B., Kulkarni, M., Shen, Y., Lim, K.J., Maimaiti, J., Wong, C.K., Luijten, M.N.H., Chong, H.C., Lim, E.H., Rancati, G., Sinha, I., Fu, Z., Wang, X., Connolly, J.E., Crasta, K.C., 2018. Chromosomal instability-induced senescence potentiates cell non-autonomous tumourigenic effects. Oncogenesis 7, 62.
Heneka, M.T., McManus, R.M., Latz, E., 2018. Inflammasome signalling in brain function and neurodegenerative disease. Nat. Rev. Neurosci. 19, 610–621.
Hernandez-Segura, A., de Jong, T.V., Melov, S., Guryev, V., Campisi, J., Demaria, M., 2017. Unmasking transcriptional heterogeneity in senescent cells. Curr. Biol. 27 (2652-2660), e2654.
Hernandez-Segura, A., Nehme, J., Demaria, M., 2018. Hallmarks of cellular senescence. Trends Cell Biol. 28, 436–453.
Hoare, M., Ito, Y., Kang, T.W., Weekes, M.P., Matheson, N.J., Patten, D.A., Shetty, S., Parry, A.J., Menon, S., Salama, R., Antrobus, R., Tomimatsu, K., Howat, W., Lehner, P.J., Zender, L., Narita, M., 2016. NOTCH1 mediates a switch between two distinct secretomes during senescence. Nat. Cell Biol. 18, 979–992.
Iourov, I.Y., Vorsanova, S.G., Liehr, T., Yurov, Y.B., 2009. Aneuploidy in the normal, Alzheimer's disease and ataxia-telangiectasia brain: differential expression and pathological meaning. Neurobiol. Dis. 34, 212–220.
Ivanov, A., Pawlikowski, J., Manoharan, I., van Tuyn, J., Nelson, D.M., Rai, T.S., Shah, P.P., Hewitt, G., Korolchuk, V.I., Passos, J.F., Wu, H., Berger, S.L., Adams, P.D., 2013. Lysosome-mediated processing of chromatin in senescence. J. Cell Biol. 202, 129–143.
Janzen, V., Forkert, R., Fleming, H.E., Saito, Y., Waring, M.T., Dombkowski, D.M., Cheng, T., DePinho, R.A., Sharpless, N.E., Scadden, D.T., 2006. Stem-cell ageing modified by the cyclin-dependent kinase inhibitor p16INK4a. Nature 443, 421–426.
Jeon, O.H., Kim, C., Laberge, R.M., Demaria, M., Rathod, S., Vasserot, A.P., Chung, J.W., Kim, D.H., Poon, Y., David, N., Baker, D.J., van Deursen, J.M., Campisi, J., Elisseeff, J.H., 2017. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat. Med. 23, 775–781.
Jurk, D., Wang, C., Miwa, S., Maddick, M., Korolchuk, V., Tsolou, A., Gonos, E.S., Thrasivoulou, C., Saffrey, M.J., Cameron, K., von Zglinicki, T., 2012. Postmitotic neurons develop a p21-dependent senescence-like phenotype driven by a DNA damage response. Aging Cell 11, 996–1004.
Kang, T.W., Yevsa, T., Woller, N., Hoenicke, L., Wuestefeld, T., Dauch, D., Hohmeyer, A., Gereke, M., Rudalska, R., Potapova, A., Iken, M., Vucur, M., Weiss, S., Heikenwalder, M., Khan, S., Gil, J., Bruder, D., Manns, M., Schirmacher, P., Tacke, F., Ott, M., Luedde, T., Longerich, T., Kubicka, S., Zender, L., 2011. Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. Nature 479, 547–551.
