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Review

Evidence of sex differences in cellular senescence

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ABSTRACT

Biological sex is a factor in many conditions, including aging, neurodegenerative disease, cancer, and more. For each of these, men and women display distinct differences in disease development and progression. To date, studies on the molecular basis of such differences have largely focused on sex hormones, typically highlighting their neuroprotective benefits. However, new research suggests that cellular senescence may underlie sex differences in both neurological and non-neurological pathologies. Cellular senescence—stable proliferative arrest with a unique pro-inflammatory phenotype—occurs in response to persistent DNA damage signaling, safeguarding against tissue-level consequences of DNA damage (e.g., tumorigenesis). Though critical for maintaining tissue health, senescence has also been implicated in disease. Indeed, senescent cell accumulation occurs in multiple disease contexts, and the elimination of such cells (via senolytic therapies) alleviates associated disease hallmarks. If cell senescence is a driver of pathophysiology, sex differences in cellular senescence may underlie sex-specific disease outcomes. This review summarizes evidence of sex differences in cellular senescence—highlighting findings from both human and animal studies—and briefly discusses the potential relevance of sex chromosome epigenetics and mosaicism. Current studies show that female sex is associated with greater susceptibility to DNA damage and greater likelihood of senescence onset, despite additional evidence that estrogen protects against genotoxic insult and inhibits senescence regulatory proteins. Further studies on sex differences in cellular senescence are needed, both to verify whether findings from animal studies hold true in human contexts and to validate whether senescence manifests differently between men and women following comparable senescence-inducing stimuli.

1. Introduction

For many diseases, men and women display significant differences in incidence, symptomatology and prognosis. This is true for ageing and age-related frailty (Colafella and Denton, 2018; Fischer and Riddle, 2018; Hägg and Jylhävä, 2021), neurodegenerative conditions like Alzheimer's Disease (AD) (Ardekani et al., 2016; Barnes et al., 2005; Takizawa et al., 2015) and Parkinson's Disease (PD) (McLean et al., 2011; Miller and Cronin-Golomb, 2010; Wooten et al., 2004), anxiety and mood disorders (Albert, 2015; Bekker and van Mens-Verhulst, 2007; Dahodwala et al., 2016; McHenry et al., 2014; Seedat et al., 2009), cancer (Rubin et al., 2020; Sun et al., 2014), mild traumatic brain injury (mTBI) (Bazarian et al., 2010; Gupte et al., 2019; Haynes and Goodwin, 2021; Merritt et al., 2019; Mikolić et al., 2021), and various age-related organ system dysfunctions, including osteoarthritis (Pereira et al., 2011; Yang et al., 2020), hepatic steatosis (Clark et al., 2002; Lonardo et al., 2019), liver fibrosis (Lonardo et al., 2019) and atherosclerosis (Man et al., 2020). While women—on average—have a higher life expectancy (Colafella and Denton, 2018; Fischer and Riddle, 2018; Tower, 2006), lower risk of cancer incidence (Rubin et al., 2020; Sun et al., 2014) and lower risk of PD than men (Dahodwala et al., 2016; Miller and Cronin-Golomb, 2010; Wooten et al., 2004), they also have a higher risk of AD (Ardekani et al., 2016; Barnes et al., 2005; Subramaniapillai et al., 2021; Takizawa et al., 2015), greater likelihood of being diagnosed with depression (Albert, 2015) and greater likelihood of experiencing worse post-mTBI symptoms (Bazarian et al., 2010; Merritt et al., 2019; Mikolić et al., 2021).

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Presently, research on the molecular basis of such sex differences is lacking (Kim and Kim, 2020; Rubin et al., 2020), and where research has been done (i.e., largely in the context of neurological disease), most studies have focused on the neuroprotective benefits of sex hormones (e.g., their ability to combat excitotoxic events, decrease neurodegeneration-promoting oxidative stress, promote neuron viability, protect against microvascular and mitochondrial dysfunction, etc.) (Engler-Chiurazzi et al., 2017; Gurvich et al., 2020; Haynes and Goodwin, 2021; McHenry et al., 2014; Pike, 2017; Pike et al., 2009; Sumien et al., 2021). New research, however, suggests that one particular biological phenomenon may underlie sex differences in both neurological and non-neurological pathologies: cellular senescence.

Cellular senescence is a state of stable cell cycle arrest that features a pro-inflammatory senescence-associated secretory phenotype (SASP) (Di Micco et al., 2021; Hägg and Jylhävä, 2021; Kuilman et al., 2010; Kumari and Jat, 2021). Cells undergo senescence in response to the onset and persistence of DNA damage that gives rise to deleterious or cancer-causing mutations (Vijg, 2021). By halting proliferation, cell senescence prevents such mutations from being propagated (Campisi, 2005; Rubin et al., 2020). Further, by secreting pro-inflammatory factors, senescent cells recruit the immune system to facilitate their own elimination and subsequent replacement with progenitor cells (Colafella and Denton, 2018; Guerrero et al., 2021; Xue et al., 2007), thereby safeguarding against tumorigenesis. Beyond cancer prevention, cell senescence also plays a role in embryogenesis and tissue repair (Di Micco et al., 2021). However, although cell senescence is an important mechanism for maintaining tissue health, there is evidence that the chronic presence of senescent cells contributes to disease in later stages of life or following injury (Baker et al., 2011; Guerrero et al., 2021; Salminen et al., 2011; Schwab et al., 2021).

Evidence of senescent cell accumulation has been found for multiple diseases, including aging and progeria (Baker et al., 2016, 2011, 2008; Salminen et al., 2011; Wang et al., 2021), neurodegenerative disease (Bussian et al., 2018; Chinta et al., 2018; Guerrero et al., 2021; Hou et al., 2019; Musi et al., 2018), anxiety and mood disorders (Diniz, 2018; Ferrucci and Fabbri, 2018; Ogrodnik et al., 2019), cancer (Kuilman et al., 2010), and age-related organ system dysfunction (Childs et al., 2016; Di Micco et al., 2021; Jeyapalan and Sedivy, 2008; Liu and Liu, 2020; Ogrodnik et al., 2017; Papatheodoridi et al., 2020; Roos et al., 2016; Wang et al., 2019). Indeed, both in aged wild-type mice and young progeroid mice, expression of cell senescence biomarkers is much higher than in young wild-type mice (Baker et al., 2016, 2011, 2008; Salminen et al., 2011). Likewise, senescence markers are present at higher concentrations in post-mortem tissue from AD and PD humans and mice (i.e., mouse models of AD and PD) than in tissue from healthy individuals (Bhat et al., 2012; Chinta et al., 2018; He et al., 2013; Tan et al., 2014). In addition to age-related disease, there is evidence of senescent cell accumulation following certain types of physical trauma. In the brains of male athletes with histories of repetitive mTBI (Schwab et al., 2019), as well as in mice models of mTBI (Tominaga et al., 2019), senescence markers are significantly increased compared to non-injured controls. Thus, there is a clear association between cellular senescence and various diseases.

Cellular senescence is not believed to simply coincide with disease, however. Senescent cell accumulation is believed to be a disease-causing factor because the elimination of senescent cells by senolytic therapies (Kirkland and Tchkonia, 2020) has been shown to reduce the severity of disease hallmarks and improve health outcomes. In ageing and progeroid mice, elimination of senescent cells increases lifespan (Baker et al., 2016), reduces age-related tissue deterioration (Baker et al., 2016), and delays the onset of progeria-specific pathological phenotypes (Baker et al., 2011, 2008). In mouse models of AD, the clearance of senescent cells reduces density of neurofibrillary tangles, total ventricular enlargement (Musi et al., 2018), and cognitive decline (Bussian et al., 2018). In mice where characteristic features of PD are induced by the herbicide paraquat, treatment with the senolytic pro-drug ganciclovir prevents a decline in dopaminergic neurons, prevents a decline in neurogenesis, and maintains motor neuron function (Chinta et al., 2018). Clearance of senescent cells has also been shown to alleviate the severity of senescence-associated diseases like osteoarthritis, hepatic steatosis, and atherosclerosis (Ogrodnik et al., 2019, 2017). Because there is evidence that senescent cells accumulate during disease, and because the selective clearance of senescent cells in diseased organisms reduces the severity of disease hallmarks, there are grounds to suspect that the accumulation of senescent cells is directly responsible for the development of these diseases, including those with known sex differences.

Presently, although cellular senescence has been implicated in diseases with known sex differences, little is known about whether biological sex is a factor in senescence. If cellular senescence is suspected to be the mechanism that drives pathophysiological changes in various body tissues, it is necessary to question whether sex differences in cellular senescence underlie sex differences in clinical phenotypes. Therefore, the present paper will summarize all evidence of sex differences in cellular senescence, highlighting differences in DNA damage tolerance, the DNA damage response (DDR), regulation of senescence growth arrest, and the influence of sex steroid hormones on DNA damage, cell senescence onset, and the SASP.

