Cellular senescence and Alzheimer disease: the egg and the chicken scenario

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Abstract | Globally, 50 million people live with dementia, with Alzheimer disease (AD) being responsible for two-thirds of the total cases. As ageing is the main risk factor for dementia-related neurodegeneration, changes in the timing or nature of the cellular hallmarks of normal ageing might be key to understanding the events that convert normal ageing into neurodegeneration. Cellular senescence is a candidate mechanism that might be important for this conversion. Under persistent stress, as occurs in ageing, both postmitotic cells — including neurons — and proliferative cells — such as astrocytes and microglia, among others — can engender a state of chronic cellular senescence that is characterized by the secretion of pro-inflammatory molecules that promote the functional decline of tissues and organs. Ablation of senescent cells has been postulated as a promising therapeutic venue to target the ageing phenotype and, thus, prevent or mitigate ageing-related diseases. However, owing to a lack of evidence, it is not possible to label cellular senescence as a cause or a consequence of neurodegeneration. This Review examines cellular senescence in the context of ageing and AD, and discusses which of the processes — cellular senescence or AD — might come first.

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Near to 50 million people live with dementia worldwide[1]. Alzheimer disease (AD) is responsible for nearly two-thirds of all dementia cases[2], with Lewy body dementia, vascular dementia and frontotemporal dementia (FTD) being the other most common causes. Lewy body dementia, vascular dementia and FTD, along with mixed dementias, are jointly designated AD-related dementias (ADRDs)[3,4]. Ageing is the main risk factor for dementia-related neurodegeneration[5]. However, despite the efforts made to dissect the molecular mechanisms through which the ageing process might lead to selective neurodegeneration in AD and ADRDs, these mechanisms are still unclear.

Compelling evidence indicates that abnormal protein accumulation in the brain is a key mechanism underlying the neurotoxicity observed in these age-related disorders[6,7]. Indeed, selective aggregation of misfolded proteins is a hallmark of these diseases. The intracellular aggregation of tau[8–10] and extracellular amyloid-β (Aβ) deposition are features of AD[11,12], α-synuclein accumulation is a hallmark of Lewy body dementia[13] and some cases of FTD are characterized by cytoplasmic inclusions containing TAR DNA-binding protein 43 (TDP43)[14,15]. However, data obtained from the brains of individuals without dementia, ranging in age from 50 to more than 100 years, showed that these proteins also accumulate with ageing in people without cognitive impairment. Abnormal tau was found in brain tissue from 98% of unaffected individuals, whereas Aβ, TDP43 and α-synuclein were detected in brain tissue in 47%, 36% and 19% of such individuals, respectively[16]. Indeed, almost 50% of the brains assessed in this study showed a concomitant accumulation of Aβ and tau[16]. Abnormal protein accumulation might represent preclinical stages of these diseases or may be a common hallmark of the aged brain[17]. This raises the question of whether protein accumulation observed in neurodegenerative brains is the result of accelerated or off-track ageing and, if so, what proteinopathy-independent events might unleash this conversion.

As stated by Lopez-Otin et al. in 2013, the following processes could be considered the hallmarks of ageing: "genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication"[18]. These processes may also play a key role in multiple neurodegenerative diseases[19]. Among them, senescence has been recently revisited for a potential primary role in neurodegeneration, and dementias in particular (reviewed in REF.[20]). Cellular senescence is defined as a permanent arrest of the proliferative state of the cell[21,22].