Kerur, N., Fukuda, S., Banerjee, D., Kim, Y., Fu, D., Apicella, I., Varshney, A., Yasuma, R., Fowler, B.J., Baghdasaryan, E., Marion, K.M., Huang, X., Yasuma, T., Hirano, Y., Serbulea, V., Ambati, M., Ambati, V.L., Kajiwara, Y., Ambati, K., Hirahara, S., Bastos-Carvalho, A., Ogura, Y., Terasaki, H., Oshika, T., Kim, K.B., Hinton, D.R., Leitinger, N., Cambier, J.C., Buxbaum, J.D., Kenney, M.C., Jazwinski, S.M., Nagai, H., Hara, I., West, A.P., Fitzgerald, K.A., Sadda, S.R., Gelfand, B.D., Ambati, J., 2018. cGAS drives noncanonical-inflammasome activation in age-related macular degeneration. Nat. Med. 24, 50–61.
Kim, S.U., de Vellis, J., 2005. Microglia in health and disease. J. Neurosci. Res. 81, 302–313.
Kim, Y.H., Choi, Y.W., Lee, J., Soh, E.Y., Kim, J.H., Park, T.J., 2017. Senescent tumor cells lead the collective invasion in thyroid cancer. Nat. Commun. 8, 15208.
Knouse, K.A., Wu, J., Whittaker, C.A., Amon, A., 2014. Single cell sequencing reveals low levels of aneuploidy across mammalian tissues. Proc. Natl. Acad. Sci. 111, 13409–13414.
Kreienkamp, R., Graziano, S., Coll-Bonfill, N., Bedia-Diaz, G., Cybulla, E., Vindigni, A., Dorsett, D., Kubben, N., Batista, L.F.Z., Gonzalo, S., 2018. A cell-intrinsic interferon-like response links replication stress to cellular aging caused by progerin. Cell Rep. 22, 2006–2015.
Krishnamurthy, J., Torrice, C., Ramsey, M.R., Kovalev, G.I., Al-Regaiey, K., Su, L., Sharpless, N.E., 2004. Ink4a/Arf expression is a biomarker of aging. J. Clin. Invest. 114, 1299–1307.
Krtolica, A., Parrinello, S., Lockett, S., Desprez, P.Y., Campisi, J., 2001. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. Proc. Natl. Acad. Sci. 98, 12072–12077.
Kuilman, T., Michaloglou, C., Vredeveld, L.C., Douma, S., van Doorn, R., Desmet, C.J., Aarden, L.A., Mooi, W.J., Peeper, D.S., 2008. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. Cell 133, 1019–1031.
Lenain, C., Gusyatiner, O., Douma, S., van den Broek, B., Peeper, D.S., 2015. Autophagy-mediated degradation of nuclear envelope proteins during oncogene-induced senescence. Carcinogenesis 36, 1263–1274.
Li, T., Cheng, H., Yuan, H., Xu, Q., Shu, C., Zhang, Y., Xu, P., Tan, J., Rui, Y., Li, P., Tan, X., 2016. Antitumor activity of cGAMP via stimulation of cGAS-cGAMP-STING-IRF3 mediated innate immune response. Sci. Rep. 6, 19049.
Liu, D., Hornsby, P.J., 2007. Senescent human fibroblasts increase the early growth of xenograft tumors via matrix metalloproteinase secretion. Cancer Res. 67, 3117–3126.
Liu, Y., Sanoff, H.K., Cho, H., Burd, C.E., Torrice, C., Ibrahim, J.G., Thomas, N.E., Sharpless, N.E., 2009. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. Aging Cell 8, 439–448.
Liu, S., Kwon, M., Mannino, M., Yang, N., Renda, F., Khodjakov, A., Pellman, D., 2018. Nuclear envelope assembly defects link mitotic errors to chromothripsis. Nature 561, 551–555.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Ly, P., Teitz, L.S., Kim, D.H., Shoshani, O., Skaletsky, H., Fachinetti, D., Page, D.C., Cleveland, D.W., 2017. Selective Y centromere inactivation triggers chromosome shattering in micronuclei and repair by non-homologous end joining. Nat. Cell Biol. 19, 68–75.