2. Molecular basis of cellular senescence

Cellular senescence can occur in response to many different inducers, including telomere erosion (Carroll and Korolchuk, 2018; Kuilman et al., 2010; Mikuła-Pietrasik et al., 2020), oncogene activation (Bartek et al., 2007; Carroll and Korolchuk, 2018; Di Micco et al., 2021; Kuilman et al., 2010; Serrano et al., 1997), and genotoxic stressors like oxidative stress, ionizing radiation, ultraviolet radiation, and exogenous chemical agents (Chatterjee and Walker, 2017; Mikuła-Pietrasik et al., 2020; Saleh et al., 2020; Zdanov et al., 2006; Zhao et al., 2004). Since each inducer is regarded as a cause of a distinct type of senescence (e.g., Replicative Senescence, Oncogene-Induced Senescence, Stress-Induced Premature Senescence), they are often discussed separately. However, all of these inducers ultimately cause senescence by generating DNA damage and/or inducing DDR signaling. Indeed, telomere uncapping initiates DDR signaling directly (Chatterjee and Walker, 2017), oncogene activation leads to DNA hyper-replication and subsequent replication stress (Di Micco et al., 2021, 2006), and oxidative stress produces replication stress as well as single-strand breaks (SSBs) (Venkatachalam et al., 2017). Further, chemotherapeutic drugs (e.g., etoposide, cisplatin) and radiation can induce the formation of both single and double-strand breaks (DSBs) (Chatterjee and Walker, 2017; Song et al., 2021) (Fig. 1). Cellular senescence is therefore tied to the intrinsic cellular DDR.

During the cellular DDR, DNA damage is sensed by specialized protein complexes (Ciccia and Elledge, 2010; Moreno-Herrero et al., 2005; Stracker et al., 2004; Weiss et al., 2002; Zou and Elledge, 2003) that recruit kinases ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) to sites of DNA damage. ATM and ATR phosphorylate a diverse set of proteins that cooperate to improve chromatin stability and support the recruitment of other DDR factors (Ciccia and Elledge, 2010;

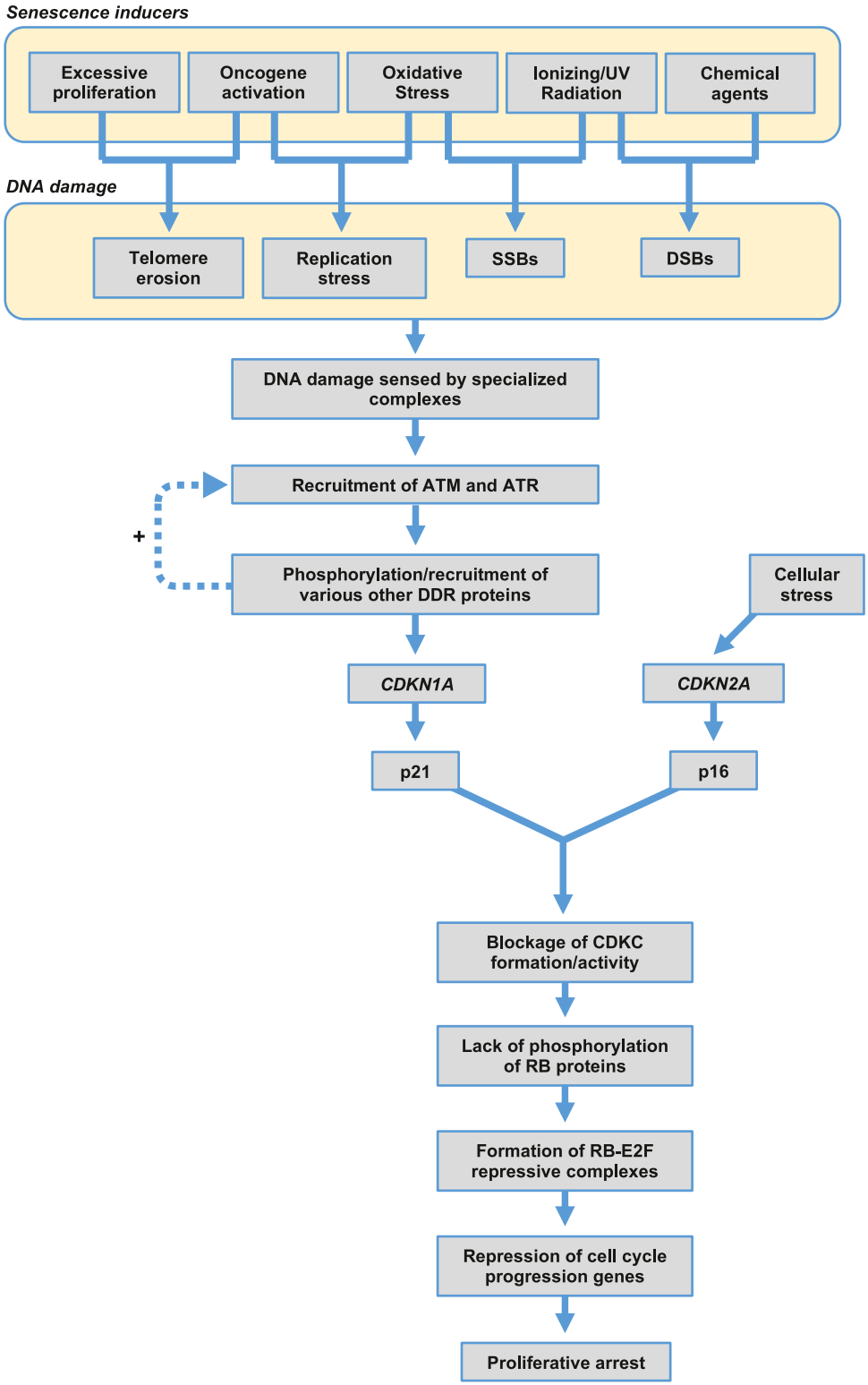

Fig. 1. Summary of senescence growth arrest establishment. Senescence-inducing stimuli contribute to the generation of various types of DNA damage. Damage is detected by sensor complexes that recruit ATM and ATR kinases. These kinases activate DDR proteins (e.g., H2AX, 53BP1, MDC1, Chk1, and Chk2, p53, etc.) which cooperate to enforce a positive feedback loop necessary for proper initiation of proliferative arrest. The p53-p21 and p16-pRB arms of the senescence response are coordinately induced and together maintain long-term cell cycle arrest.

d'Adda di Fagagna, 2008). To name a few, this includes histone variant H2AX, which, when phosphorylated into γH2AX—a common marker of DSB formation and DDR activation (Bielak-Zmijewska et al., 2018; Ksiazek et al., 2009; Pazolli et al., 2012; Venkatachalam et al., 2017)—recruits additional ATM complexes (Kumari and Jat, 2021; Mah et al., 2010); 53BP1, which facilitates further recruitment of ATM to γH2AX and also binds/stabilizes transcription factor p53 (Cuella-Martin et al., 2016; d'Adda di Fagagna, 2008; Pedram et al., 2009); mediator of DNA damage checkpoint protein 1 (MDC1), a mediator protein which interacts with γH2AX to recruit ATM and other DDR protein complexes (d'Adda di Fagagna, 2008; Zou et al., 2015); and kinases Chk1 and Chk2, which promote cell cycle arrest by mediating chromatin modifications that prevent transcription of cell cycle progression genes (Ciccia and Elledge, 2010; Mikuła-Pietrasik et al., 2020; Pedram et al., 2009). Among the proteins that are directly phosphorylated by ATM (Kumari and Jat, 2021) and ATR (Pedram et al., 2009) is p53. When stabilized, p53 activates the p53 cell cycle checkpoint by upregulating transcription of *CDKN1A*, the gene which encodes p21 (Engeland, 2018; Kumari and Jat, 2021). p21 is a cyclin-dependent kinase inhibitor (CDKI) responsible for prompting cell cycle exit (the means by which p21 accomplishes this will be described in greater detail below) (Kumari and Jat, 2021). This arrangement forms the p53-p21 pathway, which is one of 2 primary pathways responsible for facilitating senescence-associated cell cycle arrest. p21 upregulation, which gradually declines after a dramatic initial increase, is complemented by a gradual rise in the expression of p16, another CDKI (Alcorta et al., 1996). The upregulation of p16 occurs parallel to (but independently of) p53-p21 pathway activation, in response to cellular stress and by unknown means (Liu et al., 2019; McConnell et al., 1998; Palmero et al., 1997; Serrano et al., 1996). The upregulation of p16 represents the start of the p16-pRB pathway, which is the second pathway that governs senescence growth arrest. The p53-p21 and p16-pRB pathways converge at the inhibition of CDKs, through the actions of p21 and p16 (Fig. 1): collectively, p21 and p16 bind/inhibit all CDKs, preventing the phosphorylation of various CDK target substrates, including retinoblastoma (RB) family suppressor proteins (Kumari and Jat, 2021; Wang et al., 2019). Without phosphorylation, RB proteins remain active and bind/sequester E2F family transcription factors, forming repressive complexes (e.g., DREAM). These repressive complexes recruit histone deacetylases and bind cell cycle progression genes, preventing their transcription (Kumari and Jat, 2021; Wang et al., 2019). While the similarity between the p53-p21 and p16-pRB pathways (i.e., with respect to their functional outcomes) may initially appear redundant, their functional relatedness is ultimately complementary because of how they are temporally offset. Where p53-p21 is activated quickly and initiates proliferative arrest as part of the rapidly acting DDR, p16-pRB is slower to become active, functioning to prolong and maintain this state of arrest (Alcorta et al., 1996; Ben-Porath and Weinberg, 2005; Kumari and Jat, 2021) while also serving as a second barrier to cell cycle re-entry should p53-p21 fail (Beauséjour et al., 2003; Mikuła-Pietrasik et al., 2020). This is how the p53-p21 and p16-pRB pathways cooperate to achieve stable cell cycle arrest during cellular senescence.