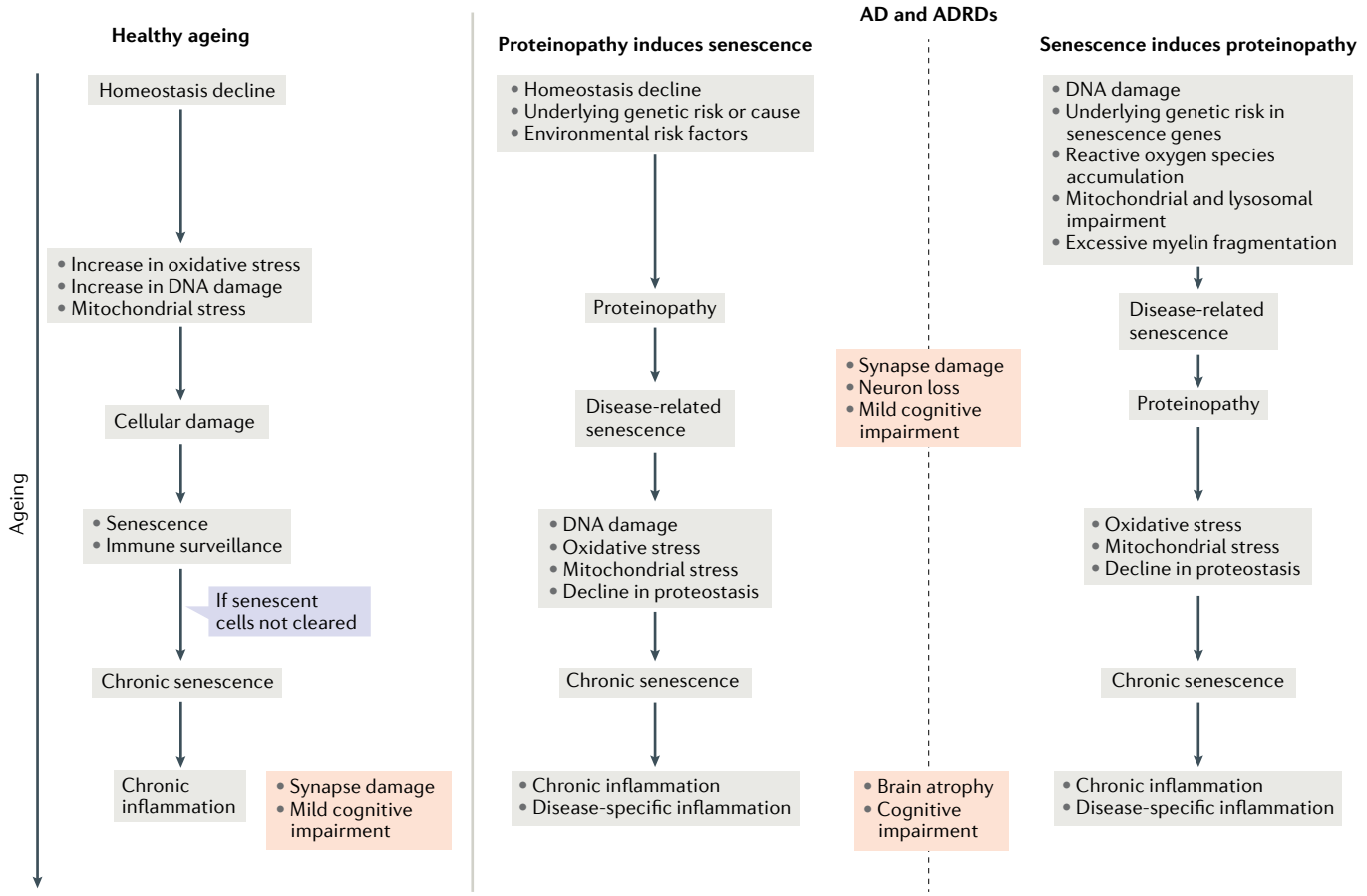

Fig. 1 | **Role of senescence in the context of ageing, Alzheimer disease and Alzheimer disease-related dementias.** Various processes possibly contributing to healthy ageing versus Alzheimer disease (AD)-related pathophysiology, with a focus on when senescence may play a role. In healthy individuals, there is a decline in the homeostasis capacity with ageing that contributes to the accumulation of different cellular stressors, such as oxidative stress, DNA damage and mitochondrial stress, among others. As a consequence, cells accumulate damage with ageing. Senescence may be activated as a homeostatic mechanism at first, but if senescent cells are not cleared then the accumulation of senescent cells becomes greater with time, triggering a chronic inflammatory response that contributes to chronic low-grade inflammation (inflammaging) and that participates in tissue decline. Inflammation induces synapse damage and contributes to cognitive decline. Individuals with AD, including individuals carrying genetic mutations associated with the disease, are exposed to additional internal stressors associated with neurodegeneration that will trigger proteinopathy. Recent data show that toxic protein aggregation, such as tau aggregation and amyloid plaque deposition[27,28], acts as a pro-senescence stimulus and induces cellular senescence in different brain cell types, leading to local inflammation in the tissues targeted by the disease. This inflammation, in combination with the toxic protein aggregation, contributes to a greater accumulation of stressors within the cells. The resulting cellular damage, in combination with the local senescence, boosts the ageing phenotype and contributes to chronic senescence. There is a third scenario, also associated with the role of senescence in AD and AD-related dementias (ADRDs), in which other proteinopathy-independent mechanisms might trigger senescence activation. This proposal is based on previous work showing that the formation of senescent cells precedes tau aggregation in the MAPT^{P301S}PS19 mouse model of tauopathy (REF.[26]), but this has not yet been widely explored in AD. In this proposal, factors such as excessive myelin fragmentation or a higher burden of genetic risk variants for cellular senescence could induce senescence in the absence of proteinopathy. The accumulation of tissue-specific senescence could generate a harmful environment for cells, making them more susceptible to toxic protein aggregation, and induce proteinopathy, both contributing to chronic senescence and boosting neural loss and cognitive decline.

Under severe or chronic stress, as occurs in ageing, both postmitotic and proliferative cells can activate a cellular senescence mechanism characterized by the secretion of pro-inflammatory molecules — referred to as the senescence-associated secretory phenotype (SASP)[23]. Prolonged exposure to the SASP leads to pathological changes that contribute to tissue and organ decline that is associated with ageing and neurodegeneration[24,25]. However, based on current knowledge, we cannot determine whether cellular senescence is a cause or a consequence of ageing and neurodegeneration (FIG. 1). Since 2018, several publications have highlighted the clearance of senescent cells as a new potential therapeutic approach to AD-associated neurodegeneration[26–28]. The development of this approach would benefit from a better understanding of the role of senescence in ageing and neurodegeneration. Thus, we think it is timely and necessary to explore whether there is a causal

relationship between cellular senescence and AD in the context of ageing.

The mechanism by which cellular senescence is linked to neurodegeneration in AD and ADRDs is not understood[29]. How do these two events — cellular senescence and neurodegeneration — influence each other during ageing: is cellular senescence a response to neurodegenerative damage, or perhaps the trigger? In this Review, we provide an overview of the evidence for cellular senescence in ageing and dementia-related neurodegeneration and we address potential mechanisms that might explain the role of senescence in the onset and progression of such neuronal loss. Finally, we discuss new therapeutic approaches targeting senescence as promising options for the future treatment of AD and ADRDs.

Cellular senescence

Mammalian cells have the exceptional ability to adapt to perturbations in the extracellular and intracellular environments. Perturbations in a cell's microenvironment promote the activation of metabolic and molecular changes to ensure cell survival. Despite these adaptive mechanisms, chronic or severe, irreparable damage will terminate the damaged cell to preserve an organism's life. The termination of a damaged cell refers to the end of the normal physiological status of the cell. This can happen through cellular division inactivation, a state known as senescence, or by the elimination of the damaged cells, a process known as regulated cell death[30]. Even if the mechanism is not completely understood, the cell cycle regulator p53 has a key role in controlling the decision to activate pro-apoptotic regulators in response to severe damage or to regulate $p21^{Cip1}$ transcription to induce senescence in response to a milder but still damaging insult[31,32]. Therefore, when the damage is severe enough but is not lethal, cells switch to a permanent, non-proliferating state[33–35]. This state is characterized by an inflammatory phenotype known as the SASP, in which a cell secretes activated interleukins, chemokines, extracellular matrix components, metalloproteinases, growth factors and other signalling molecules[36–38]. The SASP pro-inflammatory signal activates an innate immune response that aims to clear senescent cells[39,40]. However, a sustained induction of senescence, or even more moderate levels of senescence when the immune system is impaired[41], can lead to a large accumulation of senescent cells that triggers a chronic inflammatory state with detrimental effects on neighbouring cells and the whole organism.

Cellular senescence was first observed in cultured normal human fibroblasts that have lost the ability to replicate after a certain number of cellular passages[33]. Since then, almost all mammalian proliferative cells — such as lymphocytes[42], keratinocytes[43], pancreatic cells[44,45] and renal epithelial cells (for a review, see REF.[46]) — have been shown susceptible to becoming senescent. Even postmitotic cells, including neurons[47–49], cardiomyocytes[50,51], osteoclasts[52] and osteocytes[53], can switch to a physiological state that resembles senescence in a myriad of conditions related to ageing, health and disease[46].

Cellular senescence activation under regulated conditions is also required to ensure normal tissue homeostasis during development and tissue remodelling[54] and for wound healing[55], and acts as a potent tumour suppressor[56,57]. Thus, cellular senescence may be understood as an example of antagonistic pleiotropy[58]: it can mediate cell survival and adaptation in response to an acute insult, but it can be cytotoxic when there is a chronic insult.