Ma, F., Li, B., Liu, S.Y., Iyer, S.S., Yu, Y., Wu, A., Cheng, G., 2015. Positive feedback regulation of type I IFN production by the IFN-inducible DNA sensor cGAS. J. Immunol. 194, 1545–1554.
Maass, K.K., Rosing, F., Ronchi, P., Willmund, K.V., Devens, F., Hergt, M., Herrmann, H., Lichter, P., Ernst, A., 2018. Altered nuclear envelope structure and proteasome function of micronuclei. Exp. Cell Res. 371, 353–363.
Macedo, J.C., Vaz, S., Logarinho, E., 2017. Mitotic dysfunction associated with aging hallmarks. Adv. Exp. Med. Biol. 1002, 153–188.
Macedo, J.C., Vaz, S., Bakker, B., Ribeiro, R., Bakker, P.L., Escandell, J.M., Ferreira, M.G., Medema, R., Foijer, F., Logarinho, E., 2018. FoxM1 repression during human aging leads to mitotic decline and aneuploidy-driven full senescence. Nat. Commun. 9, 2834.
Mackenzie, K.J., Carroll, P., Martin, C.A., Murina, O., Fluteau, A., Simpson, D.J., Olova, N., Sutcliffe, H., Rainger, J.K., Leitch, A., Osborn, R.T., Wheeler, A.P., Nowotny, M., Gilbert, N., Chandra, T., Reijns, M.A.M., Jackson, A.P., 2017. cGAS surveillance of micronuclei links genome instability to innate immunity. Nature 548, 461–465.
Margolis, S.R., Wilson, S.C., Vance, R.E., 2017. Evolutionary origins of cGAS-STING signaling. Trends Immunol. 38, 733–743.
Mathur, V., Burai, R., Vest, R.T., Bonanno, L.N., Lehallier, B., Zardeneta, M.E., Mistry, K.N., Do, D., Marsh, S.E., Abud, E.M., Blurton-Jones, M., Li, L., Lashuel, H.A., Wyss-Coray, T., 2017. Activation of the STING-Dependent type I interferon response reduces microglial reactivity and neuroinflammation. Neuron 96 (1290-1302), e1296.
Matsuura, S., Matsumoto, Y., Morishima, K., Izumi, H., Matsumoto, H., Ito, E., Tsutsui, K., Kobayashi, J., Tauchi, H., Kajiwara, Y., Hama, S., Kurisu, K., Tahara, H., Oshimura, M., Komatsu, K., Ikeuchi, T., Kajii, T., 2006. Monoallelic BUB1B mutations and defective mitotic-spindle checkpoint in seven families with premature chromatid separation (PCS) syndrome. Am. J. Med. Genet. A 140, 358–367.
McQuibban, G.A., Gong, J.H., Wong, J.P., Wallace, J.L., Clark-Lewis, I., Overall, C.M., 2002. Matrix metalloproteinase processing of monocyte chemoattractant proteins generates CC chemokine receptor antagonists with anti-inflammatory properties in vivo. Blood 100, 1160–1167.
Melk, A., Schmidt, B.M., Takeuchi, O., Sawitzki, B., Rayner, D.C., Halloran, P.F., 2004. Expression of p16INK4a and other cell cycle regulator and senescence associated genes in aging human kidney. Kidney Int. 65, 510–520.
Melo Pereira, S., Ribeiro, R., Logarinho, E., 2019. Approaches towards longevity: reprogramming, senolysis, and improved mitotic competence as anti-aging therapies. Int. J. Mol. Sci. 20.
Mendivil-Perez, M., Velez-Pardo, C., Kosik, K.S., Lopera, F., Jimenez-Del-Rio, M., 2019. iPSCs-derived nerve-like cells from familial Alzheimer's disease PSEN 1 E280A reveal increased amyloid-beta levels and loss of the Y chromosome. Neurosci. Lett. Suppl. 703, 111–118.