Although proliferative arrest is not unusual for cells experiencing DNA damage, senescence growth arrest is typically permanent, unlike other types of cell cycle arrest. Cells will often enter a state of temporary arrest—cell quiescence—in response to transient stress, later re-entering the cell cycle once all damaged DNA has been repaired (Pack et al., 2019). Like in senescence, this arrest is facilitated by p53. However, cell senescence only occurs in response to stress that is extensive or persistent, and it also requires activation of the mammalian target of rapamycin (mTOR) pathway (a pathway that regulates cell growth and metabolism) (Kumari and Jat, 2021; Papadopoli et al., 2019; Parrinello et al., 2003; Rodier et al., 2009). Though p53 typically inhibits the mTOR pathway (such as in cell quiescence), during cell senescence, the mTOR pathway is active regardless of p53 activity (Hasty et al., 2013; Korotchkina et al., 2010) (the means by which p53 is prevented from suppressing mTOR in senescence contexts is unknown). Thus, even though senescence growth arrest is mediated by canonical DDR pathways, it represents a distinct cellular response to persistent DNA damage.

Cellular senescence is further distinguished from other responses to persistent DNA damage (e.g., cell quiescence, apoptosis, malignant transformation) by the SASP, which consists of various pro-inflammatory and microenvironment-modifying factors. Although it is usually induced alongside senescence-associated proliferative arrest and—like proliferative arrest—occurs in response to DNA-damaging senescence inducers (Acosta et al., 2013; Chen et al., 2015; Freund et al., 2011; Herranz et al., 2015; Xu et al., 2015; Zhang et al., 2018), the SASP is primarily governed by pathways that are distinct from those which facilitate cell cycle arrest. These pathways include (but are not limited to): p38MAPK (Freund et al., 2011), JAK2/STAT3 (Xu et al., 2015), inflammasome (Acosta et al., 2013), mTOR (Herranz et al., 2015; Laberge et al., 2015), macroH2A1 and ATM (Chen et al., 2015), and PI3K (Zhang et al., 2018), which have all been separately implicated in SASP regulation. When activated, these pathways produce the SASP by mediating upregulation of genes that encode SASP factors (e.g., via activity of transcription factor NF-κB, which is promoted by the mTOR pathway) (Herranz et al., 2015) and by facilitating post-translational modification of SASP factor precursors (e.g., via activity of inflammasome protein complexes) (Acosta et al., 2013) (Fig. 2).

The various factors that are generated by SASP pathways are secreted, either directly or by ectodomain shedding (i.e., as transmembrane proteins) (Kumari and Jat, 2021), for 2 purposes: firstly, to trigger senescence in adjacent cells through paracrine signaling, thereby protecting against tumor formation (Rubin et al., 2020), and secondly, to promote inflammation and recruitment of various immune cells, resulting in the clearance of senescent cells and replacement with progenitor cells (Colafella and Denton, 2018; Guerrero et al., 2021; Xue et al., 2007). The core SASP program consists of pro-inflammatory chemokines IL-6, IL-8, and MCP-1 (Di Micco et al., 2021), which induce paracrine senescence. Inflammation and tissue repair are mediated by dozens of other SASP factors, including growth factors, mitogens, and various molecules that stimulate extracellular matrix remodeling (e.g., matrix metalloproteinases [MMPs], serine protease inhibitors, tissue inhibitors of metalloproteinases) (Di Micco et al., 2021; Pazolli et al., 2012). The SASP therefore complements senescence growth arrest, enhancing its protective effects by inducing senescence in adjacent cells and contributing to the overall maintenance of tissue health by stimulating repair.

Unfortunately, the same features of cellular senescence that confer protective benefits become deleterious when left unresolved. As people age, the capacity of their immune system for immunosurveillance gradually declines (this is known as immunosenescence), allowing for the accumulation of senescent, SASP-exhibiting cells (Guerrero et al., 2021). When metabolically active senescent cells are chronically present, SASP factors are continually secreted, generating a chronic inflammatory state associated with both inflammageing (Sharma, 2021) and pro-oncogenic effects (Di Micco et al., 2021; Kuilman et al., 2010). However, immunosenescence does not necessarily result from ageing alone. SASP factors themselves may even contribute to the onset of immunosenescence as part of a positive feedback loop. In one

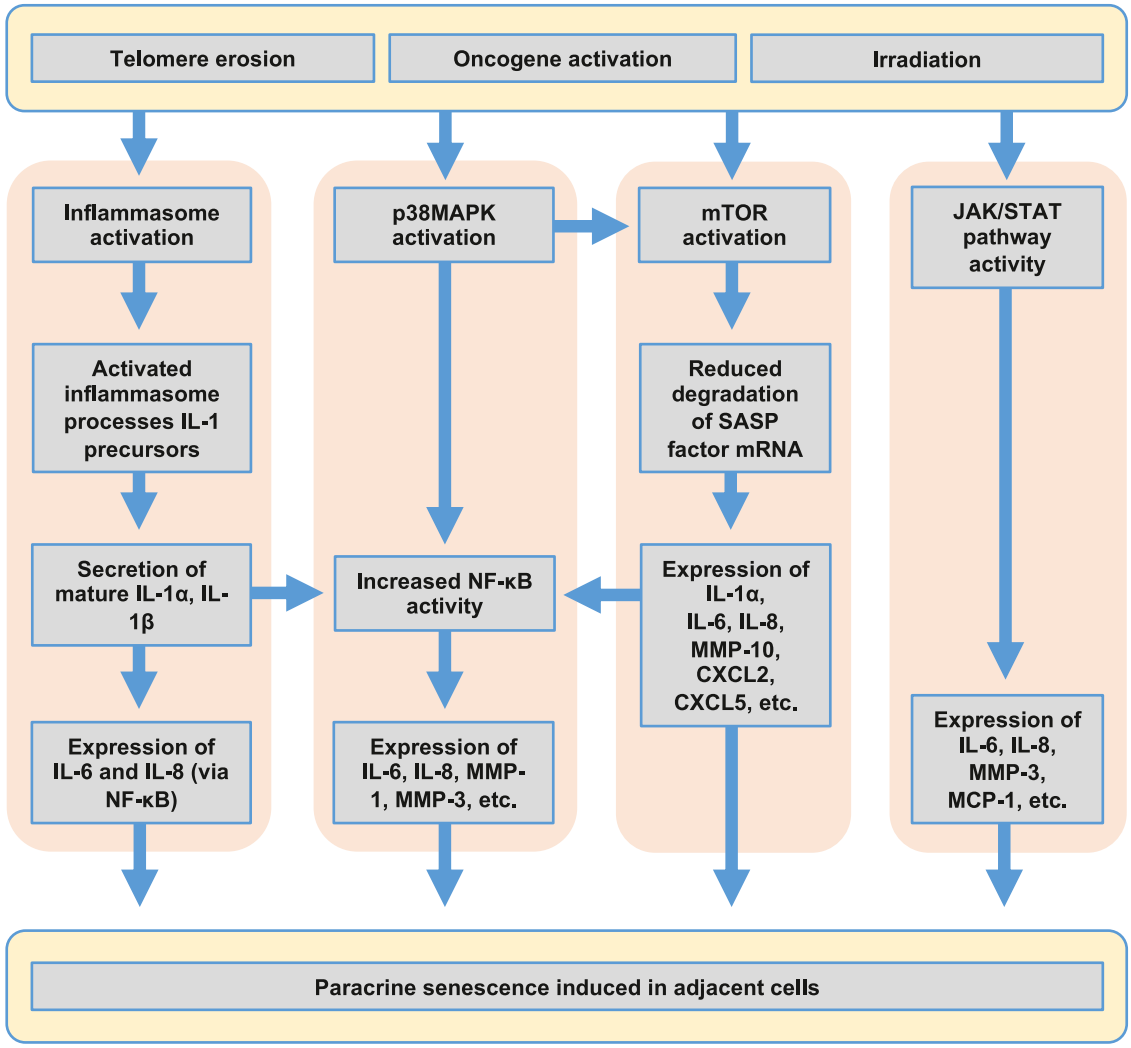

Fig. 2. Summary of a few molecular pathways implicated in the SASP. Each of these pathways has been studied independently, with their relevance to the SASP having been investigated by separate authors. Inhibition of a single pathway is sufficient to suppress the overall SASP, despite interconnectivity between these pathways at multiple junctions.

study by Ogata et al. (2021), the extended secretion of SASP factors by senescent fibroblasts was shown to impair the apoptosis-mediating and phagocytic activities of macrophages, preventing senescent cell elimination. Senescent cells may also upregulate surface proteins that inhibit various immune cells (e.g., natural killer cells, CD8+ T cells) (Sharma, 2021). As such, some authors suggest that cellular senescence is ultimately antagonistically pleiotropic (Campisi, 2005; Chinta et al., 2018), offering protective benefits in earlier stages of life but generating problems later on as senescent cells accumulate and give rise to a chronic, SASP-driven inflammatory state that drives various forms of cellular dysfunction. Indeed, senescent microglia—which themselves display impaired autophagy, leading to the accumulation of amyloid-β plaques (Guerrero et al., 2021)—induce paracrine senescence in astrocytes, whose SASP then mediates neurotoxic effects on surrounding cells through pro-inflammatory factors (Guerrero et al., 2021; Limbad et al., 2020; Turnquist et al., 2016). In further consideration of how cellular senescence might contribute to chronic health problems with sex-specific clinical phenotypes, the upcoming section will evaluate existing evidence that cellular senescence is influenced by biological sex.