Senescence is inevitable in ageing as a consequence of damage accumulation throughout an individual's life. Accumulation of cellular damage will change an organism's physiological and metabolic state during the lifespan, and will, in turn, eventually trigger the activation of deleterious genes. In other words, the irremediable accumulation of DNA and oxidative damage, telomere shortening and the impairment of repair mechanisms and immune system function will engender a chronic accumulation of senescent cells over time, leading to sustained inflammatory stress activation as an organism grows older.

Cellular senescence mechanisms

At the molecular level, cellular senescence is a dynamic multistage process that can be activated by different stimuli and can respond to many different needs of the cells[59,60] (FIG. 2). The heterogeneous nature of the process complicates our understanding of the cellular events involved in the induction and progression of senescence and raises the question of whether there are different types of senescence based on the mechanisms underlying its induction. It is especially challenging to dissect the timeline of ageing-related senescence in vivo because of the lack of specific and robust markers for senescence and the difficulty in following the process in living organisms. Indeed, the knowledge regarding cellular senescence's molecular players is mostly based on in vitro experiments. Several pro-senescent stimuli have been described in vitro and in vivo, for example, telomere shortening[61,62], DNA damage[63], reactive oxygen species[64,65], mitogenic and oncogenic signalling (which triggers oncogene-induced senescence)[66], ionizing radiation[67], mitochondrial dysfunction[68], lysosomal alteration[69], abnormal tau aggregation (as shown through expressing human P301L mutant tau in mice)[27], amyloid deposition[28,70] and mitochondrial DNA damage[71]. Most of the pro-senescent stimuli converge on DNA damage, which is the quintessential signal for senescence induction and activates a DNA damage response[72].

After DNA is damaged, double-strand breaks are sensed by multiprotein complexes that participate in the recruitment of the specialized serine/threonine kinase proteins ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3-related protein) to the site of the lesion, where they are activated and mediate the phosphorylation of the histone H2AX (γH2AX)[73]. This initiates a positive feedback loop in which γH2AX, in combination with DNA damage response mediators, such as MC1 and p53-binding protein 1 (REFS[74–76]), recruits to the DNA and activates more ATM, which leads to further phosphorylation of H2AX. This loop allows γH2AX to spread along the chromatin, and it

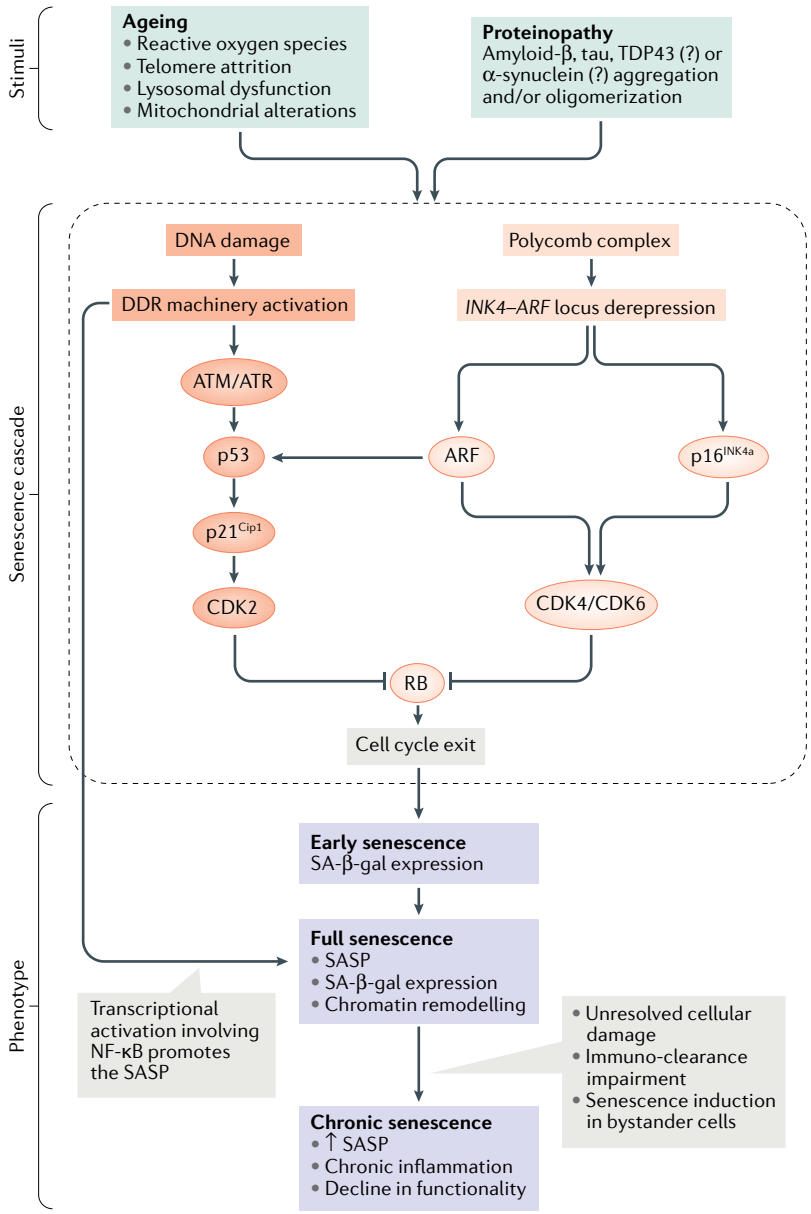

Fig. 2 | **Cellular mechanisms and phenotypic features of senescent cells in ageing and neurodegeneration.** Cellular senescence is a complex process triggered by a myriad of pro-senescent stimuli related to ageing, such as reactive oxygen species, telomere attrition, lysosomal dysfunction and mitochondrial alterations, among others. Recently, Alzheimer disease (AD)-related proteinopathy events have also been related to senescence induction, such as amyloid deposition and tau aggregation. TAR DNA-binding protein 43 (TDP43) and α-synuclein might also be potential candidates to induce senescence, but there are still no publications that support this claim. DNA damage is one of the main signals that induces cellular senescence activation. DNA damage activates the DNA damage response (DDR) machinery, responsible for p53–$p21^{Cip1}$ axis activation, which in turn blocks cyclin-dependent kinase 2 (CDK2) activity, resulting in retinoblastoma (RB) hypophosphorylation and cell cycle exit. *INK4–ARF* locus derepression is another senescence activation mechanism. The *INK4–ARF* locus is repressed in normal cells by polycomb proteins and epigenetic factors, but when activated it promotes the expression of ARF (murine $p19^{ARF}$ and human $p14^{ARF}$), which is known to prevent p53 degradation, and the expression of $p16^{INK4a}$, which consequently inhibits CDK4 and CDK6 and leads to RB hypophosphorylation and long-lasting arrest of the cell cycle. DNA damage and *INK4–ARF* locus derepression converge in RB hypophosphorylation and it is thought that the two paths act together to induce and maintain senescence in ageing and neurodegeneration. As a consequence of the cell cycle arrest, cells enter into an early senescence stage that evolves to full senescence, characterized by the senescence-associated secretory phenotype (SASP). The DDR regulates the induction of SASP through the activation of the transcription factor NF-κB. In addition, epigenetic regulation also acts at the promoters of the genes encoding IL-6 and IL-8, both of which are constituents of the SASP. If fully senescent cells are not cleared, they evolve to a state of late senescence (also known as chronic senescence). The accumulation of senescent cells in this stage occurs in ageing and neurodegeneration and leads to chronic inflammation, which contributes to organ and tissue decline. Three main factors contribute to late senescence transition: first, sustained and chronic damage; second, a reduction in the capacity of the immune system to remove senescent cells in aged individuals; and, third, the capacity of senescent cells to induce senescence in their surroundings. ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; SA-β-gal, senescence-associated β-galactosidase.