Minamino, T., Orimo, M., Shimizu, I., Kunieda, T., Yokoyama, M., Ito, T., Nojima, A., Nabetani, A., Oike, Y., Matsubara, H., Ishikawa, F., Komuro, I., 2009. A crucial role for adipose tissue p53 in the regulation of insulin resistance. Nat. Med. 15, 1082–1087.
Molofsky, A.V., Slutsky, S.G., Joseph, N.M., He, S., Pardal, R., Krishnamurthy, J., Sharpless, N.E., Morrison, S.J., 2006. Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. Nature 443, 448–452.
Mosch, B., Morawski, M., Mittag, A., Lenz, D., Tarnok, A., Arendt, T., 2007. Aneuploidy and DNA replication in the normal human brain and Alzheimer's disease. J. Neurosci. 27, 6859–6867.
Mukherjee, A.B., Thomas, S., 1997. A longitudinal study of human age-related chromosomal analysis in skin fibroblasts. Exp. Cell Res. 235, 161–169.
Mukherjee, A.B., Alejandro, J., Payne, S., Thomas, S., 1996. Age-related aneuploidy analysis of human blood cells in vivo by fluorescence in situ hybridization (FISH). Mech. Ageing Dev. 90, 145–156.
Mulla, W.A., Seidel, C.W., Zhu, J., Tsai, H.J., Smith, S.E., Singh, P., Bradford, W.D., McCroskey, S., Nelliat, A.R., Conkright, J., Peak, A., Malanowski, K.E., Perera, A.G., Li, R., 2017. Aneuploidy as a cause of impaired chromatin silencing and mating-type specification in budding yeast. eLife 6, e27991.

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, 1104–1118.
Nagaoka, S.I., Hassold, T.J., Hunt, P.A., 2012. Human aneuploidy: mechanisms and new insights into an age-old problem. Nat. Rev. Genet. 13, 493–504.
Ng, K.W., Marshall, E.A., Bell, J.C., Lam, W.L., 2018. cGAS-STING and Cancer: dichotomous roles in tumor immunity and development. Trends Immunol. 39, 44–54.
Nicholson, J.M., Cimini, D., 2011. How mitotic errors contribute to karyotypic diversity in cancer. Adv. Cancer Res. 112, 43–75.
Nicholson, J.M., Macedo, J.C., Mattingly, A.J., Wangsa, D., Camps, J., Lima, V., Gomes, A.M., Doria, S., Ried, T., Logarinho, E., Cimini, D., 2015. Chromosome mis-segregation and cytokinesis failure in trisomic human cells. eLife 4, e05068.
Niedernhofer, L.J., Robbins, P.D., 2018. Senotherapeutics for healthy ageing. Nat. Rev. Drug Discov. 17, 377.
Ogrodnik, M., Miwa, S., Tchkonia, T., Tiniakos, D., Wilson, C.L., Lahat, A., Day, C.P., Burt, A., Palmer, A., Anstee, Q.M., Grellscheid, S.N., Hoeijmakers, J.H.J., Barnhoorn, S., Mann, D.A., Bird, T.G., Vermeij, W.P., Kirkland, J.L., Passos, J.F., von Zglinicki, T., Jurk, D., 2017. Cellular senescence drives age-dependent hepatic steatosis. Nat. Commun. 8, 15691.
Oromendia, A.B., Dodgson, S.E., Amon, A., 2012. Aneuploidy causes proteotoxic stress in yeast. Genes Dev. 26, 2696–2708.
Oubaha, M., Miloudi, K., Dejda, A., Guber, V., Mawambo, G., Germain, M.A., Bourdel, G., Popovic, N., Rezende, F.A., Kaufman, R.J., Mallette, F.A., Sapieha, P., 2016. Senescence-associated secretory phenotype contributes to pathological angiogenesis in retinopathy. Sci. Transl. Med. 8, 362ra144.