3. Sex differences in cellular senescence

Since many inducers of cellular senescence are known to generate DNA damage and initiate DDR signaling, this summary of evidence of sex differences in cellular senescence will begin by highlighting evidence of sex differences in the molecular mechanisms that respond to genotoxic insult. A summary of all evidence of sex differences in cellular senescence included in the present paper is given by Tables 1–3 and Fig. 3.

3.1. DNA damage response

To date, the studies that have reported sex differences in DDR have shown evidence of a lower capacity for DNA repair in women, despite similar DNA damage burden between sexes across the lifespan. In a study on DSB repair (DSBR) by non-homologous end joining (NHEJ) in peripheral blood lymphocytes, Rall-Scharpf et al. (2021) found that DSBR activity declines in women—but not in men—with age, as indicated by changes in mRNA/protein levels of NHEJ pathway activity markers (i.e., ATM, Bloom syndrome protein [BLM], NHEJ protein Ku70). Separately, a study on SSB repair (SSBR) in peripheral blood mononuclear cells

Table 1
Evidence of sex differences in cellular senescence, in terms of the DNA damage response and the functional role of p53.

Section/Topic	Finding(s)	Experimental model	Reference(s)
3.1/DNA damage repair	DSBR via NHEJ declines with age in women, but not in men	Human, peripheral blood lymphocytes	Rall-Scharpf et al. (2021)
	Following gamma-irradiation, SSBR activity is lower in women than men	Human, peripheral blood mononuclear cells	Trzeciak et al. (2008)
3.1/Senescence onset	Following UV-irradiation, female cells undergo senescence while male cells undergo apoptosis	Rat, vascular smooth muscle cells	Malorni et al. (2008)
	During p53 inactivation, there is greater phosphorylation/inactivation of RB proteins in male cells than female cells	Mouse (Mes-GBM), astrocytes	Sun et al. (2014)
	Following etoposide exposure, female cells undergo senescence while male cells undergo malignant transformation	Mouse (Mes-GBM), astrocytes	Kfoury et al. (2018)
	Greater accumulation of senescence markers in male cells than female cells (shown by elevated mRNA levels of p21, p16)	Mouse, peripheral lymphocytes	Yousefzadeh et al. (2020)
3.2/Activity of regulatory proteins	p53 overexpression increases lifespan of males, but shortens lifespan of females	Drosophila, organism	Waskar et al. (2009)
	A reduced-activity allele of p53 is associated with increased lifespan in females but not males	Human, organism	Groß et al. (2014)
	p53 regulates lncRNA Xist (implicated in X-chromosome inactivation)	-	Rubin et al. (2020)

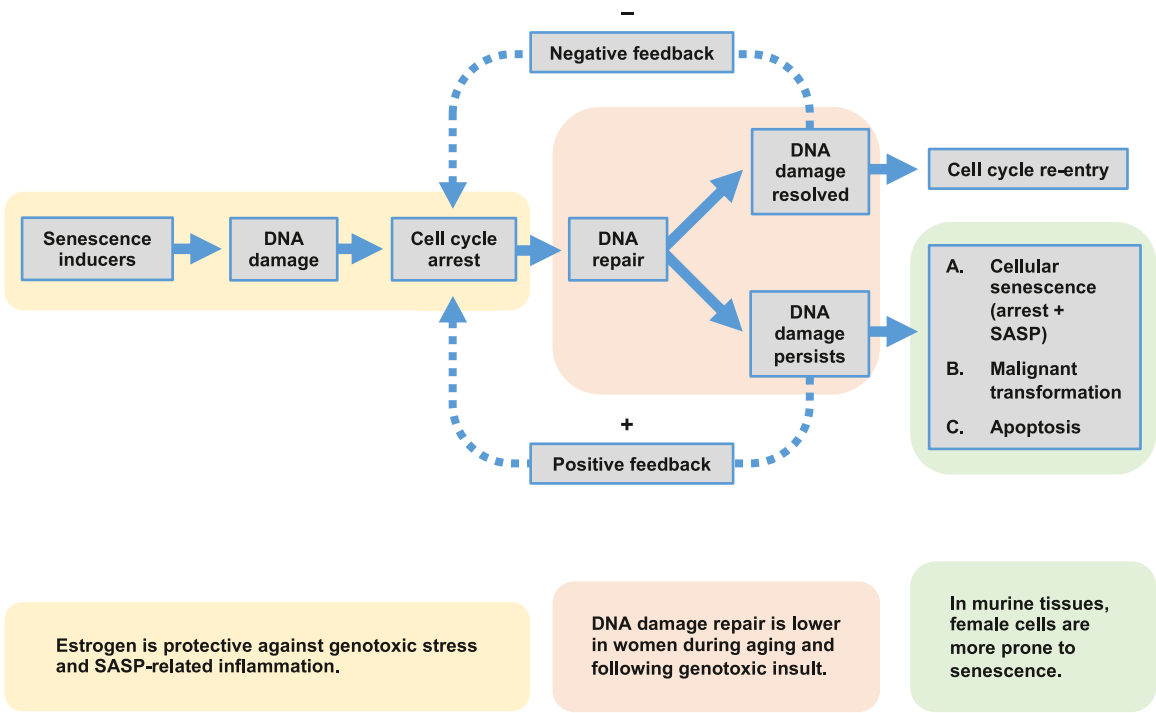

Fig. 3. Existing evidence of sex differences in cellular senescence can be grouped into 3 categories. These categories include: (A) sex differences in DNA repair, (B) sex differences in tendency to undergo senescence following genotoxic stress, and (C) the effect of sex steroid hormones on the molecular basis of cellular senescence.

(PBMCs) by Trzeciak et al. (2008) found that, following gamma-irradiation-induced DNA damage, PBMCs from white women display lower SSBR activity than PBMCs from white men, as measured by a SSBR-specific comet assay. Given that SSBR and DSBR activity appear lower in cells of female origin, it would seem natural to expect that women are more susceptible to DNA damage accumulation. However, studies on the formation of γH2AX in human PBMCs and human lymphocytes report that while age and race are factors in γH2AX formation, biological sex is not (Garm et al., 2013; Sharma et al., 2015). Based on these findings alone, there is no immediately obvious relationship between biological sex and DNA damage burden.

Although a lower capacity for SSBR and DSBR in female cells has not been shown to correlate with increased DNA damage burden, there is evidence that female cells have a greater tendency to undergo cellular senescence than male cells, which instead tend to undergo apoptosis or malignant transformation. It remains unclear why some cells undergo apoptosis or malignant transformation while others become senescent, but the fact that these responses are so distinct—with senescent cells actively resisting both apoptosis (e.g., by downregulating pro-apoptotic caspase-3) (Marcotte et al., 2004) and excessive cell proliferation—suggests that intrinsic cellular characteristics (e.g., biological sex) influence cell fate. In response to UV-irradiation, female rat vascular smooth

Table 2
Evidence of sex differences in cellular senescence, in terms of the functional role of estrogen.

Section/Topic	Finding(s)	Experimental model	Reference(s)
3.3.1/Estrogen (DNA damage)	Estrogen reduces oxidative stress by suppressing ROS release (direct interaction with mitochondria)	Mouse, skeletal muscle cells	Torres et al. (2018)
	Estrogen reduces oxidative stress by suppressing ROS release (via mitochondrial estrogen receptors)	Rat, primary neurons/hippocampal cells; human, cerebral endothelial cells	Lejri et al. (2018); Razmara et al. (2008)
	Estrogen prevents DNA fragmentation induced by H_2O_2 or etoposide	Mouse, skeletal muscle cells	Vasconsuelo et al. (2008)
	Estrogen promotes expression and activity of telomerase	Human, leukocytes/vascular smooth muscle cells/endothelial progenitor cells; human (post-menopausal), arterial tissue	Emmerson and Hardman (2012); Walker et al. (2016)
3.3.1/Estrogen (molecular basis of senescence)	Estrogen inhibits Chk1, γH2AX, ATR (thereby suppressing p21 expression)	Human, ER-positive breast cancer cells	Pedram et al. (2009)
	Inhibition of ER-α leads to increased levels of SA-β-gal and unphosphorylated RB family proteins	Human, mammary epithelial cells/breast cancer cells	Liu et al. (2016)
	Estrogen typically increases expression of WRN (which normally prevents senescence)	Human, breast cancer cells	Lee et al. (2010)
3.3.1/Estrogen (absence)	Post-menopausal individuals display increased telomere shortening	Human (post-menopausal), arterial tissue	Walker et al. (2016)
	Post-menopausal individuals display reduced markers of anti-inflammatory macrophage activity	Human (post-menopausal), blood-derived macrophages	Toniolo et al. (2015)
	Cells from OVX individuals feature upregulation of p53, p21, and SASP factors, as well as induction of the JAK/STAT pathway	Mouse (OVX), bone marrow mesenchymal stem cells	Wu et al. (2020)
3.3.1/Estrogen (administration)	Estrogen prevents the production of TNF and IL-10 by activated M1 macrophages	Human, blood-derived macrophages	Toniolo et al. (2015)
	Estrogen reverses OVX-driven induction of p53, p21, and SASP factors, as well as OVX-driven induction of the JAK/STAT pathway	Mouse (OVX), bone marrow mesenchymal stem cells	Wu et al. (2020)
	MHT reduces the expression of SASP factors (GDF-15, TNFR1, Fas)	Human (post-menopausal), organism	Faubion et al. (2020)
	MHT reduces the expression of SASP factors (IFN-γ, MCP-1, MMP-2, MMP-9, TNF)	Human (post-menopausal), platelet cells	Miller et al. (2016)
	Estrogen prevents angiotensin-induced senescence	Human, endothelial progenitor cells	Imanishi et al. (2005)
	Following UV-irradiation, estrogen reduces p53 expression and promotes cell survival/proliferation	Mouse, subventricular zone neural stem cells	Kim and Casaccia-Bonnefil (2009)
	Estrogen can activate signaling pathways that inhibit FOXO proteins (which normally promote expression of antioxidant enzymes)	-	Tower et al. (2020)
	Estrogen and its metabolites can directly damage DNA	-	Rall-Scharpf et al. (2021); Miller (2003)
	Estrogen, via ER-α, can promote upregulation of p53	Human, embryonic kidney cells/breast cancer cells	Zou et al. (2015)
	Estrogen has been implicated in the activation of SASP regulatory pathways (e.g., p38MAPK, PI3K, mTOR)	-	Tower et al. (2020)