has been found up 2 Mb from the lesion site[72]. When the local activity of ATM and ATR passes a certain threshold, phosphorylated ATM and ATR are capable of activating the checkpoint kinases CHK1 and CHK2 (REF.[77]), which diffuse into the nucleus, finally leading to activation of p53 (REF.[78]). Activated p53 promotes the transcription of the cyclin-dependent kinase inhibitor $p21^{Cip1}$, which in turn blocks cyclin-dependent kinase 2 (CDK2) activity, resulting in retinoblastoma hypophosphorylation and cell cycle exit[79,80] (FIG. 2).

As damage progresses, senescent cells enter a senescent state marked by $p16^{INK4a}$ upregulation, which consequently inhibits the kinases CDK4 and CDK6 and leads to a long-lasting arrest of the cell cycle. The INK4–ARF locus is repressed in normal cells by polycomb proteins and epigenetic factors, but its activation leads to the expression of $p16^{INK4a}$ and ARF (murine $p19^{ARF}$ and human $p14^{ARF}$)[81,82], which are known to prevent p53 degradation[83]. How the *INK4–ARF* locus is derepressed in ageing is not completely understood, but the expression of both $p16^{INK4a}$ and $p19^{ARF}$ is increased in rodents[84,85] and human tissues[86,87] with ageing. The activation of the transcription factor protein C-ets-1 (ETS1) has been found to be correlated with *INK4–ARF* locus derepression across different tissues in old rodents[84], suggesting that ETS1 could regulate *INK4–ARF* activation. It seems that $p21^{Cip1}$ and $p16^{INK4a}$ have complementary roles, as $p21^{Cip1}$ is required for senescence induction but is not upregulated in fully senescent cells[88] (FIG. 2).

After exiting the cell cycle, cells enter into an early senescence state in which they undergo transcriptomic changes that aim to initiate the SASP. The DNA damage response is also behind the regulation of this secretory

INK4–ARF locus
A locus containing two genes, *CDKN2A* and *CDKN2B*. *CDKN2A* encodes two proteins, $p16^{INK4a}$ and ARF (known as $p14^{ARF}$ in humans and $p19^{ARF}$ in mice). Both proteins are cell cycle regulators that act as tumour suppressors and play an essential role in the induction and maintenance of senescence. *CDKN2B* encodes $p15^{INK4b}$, a cyclin-dependent kinase inhibitor.

Sterile inflammation
A pathogen-free inflammatory process that can be triggered by an acute stimulus, such as ischaemia reperfusion injury, trauma or toxin exposure, or a chronic stimulus, as occurs in chronic diseases and ageing. Damaged cells produce and release damage-associated molecular patterns that activate innate immune cells, which release cytokines and chemokines, further activating an adaptive immune response. Unresolved and prolonged sterile inflammation is detrimental and contributes to ageing.

Inflammaging
Chronic and low-grade inflammation that is associated with ageing and contributes to the pathology of age-related disease. Three main stimuli sustain inflammaging: cell debris accumulation, microbial products from human microbiota and cellular senescence.

Senolytic
A small molecule that selectively eliminates senescent cells. The majority of senolytic compounds aim to target the anti-apoptotic members of the B cell lymphoma 2 (BCL-2) protein family, as they have been shown to be upregulated in senescent cells. Other senolytic strategies have explored impeding p53 activation, by blocking either the interaction of the E3 ubiquitin ligase MDM2 with p53 or the interaction of p53 with forkhead box protein O4 (FOXO4). More recently, drugs have been designed that get converted into cytotoxic compounds in senescent cells, inducing apoptosis, through cleavage by lysosomal β-galactosidase.

phenotype through the activation of the transcription factor NF-κB, which regulates the expression of the genes encoding IL-6 and IL-8, both of which are constituents of the SASP[25]. At this stage, cells transition to full senescence. The SASP is the main feature of fully senescent cells, but they also exhibit senescence-associated β-galactosidase activity[89]. β-Galactosidase is a lysosomal enzyme that accumulates in senescent cells, is histochemically detectable at pH 6 (REF.[90]) and is widely used as a senescence marker in vitro and in vivo. Fully senescent cells also show other markers of senescence, such as heterochromatin remodelling, loss of lamin-B1, accumulation of dysfunctional mitochondria and lysosomes, and cellular shape changes, among others.

If they are not properly cleared, fully senescent cells enter a period known as late senescence (also known as chronic senescence in vivo), and this stage of senescence has been found to be associated with neurodegeneration[24]. Late senescence is also characterized by a more complex SASP, in that it comprises a more heterogeneous composition of molecules (for a review, see REF.[24]).

The SASP contributes to reinforce the senescent phenotype in autocrine and paracrine manners and might induce senescence in bystander cells[91]. The senescence-induced bystander effect may explain the regional and local impact of senescence. Although only a small proportion of cells are hit by senescence initially (induced by senescence inductors), senescent cells cluster together and are able to spread senescence signals to their neighbours. In addition to the SASP, other SASP-independent mechanisms such as reactive oxygen species, metabolic signalling and other signalling pathways[91,92] act as senescence inductors in bystander cells. Cells might also rely on cell-to-cell communication: for example, senescent cultured human fibroblasts transfer senescent signalling proteins to natural killer cells using intercellular bridges, and pancreatic cells also transfer proteins to immune cells in mice[93]. Senescent fibroblasts are capable of inducing regional senescence when injected into healthy mouse skeletal muscle and skin, suggesting a major role of the bystander effect in the global impact of senescence. Healthy human fibroblasts co-cultured with replicative senescent fibroblasts acquire senescence-like features mediated through gap junctions[94]. Interestingly, conditioned medium from senescent fibroblasts alone did not induce DNA damage. Taken together, the findings above indicate that although it has not yet been well studied in the context of neurodegeneration, the bystander effect has been shown to trigger senescence in healthy cells through molecular signalling. This may explain, at least in part, how post-mitotic neurons could undergo senescence activation and shortcut cell cycle inactivation.