Paludan, S.R., 2015. Activation and regulation of DNA-driven immune responses. Microbiol. Mol. Biol. Rev. 79, 225–241.
Pandey, S., Kawai, T., Akira, S., 2014. Microbial sensing by Toll-like receptors and intracellular nucleic acid sensors. Cold Spring Harb. Perspect. Biol. 7, a016246.
Passerini, V., Ozeri-Galai, E., de Pagter, M.S., Donnelly, N., Schmalbrock, S., Kloosterman, W.P., Kerem, B., Storchova, Z., 2016. The presence of extra chromosomes leads to genomic instability. Nat. Commun. 7, 10754.
Potter, H., 1991. Review and hypothesis: alzheimer disease and Down syndrome–chromosome 21 nondisjunction may underlie both disorders. Am. J. Hum. Genet. 48, 1192–1200.
Ramanjulu, J.M., Pesiridis, G.S., Yang, J., Concha, N., Singhaus, R., Zhang, S.Y., Tran, J.L., Moore, P., Lehmann, S., Eberl, H.C., Muelbaier, M., Schneck, J.L., Clemens, J., Adam, M., Mehlmann, J., Romano, J., Morales, A., Kang, J., Leister, L., Graybill, T.L., Charnley, A.K., Ye, G., Nevins, N., Behnia, K., Wolf, A.I., Kasparcova, V., Nurse, K., Wang, L., Li, Y., Klein, M., Hopson, C.B., Guss, J., Bantscheff, M., Bergamini, G., Reilly, M.A., Lian, Y., Duffy, K.J., Adams, J., Foley, K.P., Gough, P.J., Marquis, R.W., Smothers, J., Hoos, A., Bertin, J., 2018. Design of amidobenzimidazole STING receptor agonists with systemic activity. Nature 564, 439–443.
Rehen, S.K., Yung, Y.C., McCreight, M.P., Kaushal, D., Yang, A.H., Almeida, B.S., Kingsbury, M.A., Cabral, K.M., McConnell, M.J., Anliker, B., Fontanoz, M., Chun, J., 2005. Constitutional aneuploidy in the normal human brain. J. Neurosci. 25, 2176–2180.
Ressler, S., Bartkova, J., Niederegger, H., Bartek, J., Scharffetter-Kochanek, K., Jansen-Durr, P., Wlaschek, M., 2006. p16INK4A is a robust in vivo biomarker of cellular aging in human skin. Aging Cell 5, 379–389.
Rodier, F., Campisi, J., 2011. Four faces of cellular senescence. J. Cell Biol. 192, 547–556.
Roos, C.M., Zhang, B., Palmer, A.K., Ogrodnik, M.B., Pirtskhalava, T., Thalji, N.M., Hagler, M., Jurk, D., Smith, L.A., Casaclang-Verzosa, G., Zhu, Y., Schafer, M.J., Tchkonia, T., Kirkland, J.L., Miller, J.D., 2016. Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice. Aging Cell 15, 973–977.
Sali, T.M., Pryke, K.M., Abraham, J., Liu, A., Archer, I., Broeckel, R., Staverosky, J.A., Smith, J.L., Al-Shammari, A., Amsler, L., Sheridan, K., Nilsen, A., Streblow, D.N., DeFilippis, V.R., 2015. Characterization of a novel human-specific STING agonist that elicits antiviral activity against emerging alphaviruses. PLoS Pathog. 11, e1005324.
Santaguida, S., Amon, A., 2015. Short- and long-term effects of chromosome mis-segregation and aneuploidy. Nat. Rev. Mol. Cell Biol. 16, 473–485.
Santaguida, S., Vasile, E., White, E., Amon, A., 2015. Aneuploidy-induced cellular stresses limit autophagic degradation. Genes Dev. 29, 2010–2021.