muscle cells (VSMCs) undergo senescence, while male VSMCs undergo apoptosis (Malorni et al., 2008). In instances of p53 deficiency (i.e., in mesenchymal glioblastoma, or Mes-GBM, models), male mice astrocytes display greater inactivation of RB proteins—which are active in senescent cells—than female mice astrocytes (Sun et al., 2014). In response to etoposide, female mice GBM astrocytes upregulate p21 and p16 and undergo proliferative arrest, while male cells undergo malignant transformation (Kfoury et al., 2018). Overall, these findings suggest that female cells preferentially undergo cellular senescence in response to genotoxic stress, potentially in association with a lower capacity for DNA repair. Notably, some authors report a greater accumulation of cell senescence markers (i.e., p21/p16 mRNA) in peripheral lymphocytes of male mice instead of female mice (Yousefzadeh et al., 2020). Therefore, further investigation is needed to confirm the existence of a sex-dependent bias for senescence onset, as well as the potential direction of this bias. This information is summarized in Table 1.

3.2. Functional role of p53

Presently, few major publications identify sex differences in senescence growth arrest and the pathways that facilitate it (i.e., p53-p21, p16-pRB). Some of these publications were highlighted in Section 3.1, in the context of sex differences in the cellular response to DNA damage (Kfoury et al., 2018; Malorni et al., 2008; Sun et al., 2014; Yousefzadeh et al., 2020). However, those studies focused on sex differences in changes in gene expression. To our

Table 3
Evidence of sex differences in cellular senescence, in terms of the functional roles of testosterone and progesterone.

Section/Topic	Finding(s)	Experimental model	Reference(s)
3.3.2/Testosterone	Testosterone has been implicated in the activation of SASP regulatory pathways (e.g., p38MAPK, PI3K, mTOR)	-	Tower et al. (2020)
	Testosterone prevents H_2O_2-induced apoptosis	Mouse, skeletal muscle cells	Vasconsuelo et al. (2011)
	Testosterone prevents angiotensin-induced senescence	Mouse, vascular smooth muscle cells	Chen et al. (2016)
	Testosterone prevents doxorubicin-induced senescence	Rat, embryonic cardiac muscle cells	Altieri et al. (2016)
	Androgen deprivation leads to DSB formation	Human, androgen-responsive cancer cells	Chua and Bristow (2016)
	Testosterone protects female embryos from death due to helicase mutation-driven genomic instability, partly by reducing inflammation	Mouse (embryo), organism	McNairn et al. (2019)
	Testosterone inhibits the expression of pro-inflammatory cytokines (TNF, IL-6, IL-1) in men	Human, organism	Bianchi (2019)
	Age-related decline in testosterone in men is associated with greater levels of inflammatory markers	Human, organism	Bianchi (2019)
3.3.3/Progesterone	Synthetic progesterone (megestrol acetate) induces senescence (shown by elevated p21, p16)	Human, endometrial carcinoma cells	Wang and Shi (2021)
	Progestin treatment induces senescence (shown by elevated p21, FOXO1, SA-β-gal; shown by altered cell morphology, cell cycle arrest, prolonged survival)	Human, ovarian cancer cells	Diep et al. (2013)
	Progesterone activates FOXO1 (which normally promotes senescence)	Human, endometrial stromal cells	Brighton et al. (2017)

knowledge, no studies have investigated sexually dimorphic function in any of the proteins which facilitate senescence growth arrest, with the exception of one: p53. As described in Section 2, p53 is a transcription factor that—once activated and stabilized by DDR proteins recruited in response to DNA damage—binds *CDKN1A* to promote the expression of p21, a CDKI that facilitates proliferative arrest.

While the present paper has primarily discussed p53 in terms of its contribution to senescence growth arrest, it is well-established that the activation of p53 is not strictly associated with a single type of cellular change or outcome. While p53 has been shown to initiate cellular senescence—a cell state that actively resists apoptosis—p53 can also promote apoptosis directly (Rubin et al., 2020). Additionally, while the activation of p53 occurs alongside persistent mTOR signaling during cell senescence, p53 is also known to suppress the mTOR pathway during cell quiescence (Korotchkina et al., 2010). Therefore, because p53 activation is capable of contributing to multiple types of cellular changes, it is reasonable to predict that any given outcome of p53 activation depends on a variety of factors, which potentially includes biological sex. In Drosophila, tissue-general overexpression of p53 increases the lifespan of males but shortens the lifespan of females (Waskar et al., 2009). In humans, the possession of a reduced-activity allele of p53 is associated with increased lifespan in women, but not in men carrying the same allele (Groß et al., 2014). While a definitive relationship between biological sex and functional outcomes of p53 activity cannot be drawn from this data alone, other publications do report that p53 fulfills sex-specific functions (e.g., regulation of long non-coding RNA Xist, which facilitates X-chromosome inactivation [XCI] in women) (Rubin et al., 2020). Therefore, more research is needed to clarify whether p53 function is sexually dimorphic and, if so, how this affects senescence onset in members of a particular sex. This information is summarized in Table 1.

3.3. The role of sex hormones in senescence-related pathways

Though information on their roles in DNA damage-induced cellular senescence is limited, each of the 3 primary sex steroid hormones has been observed to modulate senescence onset (either directly or indirectly) in at least one instance. As will be described below, estrogen appears to have a context-dependent role in cellular senescence, whereas testosterone and progesterone seem to primarily suppress and promote cell senescence, respectively. Evidence of sex differences in cellular senescence, in terms of the roles of sex steroid hormones, is summarized in Tables 2–3.

Notably, all major publications on sex differences in SASP highlight the regulatory role of estrogen. Thus, all evidence of sex differences in the SASP will be discussed here.

3.3.1. Estrogen

Presently, most evidence suggests that estrogen prevents cell senescence, both by protecting against senescence-inducing DNA damage and by inhibiting senescence-establishment proteins/pathways. A role for estrogen in senescence suppression has also been identified through studies on its absence (i.e., in postmenopausal women; in ovariectomized mice), as well as through studies on its administration (i.e., as menopausal hormone therapy (MHT); as estrogen treatment in cell culture).

In terms of estrogen's ability to protect against DNA damage, 2 means by which this is achieved have been well-characterized. Firstly, estrogen can reduce oxidative stress, a known cause of SSBs and replication stress (Cooke et al., 2003; Venkatachalam et al., 2017). By directly interacting with mitochondria (Torres et al., 2018) or by activating mitochondrial estrogen receptors (ERs) (Lejri et al., 2018; Razmara et al., 2008), estrogen can suppress the release of reactive oxygen species (ROS), thereby preventing ROS-induced DNA damage. In murine skeletal muscle cells, Vasconsuelo et al. (2008) found that both H_2O_2-induced and etoposide-induced DNA fragmentation can be prevented through treatment with estrogen. A second way that estrogen protects against DNA damage is by promoting telomerase activity. As cells age, telomere shortening occurs as a natural consequence of incomplete DNA replication (Barrett and Richardson, 2011). However, telomerase slows this process by catalyzing the addition of base pairs onto shortened telomeres (Barrett and Richardson, 2011), extending the amount of time before cells reach their proliferative limit. Although telomerase is typically downregulated in humans, its expression and activity are both increased in the presence of estrogen (Walker et al., 2016), as has been shown in multiple cell types, including human leukocytes, VSMCs and endothelial progenitor cells (Emmerson and Hardman, 2012; Walker et al., 2016).

Thus, estrogen can protect against multiple types of DNA damage that result from endogenous conditions.

Complementing its ability to protect against senescence-inducing DNA damage, estrogen also appears to inhibit the expression/activity of proteins that facilitate the onset of cellular senescence. In ER-positive human breast cancer cells, Pedram et al. (2009) found that, through ERα, estrogen not only inhibits ATR, Chk1, and γH2AX, but also indirectly suppresses p21 expression (i.e., inhibition of ATR prevents phosphorylation of p53, leaving p53 unable to bind the *CDKN1A* gene promoter). The anti-senescence role of estrogen identified through this study is further supported by the finding that inhibition of ERα leads to an increase in senescence-associated β-galactosidase (SA-β-gal)—a common senescence marker (Campisi and d'Adda di Fagagna, 2007)—and unphosphorylated RB protein, both in human mammary epithelial cells and human breast cancer cells (Liu et al., 2016). Aside from suppressing the activity of proteins that promote cell senescence, estrogen has also been observed to upregulate the expression of certain proteins that prevent cell senescence. This includes the Werner syndrome ATP-dependent helicase, which is essential for preventing cellular senescence and normally absent or non-functional in Werner syndrome, a senescence-associated disease (Lee et al., 2010).