The other main function of the SASP is to activate immune surveillance and to recruit both adaptive and innate immune cells to eliminate senescent cells[95]. In ageing, the accumulation of senescent cells exceeds the clearance capacity for such cells and, through the secretion of SASP-associated molecules, contributes to a chronic decline in tissues. The SASP causes a deterioration in tissue maintenance and a decrease in the regenerative potential of tissue, owing to the induction of senescence in stem cells and progenitors, and leads to sterile inflammation, contributing to inflammaging[96,97].

Overall, senescence in ageing contributes to reduced tissue function and reduced stress resistance. This is termed primary cell senescence, and leaves the tissue more vulnerable to age-related disorders. As the disease initiates, a second dosage of senescent cells may 'hit' tissues and organs in a disease-specific manner, enhancing the damage[89].

Ageing and dementia

Evidence of cellular senescence in ageing. The accumulation of senescent cells in aged tissues is an inexorable process, as the cumulative effect of the cellular damage becomes greater with ageing and is concomitant with deteriorations in cellular homeostasis and immune system function. Together, these processes increase the SASP. In keeping with the fact that senescent cells accumulate in aged tissues, it is theorized that senescence itself drives ageing (reviewed in REF.[98]). In fact, senescent cells have been found in several tissues of aged individuals as well as individuals with premature ageing syndromes, such as Werner syndrome, Cockayne syndrome and ataxia telangiectasia[99].

In an effort to establish the link between senescence and ageing, Baker et al.[100] studied the role of senescence in a mouse model of premature ageing, the BubR1-insufficient mouse line[101]. BubR1 is a kinase involved in the mitotic checkpoint to ensure correct chromosome segregation during mitosis[101,102]. BubR1-insufficient mice display a reduced lifespan and age-related phenotypes such as premature cataracts, loss of subdermal adipose tissue and muscle atrophy owing to early-onset senescence[103]. Taking advantage of the *INK-ATTAC* transgene, which allows the conditional and selective elimination of senescent cells expressing $p16^{INK4a}$, Baker et al. found that genetic ablation of $p16^{INK4a}$ early in life delays the premature ageing phenotype in these mice[100]. Elimination of senescent cells in BubR1-insufficient mice older than 5 months, which was after the onset of the premature ageing phenotype, was also able to slow the progression of the premature ageing-related decline[100]. Using a senolytic compound named ABT263 (an inhibitor of the anti-apoptotic proteins BCL-2 and BCL-xL) or selectively clearing senescent cells in sublethally irradiated transgenic mice (p16-3MR line), Chang et al. made a similar discovery: the selective elimination of senescent cells abrogates the effect of premature ageing[104]. Both studies concluded that the accumulation of senescent cells in ageing has a major role in the decline of the physiological function of cells and tissues over time and that clearing senescent cells, at least partly, ameliorates the effects of ageing. Despite this conclusion, these animal models have some limitations, as it is possible that *Bub1b* (which encodes BubR1) hypomorphism or genotoxic-induced insults directly activate stress pathways related to senescence, challenging the conclusions of both studies.

Senescence induction has also been studied in other premature ageing models in vivo. Mitochondrial

Mitochondrial dysfunction-associated senescence
A particular type of senescence observed in vitro and in vivo that is triggered by mitochondrial DNA damage. It involves activation of AMPK and subsequent activation of p53. Senescent cells induced by mitochondrial dysfunction-associated senescence exhibit a senescence-associated secretory phenotype, although it lacks IL-1-dependent factors.

dysfunction, which has been widely associated with ageing, has been shown to act as a pro-senescence stimulus in human fibroblasts lacking mitochondrial DNA[71] and, in vivo, in fat and skin senescent cells in PolgD257A homozygote mice[71]. These mice carry a proofreading-deficient version of PolG-α, the mitochondrial DNA polymerase catalytic subunit, and are therefore prone to accumulate mitochondrial DNA mutations, and they exhibit a premature ageing phenotype[105]. Mitochondrial dysfunction-associated senescence is induced by a low intracellular NAD^+/NADH ratio that mediates AMPK-mediated p53 activation with an atypical SASP that lacks IL-1-dependent factors[71].

To date, only one study has attempted to investigate the physiological contribution of the natural accumulation of senescent cells to ageing-related phenotypes in aged mice. Through the use of *INK-ATTAC* transgenic mice, the study showed that the selective elimination of senescent cells in mice older than 1 year increased the lifespan of these animals and delayed age-dependent cellular and tissue dysfunction in older mice. The amelioration of the age-dependent phenotype was due to the elimination of $p16^{INK4a}$-expressing cells in skeletal muscles, eyes, kidneys, lungs, the heart, the liver, the colon and the spleen, the accumulation of which negatively impacts longevity and health[106]. Interestingly, elimination of senescent cells also improved age-related cognitive decline in older mice, revealed by their better performance in spontaneous activity and exploratory behaviour as measured by the open-field test[106].

Evidence for cellular senescence in AD and related dementias. Ageing is the main risk factor for neurodegenerative diseases[107], so it is reasonable to argue that cellular senescence might play a major role in the ageing-related neurodegeneration process. Indeed, the occurrence of senescence in neurodegeneration has been known for years. Upregulation of cell cycle regulator proteins and other senescence markers has been found in a plethora of brain cell types in association with AD. CDK4 and its inhibitor $p16^{INK4a}$ are upregulated in pyramidal neurons in the hippocampus in brain tissue from individuals with AD[108]. In addition, senescent astrocytes, which exhibit $p16^{INK4a}$ expression and senescence-associated β-galactosidase activity, accumulate in the brain of people with AD. In vitro human astrocyte data suggest that Aβ deposition can be a trigger of senescence[109] and this mechanism could explain astrocytic senescence in human brains[109]. Aβ oligomers are also responsible for senescence induction in aged cultured microglia from rats[70] and human brains with AD[109].