Santaguida, S., Richardson, A., Iyer, D.R., M'Saad, O., Zasadil, L., Knouse, K.A., Wong, Y.L., Rhind, N., Desai, A., Amon, A., 2017. Chromosome mis-segregation generates cell-cycle-Arrested cells with complex karyotypes that are eliminated by the immune system. Dev. Cell 41 (638-651), e635.
Sapieha, P., Mallette, F.A., 2018. Cellular senescence in postmitotic cells: beyond growth arrest. Trends Cell Biol. 28, 595–607.
Senftleben, U., Cao, Y., Xiao, G., Greten, F.R., Krahn, G., Bonizzi, G., Chen, Y., Hu, Y., Fong, A., Sun, S.C., Karin, M., 2001. Activation by IKKalpha of a second, evolutionary conserved, NF-kappa B signaling pathway. Science 293, 1495–1499.
Serrano, M., Lin, A.W., McCurrach, M.E., Beach, D., Lowe, S.W., 1997. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. Cell 88, 593–602.
Shah, P.P., Donahue, G., Otte, G.L., Capell, B.C., Nelson, D.M., Cao, K., Aggarwala, V., Cruickshanks, H.A., Rai, T.S., McBryan, T., Gregory, B.D., Adams, P.D., Berger, S.L., 2013. Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and the chromatin landscape. Genes Dev. 27, 1787–1799.
Sharma, S., tenOever, B.R., Grandvaux, N., Zhou, G.P., Lin, R., Hiscott, J., 2003. Triggering the interferon antiviral response through an IKK-related pathway. Science 300, 1148–1151.
Shimi, T., Butin-Israeli, V., Adam, S.A., Hamanaka, R.B., Goldman, A.E., Lucas, C.A., Shumaker, D.K., Kosak, S.T., Chandel, N.S., Goldman, R.D., 2011. The role of nuclear lamin B1 in cell proliferation and senescence. Genes Dev. 25, 2579–2593.
Siegel, J.J., Amon, A., 2012. New insights into the troubles of aneuploidy. Annu. Rev. Cell Dev. Biol. 28, 189–214.
Simon, J.E., Bakker, B., Foijer, F., 2015. CINcere Modelling: What Have Mouse Models for Chromosome Instability Taught Us? Recent Results Cancer Res. 200, 39–60.
Sliter, D.A., Martinez, J., Hao, L., Chen, X., Sun, N., Fischer, T.D., Burman, J.L., Li, Y., Zhang, Z., Narendra, D.P., Cai, H., Borsche, M., Klein, C., Youle, R.J., 2018. Parkin and PINK1 mitigate STING-induced inflammation. Nature 561, 258–262.
Stephens, P.J., Greenman, C.D., Fu, B., Yang, F., Bignell, G.R., Mudie, L.J., Pleasance, E.D., Lau, K.W., Beare, D., Stebbings, L.A., McLaren, S., Lin, M.L., McBride, D.J., Varela, I., Nik-Zainal, S., Leroy, C., Jia, M., Menzies, A., Butler, A.P., Teague, J.W., Quail, M.A., Burton, J., Swerdlow, H., Carter, N.P., Morsberger, L.A., Iacobuzio-Donahue, C., Follows, G.A., Green, A.R., Flanagan, A.M., Stratton, M.R., Futreal, P.A., Campbell, P.J., 2011. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144, 27–40.
Stetson, D.B., Ko, J.S., Heidmann, T., Medzhitov, R., 2008. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell 134, 587–598.
Stingele, S., Stoehr, G., Peplowska, K., Cox, J., Mann, M., Storchova, Z., 2012. Global analysis of genome, transcriptome and proteome reveals the response to aneuploidy in human cells. Mol. Syst. Biol. 8, 608.
Stone, J.F., Sandberg, A.A., 1995. Sex chromosome aneuploidy and aging. Mutat. Res. 338, 107–113.
Storer, M., Mas, A., Robert-Moreno, A., Pecoraro, M., Ortells, M.C., Di Giacomo, V., Yosef, R., Pilpel, N., Krizhanovsky, V., Sharpe, J., Keyes, W.M., 2013. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell 155, 1119–1130.