Estrogen's role in senescence suppression is further demonstrated through studies on dramatic decreases in estrogen levels, which offer valuable insight into the benefits it imparts when present at higher concentrations. Following menopause, women display a significant increase in telomere shortening (Walker et al., 2016), as well as reduced markers of anti-inflammatory macrophage activity (Toniolo et al., 2015). Similarly, following ovariectomy (OVX), mouse bone marrow mesenchymal stem cells display upregulated p53 and p21, upregulated SASP factors, and induction of the JAK/STAT pathway (Wu et al., 2020). These studies on post-menopausal women and OVX mice show that dramatic declines in estrogen are associated with greater prevalence of certain senescence inducers (i.e., uncapped telomeres), increased levels of markers of senescence and inflammation, and activation of SASP regulatory pathways.

Where the absence of estrogen has been found to promote senescence and senescence-associated changes, the administration of estrogen has been found to reverse these effects. When administered to cell culture, estrogen prevents the production of tumor necrosis factor (TNF) and IL-10 (canonical SASP factors) by activated human M1 macrophages (Toniolo et al., 2015) and reverses both OVX-driven induction of JAK/STAT and OVX-driven upregulation of p53, p21, and SASP factors in mouse bone marrow stem cells (Wu et al., 2020). Similarly, MHT treatment has been found to reduce the expression of known SASP factors in both post-menopausal women (i.e., MHT treatment reduced levels of GDF-15, TNFR1, Fas) (Faubion et al., 2020) and human platelet cells (i.e., MHT treatment reduced levels of IFN-γ, MCP-1, MMP-2, MMP-9, TNF) (Miller et al., 2016). In addition to reducing the expression of SASP factors, estrogen has also been shown to prevent senescence growth arrest. In cultured human endothelial progenitor cells, estrogen treatment prevents angiotensin-induced cellular senescence, as indicated by reduced levels of SA-β-gal (Imanishi et al., 2005). Similarly, in murine subventricular zone neural stem cells exposed to UV-irradiation, estrogen treatment both reduces p53 expression and promotes cell survival and proliferation (Kim and Casaccia-Bonnefil, 2009).

Overall, the evidence summarized here suggests that estrogen primarily prevents the onset of cellular senescence and its pro-inflammatory effects by protecting against senescence-inducing DNA damage and by inhibiting senescence regulatory proteins. However, there is also evidence that estrogen is equally capable of doing the opposite (i.e., generating DNA damage; stimulating senescence regulatory pathways). For example, through ERs, estrogen can activate signaling pathways that inhibit forkhead box O (FOXO) family transcription factors, whose target genes include those which encode various antioxidant enzymes (Tower et al., 2020). By opposing the expression of antioxidant enzymes, estrogen can contribute to the persistence of ROS, resulting in greater oxidative stress—a known cause of DNA damage. It has also been established that estrogen and its metabolites can induce DNA damage directly (Miller, 2003; Rall-Scharpf et al., 2021). Beyond DNA damage, however, estrogen may promote cell senescence by modulating the activity of key regulatory pathways. In terms of senescence growth arrest, although estrogen is known to indirectly suppress the expression of *CDKN1A* through ERα-driven inhibition of ATR and subsequent inactivation of p53 (Pedram et al., 2009), *CDKN1A* is also a target gene of ERα, and can therefore be upregulated as a result of ERα activation (Zou et al., 2015). Regarding the SASP, estrogen has been implicated in the activation of multiple SASP regulatory pathways, including p38MAPK, PI3K, and mTOR (Tower et al., 2020). Therefore, while most publications report that estrogen protects against senescence-inducing DNA damage and suppresses senescence onset, whether estrogen works in favor of (or in opposition to) the establishment of cellular senescence may ultimately depend on a variety of context-specific factors. This information is summarized in Table 2.

Before moving onward to the discussion of testosterone's potential role in modulating the senescence response, it makes sense to first clarify what is known about the larger role of mitochondria in cellular senescence, given that mitochondria are targets of sex-dimorphic signals such as estrogen.

In senescent cells, there are multiple changes in the processes responsible for regulating mitochondrial numbers, morphology, and quality control. These changes include increased mitochondrial biogenesis, changes in mitochondrial fusion and fission (in favor of fusion), and reduced mitochondrial autophagy (or mitophagy) (Chapman et al., 2019). These changes result from environmental stress (Correia-Melo et al., 2016; Dalle Pezze et al., 2014; Das and Chakrabarti, 2020) and lead to the gradual accumulation of dysfunctional mitochondria, which are normally eliminated through mitochondrial fission and subsequent mitophagy (Chapman et al., 2019). Dysfunctional mitochondria display abnormal membrane potential (e.g., due to proton leakage) (Chapman et al., 2019), reduced fatty acid oxidation (Ogrodnik et al., 2017) and enhanced ROS generation (Chapman et al., 2019).

Through the generation of ROS-mediated DNA damage, mitochondria drive senescence; however, multiple studies have revealed that mitochondria are dispensable with respect to senescence-associated growth arrest. Through targeted depletion of mitochondria in human fibroblasts exposed to senescence-inducing radiation, Correia-Melo et al. (2016) found that loss of mitochondria leads to decreased p21 expression, decreased p16 expression, reduced levels of SA-β-gal, and reduced levels of key SASP factors (e.g., IL-6, IL-8). Despite these changes, however, the senescent fibroblasts continued to undergo permanent growth arrest, as shown by use of the proliferation marker Ki67 (Correia-Melo et al., 2016). Furthermore, using global transcriptomic analysis, Correia-Melo et al. (2016) determined that mitochondrial depletion has no significant effect on the normal expression of proliferation-related genes. In contrast, mitochondrial depletion was directly responsible for the downregulation of a substantial proportion of SASP genes normally upregulated during senescence (Correia-Melo et al., 2016), suggesting that mitochondria are necessary for the establishment of the SASP.

In terms of the specific mechanisms by which mitochondria promote the SASP, Vizioli et al. (2020) determined that the ROS

generated by dysfunctional mitochondria trigger a series of pathways related to the innate immune response. As described by Vizioli et al. (2020), mitochondrial ROS promote the activation of stress-activated kinase JNK, which interacts with 53BP1 (a DDR protein described in Section 2) and modulates its function in such a way that leads to the increased formation of cytosolic chromatin fragments. Such free-floating DNA fragments trigger the cGAS-STING pathway (a cytosolic DNA-sensing pathway composed of cyclic GMP-AMP synthase [cGAS] and stimulator of interferon genes [STING]), which then activates NF-κB to stimulate transcription of various SASP-related pro-inflammatory genes (Song et al., 2021; Vizioli et al., 2020).

In this review, we highlighted that estrogen interacts with mitochondria to reduce ROS production. Based on the findings by Vizioli et al. (2020) which show that mitochondrial ROS induce the SASP by promoting the generation of cytosolic chromatin fragments and inducing the cGAS-STING pathway, future research may choose to investigate the degree to which estrogen can effectively reduce the inflammatory phenotype in senescent cells, and whether this effect is specifically achieved by modulating mitochondrial ROS production and preventing subsequent cGAS-STING activation.

3.3.2. Testosterone

Although testosterone, like estrogen, has been implicated in the activation of SASP regulatory pathways (Tower et al., 2020), most other evidence suggests that testosterone primarily protects against genotoxic insult and downregulates SASP factors.

It has been well-established that, at normal physiological concentrations, androgens prevent DNA damage. Indeed, testosterone has been found to prevent a variety of conditions in which DNA damage is prominent, including H_2O_2-induced apoptosis (in mouse skeletal muscle cells) (Vasconsuelo et al., 2011), angiotensin-induced senescence (in mouse VSMCs) (Chen et al., 2016), and doxorubicin-induced senescence (in rat embryonic cardiac muscle cells) (Altieri et al., 2016). Further, as described by Chua and Bristow (2016), androgen deprivation reliably induces DSB formation in androgen-responsive human cancer cells.

Interestingly, the ability of testosterone to protect against genomic instability is not unrelated to its ability to reduce inflammation. McNairn et al. (2019) report that the anti-inflammatory effects of testosterone are specifically responsible for the survival of male mouse embryos experiencing genomic instability due to helicase mutations. Here, the presence of testosterone lowers inflammatory markers (e.g., IL-6) and increases levels of anti-inflammatory markers (e.g., IL-10). McNairn et al. (2019) found that helicase mutations are preferentially lethal in female mouse embryos, that female embryos are rescued by testosterone treatment, and that deficiency in IL-10 receptors is lethal to both male and female embryos, regardless of testosterone levels (McNairn et al., 2019). Therefore, these results suggest that the anti-inflammatory activity of testosterone confers protection against extensive DNA damage.