A recent study revealed that the formation of tau-containing neurofibrillary tangles (NFTs), hallmarks of AD, triggers a cascade of events such as metabolic changes, gene expression alterations and induction of DNA damage that are highly correlated to senescence, in both human and mouse NFT-containing neurons[27]. In particular, the study found that expression of the *INK4–ARF* locus — which encodes markers of senescence — was upregulated in the forebrain of the transgenic line rTg(tau^{P301L})4510, which expresses the human P301L mutant variant of tau (isoform 4R0N) associated with FTD. These mice develop an aggressive age-dependent tau pathology restricted to the forebrain that precedes cognitive impairment observed at an early age (around 4 months old)[110–112]. The proposed mechanism to explain these alterations is that tau aggregation, and the consequent NFT formation, trigger a cellular homeostatic mechanism to alleviate the stress associated with the proteinopathy itself. The NFT-containing neurons may upregulate *Cdkn1a* and *Cdkn2a* expression to force themselves to enter a cellular senescence-like state to avoid apoptosis and death. However, as the NFT accumulation becomes greater, the induced *Cdkn1a* and *Cdkn2a* expression triggers the SASP. Thus, tau aggregation-mediated toxicity itself seems to induce cellular senescence and inflammation. Older studies support this finding of neural senescence. Abnormal protein accumulation of the cell cycle regulators $p16^{INK4a}$ and CDK4 was found in neurons from individuals with AD more than two decades ago[49,108,113]. Although these observations led to a neuronal cell cycle re-entry interpretation[114], recent progress in understanding cellular senescence suggests that such neurons become senescent.

In a similar line of investigation, a study showed that the clearance of senescent astrocytes and microglia (defined as $p16^{INK4a}$-positive cells) in a widely used mouse model of tauopathy ($MAPT^{P301S}$PS19 mice) diminishes NFT formation and gliosis, and alleviates cognitive decline[26]. These findings suggest that senescent astrocytes and microglia promote the hyperphosphorylation of tau, a feature of AD that is important for tau aggregation and NFT formation[115]. This study[26] and the one described above[27], published within several months of each other, confirm that senescence plays a major role in tau-related pathology in mice by promoting the progression of disease.

Another recent study demonstrated that Aβ accumulation also induces senescence in both human and mouse brains but in a different cell type, namely oligodendrocyte progenitor cells (OPCs). Interestingly, OPCs accumulated in the proximity of amyloid plaques in the inferior parietal cortex of individuals with AD and showed senescence-like features, including the expression of *CDKN1A* and *CDKN2A*. These findings were confirmed by data from transgenic APP/PS1 mutant mice. These mice co-express human mutant presenilin 1 (PS1) and a mouse–human chimeric mutant variant of the amyloid precursor protein (APP), the protein from which Aβ is derived, and they exhibit features that resemble early-onset AD[116]. These animals showed a high level of amyloid deposition in the entorhinal cortex and hippocampus where senescent OPCs had accumulated (senescence was determined by the presence of senescence-associated β-galactosidase activity). Intermittent treatment of these mice with the FDA-approved senolytic compounds dasatinib and quercetin selectively killed senescent OPCs and reduced the amyloid plaque load. Consequently, the treated animals performed better in memory and learning tasks than the vehicle-treated littermates[28].

Is cellular senescence a cause or a consequence of ageing and AD? Cellular senescence and AD are tightly connected; however, based on the evidence, it is not possible to delineate clear crosstalk between senescence and AD-related proteinopathy. On the one hand, exposure to the toxic forms of Aβ or aggregated tau is enough to induce senescence in several brain cell types[27,28]. On the other hand, selective elimination of senescent cells reduces amyloid plaque deposition and the formation of NFTs in mouse brains, and consequently improves memory and learning[26,28]. Therefore, is senescence a cause or a consequence of the toxic protein aggregation?

Although the accumulation of tau in NFTs is one of the hallmarks of AD and other related dementias, such as FTD, NFT intraneural accumulation may not be directly linked to the neural loss associated with these diseases. In rTg(tau^{P301L})4510 mice, NTF-containing neurons express stress markers but only a small proportion of them die[110]. It is hypothesized that the proteinopathy associated with NFT might exert toxic effects through a non-cell autonomous mechanism[117]. Pathogenic tau aggregation induces a neuroinflammatory response by activating microglia and astrocytes[117], and it has been suggested that the chronic inflammatory state observed in AD brain tissue is responsible for the subsequent neuron loss[118]. However, anti-inflammatory treatments are not able to alleviate or prevent the neurodegenerative phenotype. For example, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) showed that naproxen or celecoxib did not improve cognitive function in individuals with AD[119]. Another trial, the Investigation of Naproxen Treatment Effects in Pre-symptomatic Alzheimer's Disease (INTREPAD), aimed to investigate the effect of low-dose naproxen on the progression of AD in presymptomatic individuals and concluded that naproxen did not reduce the progression of presymptomatic AD[120]. Non-steroidal anti-inflammatory drug trials in people with AD do not show any potential effect of these drugs on the prevention or reversion of the disease, which supports the idea that chronic inflammation may be a consequence of the pathophysiology rather than a driving force[119,120]. Some studies have found no evidence of microglial activation in AD; rather, they have found evidence of microglial senescence underlying AD pathology[121], as observed in post-mortem brains exhibiting NFT-related degeneration and/or soluble and insoluble Aβ aggregates[122]. Interestingly, in some of the brains analysed, senescent microglia (termed dystrophic microglia in this study) were detected in regions that showed no tau pathology but were predicted to develop such pathology, suggesting that the appearance of senescent microglia may precede the formation of tau pathology[122]. What is well accepted is that neuroinflammation, which is mostly driven by microglial cells and astrocytes, leads to a damaging environment for neighbouring neurons because of the reduced capacity of activated glial cells to maintain and nurture the neurons and the promotion of pro-inflammatory factors[123]. This is similar to what is observed in senescence-induced inflammation, in which the accumulation of senescent cells is progressive, starting as a primary senescence that impairs the homeostatic capacity of cells and leaves them in a state that is more susceptible to disease initiation and progression. With disease initiation, a second wave of senescence is provoked, generating a deleterious loop[89].

Which stimuli can initiate senescence? In the context of AD and ADRDs, does only ageing stimulate senescence or is another factor involved? AD and ADRDs have a polygenic component, meaning that the genetic risk associated with some forms of these diseases most likely comprises a combination of a multitude of genetic risk variants with small individual effects[124]. Several genome-wide association studies have been performed to resolve the genetic risk that contributes to AD[125,126]. The genetic liability points to the immune system and the inflammatory response as contributors to disease risk[127]. A closer look at the common genetic variation associated with AD risk reveals that individuals with AD carry a high burden of genetic risk variants in genes known to be involved in senescence[126]. These genes include those encoding bridging integrator 1 (BIN1), which can regulate senescence activation or apoptosis in response to genotoxic stress by regulating the stabilization of DNA[128], a disintegrin and metalloproteinase domain 10 (ADAM10), which mediates senescence in a genotoxic stress model in myeloid cells and primary plasma cells[129], and ADAMTS4, which is a component of the SASP in senescent chondrocytes[130]. Thus, it is possible that individuals carrying those variants and, thus, at higher risk of AD are more susceptible to senescence activation and progression, and this could explain, at least in part, a pathological transition from an asymptomatic aged individual to an individual with AD. A recent study supports this idea by suggesting that although Aβ depositions are a major trigger of the disease, the combinatory effect of multiple genetic variants within an inflammatory pathway may modify the risk of disease. The authors of this study do not mention senescence, but the work they present is a hint of how genetic variation within a biological pathway could tip the balance from normal ageing to AD[131].