Suijkerbuijk, S.J., van Osch, M.H., Bos, F.L., Hanks, S., Rahman, N., Kops, G.J., 2010. Molecular causes for BUBR1 dysfunction in the human cancer predisposition syndrome mosaic variegated aneuploidy. Cancer Res. 70, 4891–4900.
Sun, S.C., 2017. The non-canonical NF-kappaB pathway in immunity and inflammation. Nat. Rev. Immunol. 17, 545–558.
Sun, L., Wu, J., Du, F., Chen, X., Chen, Z.J., 2013. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science 339, 786–791.
Sun, Y., Coppe, J.P., Lam, E.W., 2018. Cellular Senescence: The Sought or the Unwanted? Trends Mol. Med. 24, 871–885.
Taddei, M.L., Cavallini, L., Comito, G., Giannoni, E., Folini, M., Marini, A., Gandellini, P., Morandi, A., Pintus, G., Raspollini, M.R., Zaffaroni, N., Chiarugi, P., 2014. Senescent stroma promotes prostate cancer progression: the role of miR-210. Mol. Oncol. 8, 1729–1746.
Takahashi, A., Loo, T.M., Okada, R., Kamachi, F., Watanabe, Y., Wakita, M., Watanabe, S., Kawamoto, S., Miyata, K., Barber, G.N., Ohtani, N., Hara, E., 2018. Downregulation of cytoplasmic DNases is implicated in cytoplasmic DNA accumulation and SASP in senescent cells. Nat. Commun. 9, 1249.
Tanaka, Y., Chen, Z.J., 2012. STING specifies IRF3 phosphorylation by TBK1 in the cytosolic DNA signaling pathway. Sci. Signal. 5 ra20.
Thomas, P., Harvey, S., Gruner, T., Fenech, M., 2008. The buccal cytome and micronucleus frequency is substantially altered in Down's syndrome and normal ageing compared to young healthy controls. Mutat. Res. 638, 37–47.
Thompson, S.L., Compton, D.A., 2008. Examining the link between chromosomal instability and aneuploidy in human cells. J. Cell Biol. 180, 665–672.
Thompson, S.L., Bakhoum, S.F., Compton, D.A., 2010. Mechanisms of chromosomal instability. Curr. Biol. 20, R285–295.
Torres, E.M., Sokolsky, T., Tucker, C.M., Chan, L.Y., Boselli, M., Dunham, M.J., Amon, A., 2007. Effects of aneuploidy on cellular physiology and cell division in haploid yeast. Science 317, 916–924.
Tse, C., Shoemaker, A.R., Adickes, J., Anderson, M.G., Chen, J., Jin, S., Johnson, E.F., Marsh, K.C., Mitten, M.J., Nimmer, P., Roberts, L., Tahir, S.K., Xiao, Y., Yang, X., Zhang, H., Fesik, S., Rosenberg, S.H., Elmore, S.W., 2008. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. Cancer Res. 68, 3421–3428.
van Deursen, J.M., 2014. The role of senescent cells in ageing. Nature 509, 439–446.
Vincent, J., Adura, C., Gao, P., Luz, A., Lama, L., Asano, Y., Okamoto, R., Imaeda, T., Aida, J., Rothamel, K., Gogakos, T., Steinberg, J., Reasoner, S., Aso, K., Tuschl, T., Patel, D.J., Glickman, J.F., Ascano, M., 2017. Small molecule inhibition of cGAS reduces interferon expression in primary macrophages from autoimmune mice. Nat. Commun. 8, 750.
Wang, C., Jurk, D., Maddick, M., Nelson, G., Martin-Ruiz, C., von Zglinicki, T., 2009. DNA damage response and cellular senescence in tissues of aging mice. Aging Cell 8, 311–323.