In human males, testosterone inhibits the expression of pro-inflammatory cytokines (e.g., TNF, IL-6, IL-1) as well as the formation of adipose tissue, a significant source of pro-inflammatory cytokines responsible for chronic disease (e.g., IL-6) (Bianchi, 2019). Indeed, as summarized by Bianchi (2019), studies examining the age-related decline in testosterone for men report an association with greater levels of inflammatory markers. Since these studies have primarily examined C-reactive protein—a marker of inflammation—and only a few studies have investigated levels of canonical SASP factors (e.g., IL-6, TNF), it is difficult to determine if these differences in inflammation are strictly associated with cellular senescence. However, separate studies on the effects of testosterone administration on inflammatory cytokine secretion in men provide further support for the role of testosterone in senescence suppression: across the many studies which have been conducted (as summarized by Bianchi [2019]), despite slight variance from one study to the next (partly due to differences in dosage/administration), overall, testosterone replacement therapy is found to suppress SASP inflammatory markers (Bianchi, 2019). This information is summarized in Table 3. More work is necessary to clarify whether the suppression of select SASP factors by testosterone is representative of testosterone's ability to suppress the SASP as a whole. While multiple publications demonstrate the ability of estrogen to suppress entire SASP pathways (see Section 3.3.1), similar studies for testosterone do not yet exist.

Separately, it may be valuable to consider the relationship between circulating testosterone levels and cellular senescence in the context of aromatization. Aromatase—the enzyme responsible for converting testosterone into estrogen—is expressed in many human tissues and cell types, including those of the central nervous system (CNS) (Bulun and Simpson, 1994; Sasano et al., 1998). Aromatase is necessary for developmental signaling pathways and normal activation of neuronal circuits (Roselli, 2007), and also contributes to neuroprotection. Under normal conditions in the CNS, aromatase is expressed exclusively by neurons (Roselli, 2007). However, brain injury and ischemia can trigger the expression of aromatase in reactive astrocytes as well (Roselli, 2007). The relevance of aromatase to neuroprotection has been demonstrated by Azcoitia et al. (2001), who eliminated the protective effects of testosterone in male rats by administering aromatase inhibitors. Since various authors have reported that—in mammals—androgens regulate aromatase activity in select brain regions (Abdelgadir et al., 1994; Roselli, 2007), this could be one place from which sex differences in estrogen-conferred neuroprotection and CNS-specific senescence-modulatory effects arise, with male individuals carrying greater circulating levels of testosterone. In support of this prediction are findings from one group that found that the administration of testosterone in gonadectomized rats had greater stimulatory effects on aromatase in male brains than female ones (Roselli, 1991). Further research is needed to determine whether overall aromatase activity is elevated in select brain regions of male individuals due to aromatase's sensitivity to testosterone, whether this may compensate for lower average levels of circulating estrogen (with respect to overall neuroprotective benefits), and how this may inform sex differences in cellular senescence in CNS tissue.

3.3.3. Progesterone

The effect of progesterone on DNA damage-induced cellular senescence has not been studied. However, progesterone has been implicated in cellular senescence in cancer prevention contexts, as well as in normal physiological activities. In human endometrial carcinoma cells, the synthetic progesterone megestrol acetate induces cell senescence, as indicated by elevated levels of p21 and p16 (Wang and Shi, 2021). In human ovarian cancer cells, progestin treatment induces cell senescence, as indicated by altered cell morphology, prolonged survival, SA-β-gal, G1 cell cycle arrest, and elevated levels of p21 and FOXO1 (Diep et al., 2013). In human endometrial stromal cells, progesterone activates FOXO1, which facilitates acute cell senescence (including both cell cycle arrest and SASP), as indicated by elevated levels of SA-β-gal, IL-6, and IL-8 (Brighton et al., 2017). This information is summarized in Table 3.

At this point, we have discussed the existing evidence that each of the 3 major sex hormones has a role in modulating cellular senescence. Considering that sex hormone levels fluctuate and change throughout the lifespan (e.g., with aging, during various estrous stages), it is also important to consider how they

each may influence the action of the other or whether they have any combination effects (e.g., when estrogen and progesterone are similarly elevated during pregnancy). While research on combination effects of sex hormones on SASP pathway activation or tolerance to senescence-inducing stressors (e.g., oxidative stress) has yet to be done, some insight may be obtained through work on the prevalence/action of sex hormones throughout the estrous cycle, where estrogen and progesterone change independently. In one study, Zhao et al. (2007) found that the expression of ERα in rat periodontal tissue is dynamic during the estrous cycle, with statistically significant differences in protein and mRNA levels of ERα between each of the 4 estrous stages. Similar findings were reported by Mendoza-Garcés et al. (2011), where, in rat hippocampi, the expression and distribution of both ERα and ERβ were unique to each estrous stage. If ER expression in other areas of the body is similarly dynamic, then it seems reasonable to predict that the receptor-mediated modulatory effects of estrogen on cellular senescence may also be subject to variation.

In terms of whether sex hormones might have combination effects relevant to their ability to modulate cellular senescence, the only study with potentially relevant findings comes from Dunphy et al. (2008). Building on the knowledge that full-term pregnancy reduces cancer incidence in both women (Rosner et al., 1994) and rodents (Sinha et al., 1988), Dunphy et al. (2008) found that treatment of female mice with estrogen and progesterone (i.e., simulating pregnancy-specific sex hormone serum levels) was an effective way of reducing cancer incidence. Since these authors found that treatment with estrogen and progesterone specifically suppresses tumor incidence via p53-mediated apoptosis, however, it remains to be seen whether this combination effect has any relevance to onset or suppression of cellular senescence.

4. Cellular senescence and X-inactivation

At this point, the present paper has introduced the concept of cellular senescence, the ways it has been implicated in disease, and the notion that sex differences in cellular senescence may underlie sex differences in disease prevalence, symptomatology, and prognosis. It has also reviewed the molecular events that give rise to cellular senescence, along with the evidence that such events are influenced by biological sex (e.g., sex differences in DNA repair, the modulatory role of sex steroids in senescence growth arrest and the SASP, etc.) Before we discuss the conclusions that can be tentatively drawn from this evidence, however, we must discuss one more thing: XCI.

In female mammals, one of 2 X chromosomes exists in a stable state of inactivation due to extensive transcriptional silencing (Chu et al., 2015; Csankovszki et al., 2001). This inactivation is initiated in early stages of development and maintained throughout the lifespan to ensure that the expression of X-linked genes is equal between males and females, despite differences in sex chromosome dosage (Csankovszki et al., 2001; Patrat et al., 2020). XCI is thought to be primarily mediated by the long non-coding RNA Xist (Chu et al., 2015; Senner and Brockdorff, 2009), which spreads over the X chromosome fated for inactivation, recruiting proteins with functions like chromatin modification and RNA remodeling (Chu et al., 2015; Patrat et al., 2020; Spaziano and Cantone, 2021), and promoting multiple forms of transcriptional silencing to ensure stable inactivation (e.g., methylation, hypoacetylation) (Csankovszki et al., 2001; Spaziano and Cantone, 2021).

Although XCI is meant to endure throughout the lifespan, there are multiple instances in which the inactive X chromosome (Xi) appears to undergo reactivation. Loss of XCI markers occurs in multiple types of human breast cancer, for example. In their 2005 study, Ganesan et al. (2005) found that Xist, macrohistone H2A 1.2, and histone H3K27me3—3 key indicators of XCI—were all absent from sporadic basal-like breast cancer and breast cancer type 1 susceptibility protein (BRCA1) mutant breast cancer samples. Evidence of X-reactivation is not limited to breast cancer contexts, however. In a 2019 study, Delbridge et al. (2019) observed a loss of XCI markers in embryonic neural tube cells taken from p53-deficient mice with female-exclusive neural tube defects. While the conditions examined in these studies are related by their lack of p53 functionality (sporadic basal-like breast cancer and BRCA1 mutant breast cancer are both breast cancer subtypes characterized by—among other features—p53 deficiency), loss of XCI maintenance has also been observed in conditions where p53 activity is normal; namely, in aging. In their study on transgenic mice, Schoeftner et al. (2009) found that overexpression of telomeric repeat binding factor (TRF2) resulted in severe telomere shortening and accelerated aging, but only in males. Since TRF2 protein levels in transgenic females were only slightly higher than those of wild-type mice, these authors predicted that the TRF2 gene was X-linked and subject to XCI-related silencing. Interestingly, when transgenic females were made telomerase-deficient, silencing of TRF2 expression was eliminated and the previously male-exclusive aging phenotype became visible in female mice, suggesting that telomere shortening relaxes XCI and allows for the expression of otherwise repressed genes. In light of these findings, it appears that XCI and XCI reversal have some ties with cellular senescence, at least through certain senescence-inducing stimuli and deficiency of the p53 transcription factor.

The revelation of ties between cellular senescence and XCI calls for further investigation of the subject, but it is important to consider whether this relationship should even be expected. Is there a precedent for epigenetic changes during cellular senescence? In fact, it has been well-established that various epigenetic changes can accompany both cellular senescence and select conditions which give rise to it (Chandra et al., 2015; Di Micco et al., 2021; Kumari and Jat, 2021; Sulli et al., 2012). First, consider senescence-associated heterochromatin foci (SAHF). SAHF are heterochromatin domains enriched for repressive proteins (e.g., heterochromatin protein 1) and related histone modifications (e.g., H3K9me3) (Di Micco et al., 2021; Sulli et al., 2012). These nuclear structures form in specific instances of senescence (namely, oncogene-induced senescence) and are believed to contribute to senescence growth arrest by preventing the transcription of cell cycle progression genes (Di Micco et al., 2021; Sulli et al., 2012). Beyond SAHF, epigenetic changes can occur simply as a product of aging, a senescence-associated phenomenon. In their 2018 study on aging in hematopoietic stem cells, Grigoryan et al. (2018) found aging to be associated with increased activity of cell cycle protein Cdc42, which causes reduced expression of nuclear structural protein LaminA/C, resulting in deleterious changes in the epigenetic profile of hematopoietic stem cell chromatin. It can be seen, therefore, that aging and senescence are both conditions under which epigenetic changes may take place.