Transcriptome profiles from human brains have revealed different brain cell types that could influence the onset and progression of senescence and, thus, neurodegeneration. Gene expression data for 480 human brains from individuals aged 20–80 years confirm that microglia activation is a common feature of aged brains[132]. Microglial cells exhibit a clear shift in their gene expression profile, showing a strong genetic upregulation associated with ageing. Concomitantly, with ageing, both astrocytes and oligodendrocytes exhibit a general downregulation in their gene expression profiles. Brain-wide, ageing-related gene expression changes include downregulation of myelin basic protein (MBP) and leucine-rich repeat and immunoglobin-like domain-containing protein 1 (LINGO1)[132], a negative regulator of myelination[133]. The downregulated transcriptome changes are correlated with a decrease in the number of oligodendrocytes, particularly in the frontotemporal cortex. Supporting these data, MRI revealed that the myelin water fraction, a measure of intact myelin, is negatively related to age, confirming an overall decrease in myelin content with ageing (reviewed in REF.[134]). This suggests that the loss of myelin is a common event associated with ageing and could contribute to AD pathogenesis. In fact, myelin loss and MBP play

an important role in amyloid plaque deposition[135,136]. Moreover, myelin disruption is a well-known pathological process associated with the neurodegeneration observed in AD, first described by Alois Alzheimer in 1911 (REF.[137]). A novel study using asymptomatic individuals carrying genetic risk factors for AD found myelin abnormalities in the white matter, indicating that myelin disruption may represent an early feature of the disease process[138]. In addition to these findings, carriers of the *APOE* ε4 allele (a major genetic risk factor for AD[139]) show a faster cognitive decline that is associated with an intense myelin fragmentation process[140]. Interestingly, changes in white matter, as revealed by alterations in the myelin water fraction, are observable at an early developmental stage in infants carrying the *APOE* ε4 allele[141].

Is myelin fragmentation linked to senescence in AD? Could myelin fragmentation, as an early event in AD, induce non-cell autonomous senescence and inflammation? The answers to these questions may lie in microglia, as they have an essential role in myelin maintenance. Myelin sheaths cover axons and their maintenance is regulated by a dynamic demyelination–remyelination balance that requires the coordinated activity of OPCs and microglia. OPCs differentiate into oligodendrocytes, whose main function is to generate myelin. Microglia clear myelin debris and secrete signalling factors that promote the differentiation of OPCs to become oligodendrocytes[142,143]. Remyelination decays with age and disease, and cellular senescence plays its part in the decline of myelin maintenance and consequent debris accumulation with age[69]. For example, aged OPCs acquire a slow differentiation rate and, as shown in mice, they exhibit markers of senescence. The activation of senescence could also affect their regenerative potential[144].

Microglia, as pointed to previously, are prone to acquire a senescence phenotype[145]. Microglial cells phagocytose myelin debris and degrade it by autophagy. The overload of myelin debris, as it increases with age, generates lysosomal impairment within the microglia, such as insoluble lysosomal lipofuscin inclusions that can trigger microglial senescence and immune activation in ageing[69]. The accumulation of myelin residues in microglial cells leads to upregulation of major histocompatibility complex (MHC) class II expression and decreased phagocytic capacity[69]. Ageing is associated with senescence of microglia and impaired microglial clearance functions. In particular, data indicate that microglia in aged rodent and human brains show a senescence phenotype with a reduced self-renewal capacity[121]. As myelin integrity disruption is an early event in AD, seemingly appearing at the prodrome stage[146], it is tempting to hypothesize that the excess of myelin debris in brains with AD could itself trigger microglial senescence as an early event, which could increase the susceptibility to cellular stress in the vicinity (FIG. 3). Triggering receptor expressed on myeloid cells 2 (TREM2), whose genetic variants are