Wang, H., Hu, S., Chen, X., Shi, H., Chen, C., Sun, L., Chen, Z.J., 2017. cGAS is essential for the antitumor effect of immune checkpoint blockade. Proc. Natl. Acad. Sci. 114, 1637–1642.
Weaver, B.A., Cleveland, D.W., 2006. Does aneuploidy cause cancer? Curr. Opin. Cell Biol. 18, 658–667.
Williams, G.C., 1957. Pleiotropy, Natural Selection, and the Evolution of Senescence. Evolution 11, 398–411.
Williams, B.R., Prabhu, V.R., Hunter, K.E., Glazier, C.M., Whittaker, C.A., Housman, D.E., Amon, A., 2008. Aneuploidy affects proliferation and spontaneous immortalization in mammalian cells. Science 322, 703–709.
Woo, S.R., Fuertes, M.B., Corrales, L., Spranger, S., Furdyna, M.J., Leung, M.Y., Duggan, R., Wang, Y., Barber, G.N., Fitzgerald, K.A., Alegre, M.L., Gajewski, T.F., 2014. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. Immunity 41, 830–842.
Wu, J., Sun, L., Chen, X., Du, F., Shi, H., Chen, C., Chen, Z.J., 2013. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science 339, 826–830.
Xiao, T.S., Fitzgerald, K.A., 2013. The cGAS-STING pathway for DNA sensing. Mol. Cell

51, 135–139.
Xiao, G., Harhaj, E.W., Sun, S.C., 2001. NF-kappaB-inducing kinase regulates the processing of NF-kappaB2 p100. Mol. Cell 7, 401–409.
Xie, J., Li, Y., Shen, X., Goh, G., Zhu, Y., Cui, J., Wang, L.F., Shi, Z.L., Zhou, P., 2018. Dampened STING-Dependent interferon activation in bats. Cell Host Microbe 23 (297-301), e294.
Xue, W., Zender, L., Miething, C., Dickins, R.A., Hernando, E., Krizhanovsky, V., Cordon-Cardo, C., Lowe, S.W., 2007. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature 445, 656–660.
Yang, H., Wang, H., Ren, J., Chen, Q., Chen, Z.J., 2017. cGAS is essential for cellular senescence. Proc. Natl. Acad. Sci. 114, E4612–E4620.
Yosef, R., Pilpel, N., Tokarsky-Amiel, R., Biran, A., Ovadya, Y., Cohen, S., Vadai, E., Dassa, L., Shahar, E., Condiotti, R., Ben-Porath, I., Krizhanovsky, V., 2016. Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. Nat. Commun. 7, 11190.
Yoshimoto, S., Loo, T.M., Atarashi, K., Kanda, H., Sato, S., Oyadomari, S., Iwakura, Y., Oshima, K., Morita, H., Hattori, M., Honda, K., Ishikawa, Y., Hara, E., Ohtani, N., 2013. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 499, 97–101.
Youm, Y.H., Grant, R.W., McCabe, L.R., Albarado, D.C., Nguyen, K.Y., Ravussin, A., Pistell, P., Newman, S., Carter, R., Laque, A., Munzberg, H., Rosen, C.J., Ingram, D.K., Salbaum, J.M., Dixit, V.D., 2013. Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. Cell Metab. 18, 519–532.
Yurov, Y.B., Vorsanova, S.G., Liehr, T., Kolotii, A.D., Iourov, I.Y., 2014. X chromosome aneuploidy in the Alzheimer's disease brain. Mol. Cytogenet. 7, 20.
Zhang, C.Z., Spektor, A., Cornils, H., Francis, J.M., Jackson, E.K., Liu, S., Meyerson, M., Pellman, D., 2015. Chromothripsis from DNA damage in micronuclei. Nature 522, 179–184.
Zhu, J., Tsai, H.J., Gordon, M.R., Li, R., 2018. Cellular stress associated with aneuploidy. Dev. Cell 44, 420–431.