While there are yet to be studies that provide the first explicit evidence of a direct relationship between cellular senescence and sex chromosome epigenetics, the findings summarized here provide grounds to ask the question of whether the inactive X chromosome might be subject to epigenetic changes and reactivation in the context of DNA damage-induced senescence. Notably, since the cellular mechanisms which facilitate age- and senescence-related chromatin reorganization are poorly understood (Chandra et al., 2015; Sulli et al., 2012), the whole gamut of phenomena which contribute to changes in the state of the inactive X chromosome remains to be seen. It seems there is at least one other, however: genetic mosaicism. Genetic mosaicism refers to the presence of 2 or more cell populations with distinct diploid genotypes in an indi-

vidual derived from a single ovum (Machiela et al., 2017). Genetic mosaicism results from post-zygotic mutations, or "mosaic events," which can range in size (i.e., from point mutations to chromosomal aneuploidy) but persist so long as they do not compromise cellular survival or undergo correction (Machiela et al., 2017). Though not always a pathological phenomenon (Machiela and Chanock (2013) highlight many types of mosaic chromosomal aneuploidies that appear in phenotypically normal individuals), genetic mosaicism can give rise to disorders which exist on a spectrum of severity (Machiela et al., 2017; Moog et al., 2020). In a 2016 study, Machiela et al. (2016) found that rates of X chromosome mosaicism were 4x higher than the average autosomal mosaicism rate, based on data from over 38, 000 women. They also found that X chromosome mosaicism was more likely with age, and that, based on their analysis of methylation patterns, the inactive X chromosome is more susceptible to mosaic events than the active X chromosome (Machiela et al., 2016). In all probability, Xi mosaicism grows more likely with age as a result of the rise in frequency of somatic mutations (Gorbunova et al., 2007; Vijg, 2021), which itself is due to the gradual loss in efficiency of DNA repair that occurs over time (Gorbunova et al., 2007). Given that senescence is, by design, meant to prevent the persistence and transmission of deleterious mutations, it does not seem immediately likely that cellular senescence and genetic mosaicism coincide within cell populations, even though both phenomena appear downstream of DNA damage. However, this does not mean that they cannot occur in parallel, with synergistic effects. Perhaps, for instance, Xi mosaic events allow for variations in the development of senescence-associated disease, resulting in disease states that vary by sex, on the basis of susceptibility to Xi mosaicism.

In light of these findings, and because studies on this subject remain scarce, further investigation into the potential relationship between cellular senescence and XCI is warranted. It would be valuable to determine whether DNA damage from senescence-inducing stressors other than telomere shortening produce transcriptomic or epigenetic changes similar to those observed by Schoeftner et al. (2009). It would be equally valuable to determine whether XCI reversal might lead to molecular changes that render female tissues more susceptible to DNA damage or cellular dysfunction related to cell senescence, especially since biallelic expression of X-linked genes has already been implicated in hematologic cancer development (Yildirim et al., 2013) and autoimmunity (Wang et al., 2016).

5. Concluding remarks

Presently, there is a significant lack of research on whether cellular senescence is influenced by biological sex, especially in humans. Thus far, 3 paradigms have been reliably demonstrated: the existence of sex differences in the activity of DNA repair pathways, the existence of sex differences in senescence onset in animal tissue, and the existence of roles for sex steroid hormones in modulating both senescence-inducing DNA damage and senescence regulatory pathways. Altogether, these suggest that biological sex is, in fact, a factor of cellular senescence. However, whether biological sex influences cell senescence in a significant way within human contexts, across all tissue types and organs, is yet to be confirmed. Based on the evidence summarized in this paper, 3 predictions can be made: firstly, that women have a lower capacity for DNA repair; secondly, that female cells have a greater tendency to undergo cellular senescence in response to genotoxic stress; and finally, that estrogen plays a significant role in modulating cell senescence (especially in women), both by protecting against genotoxic stress and by inhibiting key regulatory proteins. Although some of these ideas appear to exist in opposition (i.e., the notion of greater senescence burden in women, despite having higher average levels of senescence-suppressing estrogen than men), seemingly paradoxical principles are not unprecedented in the discussion on cellular senescence. Indeed, though p53 activation is known to inhibit the mTOR pathway (i.e., during cell quiescence), the p53 and mTOR pathways are both active during cell senescence (Hasty et al., 2013; Korotchkina et al., 2010). Further, though senescent cells secrete pro-inflammatory SASP factors to safeguard against tumor formation, it has also been established that chronic, SASP-driven inflammation can have pro-oncogenic effects (Di Micco et al., 2021; Krtolica et al., 2001; Kuilman et al., 2010). Therefore, not only are future studies needed to verify that biological sex influences cellular senescence in human contexts, but they are also needed to reconcile contrasting predictions about how senescence might manifest in women specifically. Such studies may take advantage of the known effect of senolytic therapies and the supposed association between female sex and senescence onset; for example, investigating whether senolytics yield greater benefits in females than males. To date, no such work has been done.

Other future research may choose to investigate other gaps in our knowledge of sex differences in cellular senescence that do not strictly fall into the 3 categories described here. This includes the suspected relationship between cellular senescence and epigenetic changes (e.g., XCI, which is highlighted in Section 4), the possibility of sex differences in the tendency to undergo cell quiescence, and the possibility of programmatic events that coordinate cellular senescence and organism-wide molecular changes associated with reproductive aging. To date, none of these subjects have been directly investigated, but tangentially related findings from other publications may offer grounds to do so. For example, one study by Labbadia and Morimoto (2015) demonstrates that the onset of reproductive maturity in *C. elegans* coincides with an organism-wide loss of proteostasis, suggesting that organismal stress response pathways may undergo remodeling to re-direct cellular resources towards optimizing reproductive fitness. Such findings might lead us to wonder whether similar shifts in stress response pathways occur during different phases of the estrous cycle, during pregnancy, or during menopause in women, as well as whether such changes might be related to onset of cellular senescence. A role for cellular senescence in female reproductive aging has already been described by Secomandi et al. (2021), who emphasize the need to understand mechanisms of reproductive aging as the average age of reproduction gradually rises, and by Velarde and Menon (2016), who highlight the positive and negative effects of senescence on reproductive fitness.

If it were confirmed that cellular senescence manifests differently between men and women in response to comparable senescence-inducing stressors, there would be substantial grounds to suspect that sex differences in cellular senescence are an important aspect of the molecular basis of sex differences in disease, especially if confirmed through studies on neurological diseases with known sex differences (e.g., AD, mTBI, etc.) Although senescence has been implicated in a range of diseases, including non-neurological ones, the prospect of cellular senescence as a disease-causing factor in neurological dysfunction is especially interesting since the CNS is largely composed of post-mitotic cells. While glial cells are known to undergo senescence growth arrest and exhibit a SASP (Guerrero et al., 2021; Limbad et al., 2020; Turnquist et al., 2016), neurons already exist in a non-dividing state. This is not to say that neurons are incapable of demonstrating characteristics of senescence; in fact, there is evidence that they can display a "senescence-like" phenotype, characterized by the accumulation of DNA damage, the chronic activation of DDR pathways, and elevated levels of various senescence markers (Fielder et al., 2017; Schwab et al., 2021). Ultimately, however, neurons are post-mitotic.

Therefore, given that the CNS is a mixture of mitotic and non-mitotic cell types, by studying cell senescence in the context of neural cells and neurological disease, there may be unique opportunities to investigate the dysfunction induced within a cell by the actions of nearby senescent cells, separately from the dysfunction a cell experiences by virtue of being senescent itself.

Although there is a wealth of evidence implicating cellular senescence in diseases with known sex differences, whether senescence is itself influenced by biological sex has not been definitively established. Therefore, the present paper has summarized all existing evidence of sex differences in DNA damage-induced senescence, emphasizing gaps in the literature, recent developments in the field, and potential future directions (e.g., investigating cell senescence and sex chromosome epigenetics). Since strong conclusions cannot yet be drawn about how senescence occurs differently between men and women, there is a need for future studies that investigate this while maintaining a focus on relevance to the development of pathological conditions, especially in terms of dysfunctions of the brain and CNS. If we can identify how cellular senescence contributes to dysfunction in cells that exist in a permanent state of growth arrest, this could provide new insights into how the phenotypic changes associated with senescence ultimately drive disease. Beyond this, if we can validate that these changes are influenced by biological sex, this could provide unprecedented support for the notion that cellular senescence is a primary driver of pathophysiology, especially for those diseases where sex differences in clinical phenotypes are so clearly present.

Submission Declaration and Verification

This manuscript has not been published previously and is not under consideration for publication elsewhere. Its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

Author Contributions

All authors took part in literature search, manuscript preparation, and editing.

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This review article did not involve the generation of new data.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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