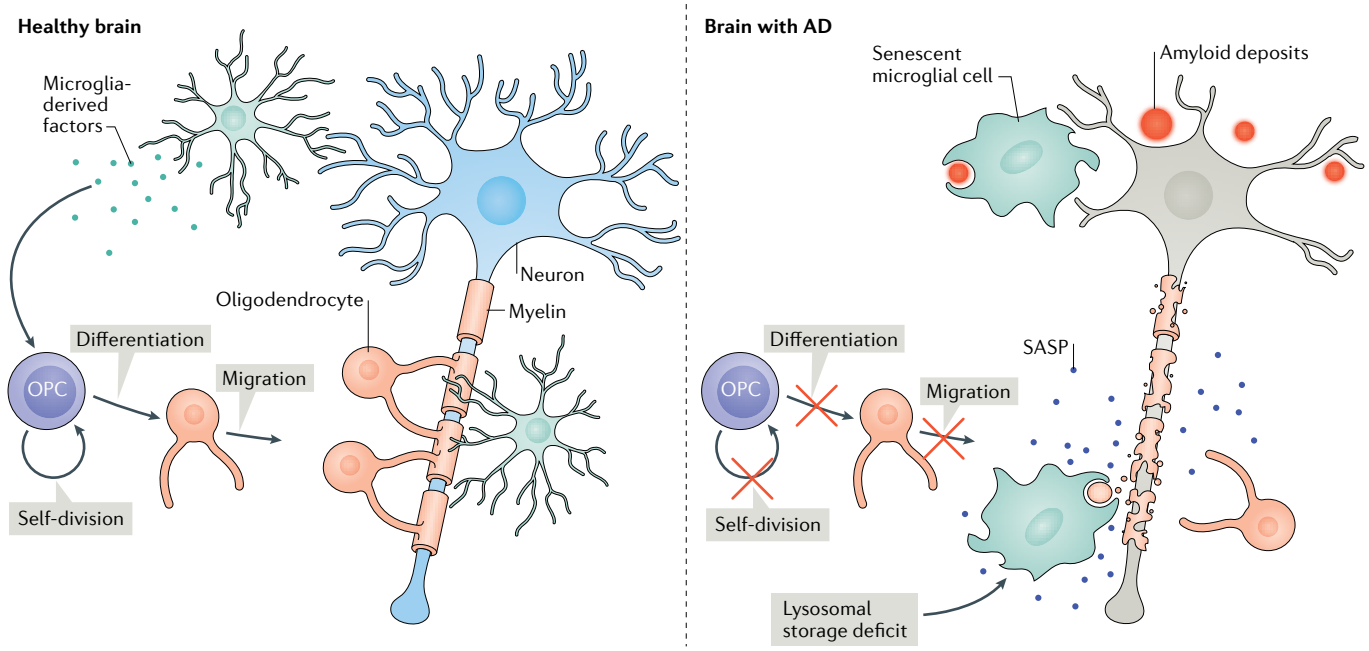

Fig. 3 | **Alzheimer disease pathology in the context of myelin fragmentation and senescence.** Alzheimer disease (AD) is characterized by the accumulation of intracellular abnormal tau and extracellular amyloid plaques. Myelin loss is an early event in the pathobiology of AD and is enhanced by the presence of extracellular amyloid plaques. Microglial cells act as macrophages and phagocytose the myelin debris and then degrade it through the autophagy–lysosomal pathway. When the accumulation of myelin debris is greater than the microglial lysosomal degradative capacity, microglial cells become senescent and release pro-inflammatory factors (collectively referred to as the senescence-associated secretory phenotype (SASP)). We propose that the activation of senescence in microglial cells has two negative outcomes that may contribute directly to the pathology observed in AD: inflammation activation, which contributes to the impairment of other cell types, such as oligodendrocytes and oligodendrocyte progenitor cells (OPCs); and loss of microglial capacity, which contributes to a greater accumulation of amyloid plaques and myelin debris. In addition, the accumulation of myelin debris could impair the remyelination process by affecting oligodendrocyte recruitment to the axons and by suppressing microglia-derived factors that are required for OPC differentiation into oligodendrocytes.

associated with AD and FTD[147], has a key role in myelin removal by microglia. Mice lacking TREM2 are not capable of myelin debris removal and develop neurodegeneration when cuprizone is administered (which is known to induce apoptosis of mature OPCs) due to a defect in remyelination[148]. Even if no data have been reported about microglial senescence induced by myelin fragmentation in individuals with AD or transgenic animal models for this disease, evidence suggests that microglia in individuals with AD undergo senescence earlier than in people without the disease[122]. After all, microglia have been largely related to senescence and may have a major role in AD pathogenesis, even if the mechanism is not yet known.

What has been largely observed is an activation of the innate immune response in the brains of people with AD. The amyloid cascade hypothesis of disease pathogenesis in AD proposes that Aβ alterations trigger a pathological cascade of reactions that include the accumulation of toxic forms of tau that cause downstream neuron loss through a non-autonomous mechanism, such as an inflammatory response of glial cells in the vicinity of the plaques[149,150]. Although this hypothesis is widely accepted, the new data from cellular senescence studies may open other possibilities. Single-cell sequence technology has allowed the identification of a subset of disease-associated microglial cells in the vicinity of Aβ deposits[151]. This particular subset of cells alters their transcriptional profile from a homeostatic state to a phagocytic–inflammatory state that is regulated by TREM2 and aims to remove such deposits. However, the sustained inflammation will later contribute to the progression of the pathology[152]. These microglial cells may resemble the dystrophic microglia observed more than a decade ago by Streit et al. in aged brains[153] and brains with AD[122]. The senescence hypothesis of AD progression suggests that genotypic factors associated with AD act as stressors and that, in combination, they interfere with signalling pathways of cell survival and maintenance, such as the senescence pathway. When the damage is chronic and is greater than the homeostatic capacity of the cell, the accumulation of senescent cells would itself be toxic in AD[154].

Targeting cellular senescence

Ablation of senescent cells has been postulated as a promising therapeutic approach to target the ageing phenotype and, thus, to prevent, delay or mitigate ageing-related diseases[155]. The aim with senolytic compounds is to rejuvenate organisms by selectively killing senescent cells[156] and their efficacy is based on the ability of senescent cells to resist apoptosis[157,158]. These cells exhibit upregulation of pro-survival pathways to protect themselves from the damaging (and pro-apoptotic) effect of the SASP[159,160]. To date, six pro-survival pathways have been detected in senescent cells: the BCL-2–BCL-xL pathway, the MDM2–p53–p21^{Cip1}–serpine elements pathway, ephrins–dependence receptors–tyrosine kinases, the PI3K–AKT–ceramide metabolic pathway, the hypoxia inducible factor 1α (HIF-1α) pathway[156] and the SP-90-dependent pathway[161]. Senolytic compounds interfere with these pro-survival pathways to let senescent cells die by apoptosis[89,159,160].

Senotherapy has been intensively explored since the first senolytic compound screening was performed in 2015 (REF.[156]). Despite senotherapy being in its infancy, preclinical data from in vitro and in vivo models indicate that it may have a promising future in the treatment of age-related diseases in humans[162–164]. A preliminary report from a phase I clinical trial using the combination of dasatinib and quercetin to treat diabetic kidney disease has demonstrated elimination of senescent cells in humans[165]; however, the limited sample size means cautious interpretation of the results is warranted.

However, the application of senolytic compounds in humans to treat or prevent dementias may be more of a challenge than for other age-related diseases because the available preclinical data come from mice and they do not develop AD or related dementias naturally, suggesting a complicated translation of the findings to humans[166]. A potential complication of the use of senolytic compounds as a therapy is that, as discussed in this Review, senescence is a natural process that occurs in a myriad of health scenarios and acts as a homeostatic mechanism, and thus the elimination of senescent cells could impair mechanisms such as wound healing[55].

Conclusions

AD and ADRDs, ageing and senescence are tightly connected events. Whether the accumulation of senescent cells is a cause or a consequence of AD-related disease progression and pathogenesis is still under debate. Previous studies indicate that the accumulation of senescent cells naturally occurs as individuals grow older and contributes to the decline of cellular and tissue functions with time. The massive accumulation of senescent cells triggers inflammatory damage that is detrimental to cells. It has been proposed that tau accumulation and Aβ aggregates activate senescence in NFT-bearing neurons and surrounding glial cells[27,69] and in OPCs[28], respectively. In this Review, we have proposed that other Aβ-independent and tau-independent mechanisms could also contribute to the accumulation of senescent cells in AD, with part of the genetic risk burden attributable to variants in cellular senescence genes or myelin fragmentation potentially promoting microglial senescence.

The evidence confirms that proteins and genes involved in the senescence pathway are tightly connected to AD and ageing. However, are any known or yet-to-be discovered genetic risk loci associated with AD involved in the senescence pathway? Evaluating the genetic contribution of these genes to susceptibility to AD could shed light on the causal relationship between senescence and AD. An interesting approach could be to see how common variation in these genes plays a role in the genetic architecture of AD by performing genome-wide heritability estimations and polygenic risk scoring using public and available genomic data sets. In addition, functional genomic studies can identify whether there are risk variants of senescence genes that impact AD through changes in the gene expression and that would place senescence in a more defined position in the cause versus consequence cascade in AD.

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