Cellular senescence: the good, the bad and the unknown

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Abstract | Cellular senescence is a ubiquitous process with roles in tissue remodelling, including wound repair and embryogenesis. However, prolonged senescence can be maladaptive, leading to cancer development and age-related diseases. Cellular senescence involves cell-cycle arrest and the release of inflammatory cytokines with autocrine, paracrine and endocrine activities. Senescent cells also exhibit morphological alterations, including flattened cell bodies, vacuolization and granularity in the cytoplasm and abnormal organelles. Several biomarkers of cellular senescence have been identified, including SA-βgal, p16 and p21; however, few markers have high sensitivity and specificity. In addition to driving ageing, senescence of immune and parenchymal cells contributes to the development of a variety of diseases and metabolic disorders. In the kidney, senescence might have beneficial roles during development and recovery from injury, but can also contribute to the progression of acute kidney injury and chronic kidney disease. Therapies that target senescence, including senolytic and senomorphic drugs, stem cell therapies and other interventions, have been shown to extend lifespan and reduce tissue injury in various animal models. Early clinical trials confirm that senotherapeutic approaches could be beneficial in human disease. However, larger clinical trials are needed to translate these approaches to patient care.

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The phenomenon of cellular senescence was discovered in the 1960s in human diploid cell strains that had exhausted their replicative potential[1]. Senescence is characterized by cell-cycle arrest in the G_1 or possibly G_2 phase, which prevents the proliferation of damaged cells[2,3]. By contrast, cellular quiescence, a reversible growth arrest state secondary to scarce nutrition and growth factors, takes place in the G_0 phase[4]. Cellular senescence occurs during embryonic development and can be induced by cellular impairment, including DNA damage, telomere shortening or dysfunction, oncogene activation or loss of tumour suppressor functions, epigenetic changes and organelle damage[5].

The principal cause of senescent stress is DNA damage[6], which activates the DNA damage response (DDR) and the canonical p53–p21 pathway[7] (FIG. 1). P21 (also known as cyclin-dependent kinase inhibitor 1) inhibits cyclin–cyclin-dependent kinase complexes that block the formation of the DREAM complex, which represses cell-cycle genes by binding their homology region[8]. Unlike DDR-induced senescence, epigenetic alterations cause senescence mainly via the p16–RB pathway[9]. p16 (also known as cyclin-dependent kinase inhibitor 2A) can inhibit the formation of cyclin D–CDK4/6 complexes and thereby prevent phosphorylation of RB and promote formation of the RB–E2F complex, which inhibits the transcription of cell-cycle genes[8]. Evidence suggests that p21 is mainly activated early during the evolution of senescence, whereas p16 maintains cellular senescence[10].

The senescence-associated secretory phenotype (SASP) is an important feature of senescent cells that comprises the release of numerous cytokines, chemokines, growth factors and proteases[11], which are sometimes enclosed within microparticles, into the extracellular environment. Many cell types also release extracellular vesicles, which contain cellular contents, including proteins, lipids and nucleic acids. Extracellular vesicles have a role in inter-cellular communication, and altered extracellular vesicle cargoes are important components of the SASP[12]. Through the release of SASP factors, senescence can modulate pathways in neighbouring cells and tissues as well as at remote sites. Notably, senescent cells that are induced by different stress stimuli may manifest distinctive SASP components[13].

Cellular senescence has beneficial biological functions in the regulation of embryonic development, wound healing, resolution of fibrosis and tumour suppression. However, prolonged senescence can result in deleterious sequelae, including tumour development,

Key points

- Cellular senescence regulates physiological and homeostatic processes, particularly during embryonic development and wound healing, but can also be a pathological process that contributes to ageing, various diseases and metabolic disorders.
- Senescent cells are characterized by morphological alterations including large, flat bodies and organelle abnormalities, as well as loss of physiological functions, an inability to proliferate and the senescence-associated secretory phenotype.
- SABG, p21 and p16 are the most commonly used senescence markers but have limitations; novel non-invasive approaches are needed to detect cellular senescence with high sensitivity and specificity in vitro.
- Cellular senescence is involved in the pathogenesis of chronic kidney disease and acute kidney injury, but also seems to have a protective role in the early stages of acute kidney injury.
- Senescence-targeting interventions, including senolytic drugs conjugated to antibodies against β2-microglobulin, chimeric antigen receptor T cells and anti-ageing vaccines, show promise for clinical application.
- Clinical trials are needed to assess the safety and efficacy of senotherapeutic approaches, optimize treatment regimens and develop more individualized and standardized treatment strategies.

chronic inflammation, immune deficit and stem cell exhaustion. Interest in cellular senescence and in senescence-modulating interventions is increasing owing to observations that in addition to driving ageing, cellular senescence has important roles in the pathogenesis of chronic diseases, including osteoporosis, metabolic syndrome, type 2 diabetes mellitus, cancer, reproductive ageing, atherosclerosis, neurodegeneration, glaucoma and chronic kidney disease (CKD). In this Review, we describe the mechanisms, hallmarks and consequences of cellular senescence, as well as the therapeutic potential of senescence-targeting interventions.

Senescence in physiology and pathology

Diverse types of stimuli trigger senescence, reflecting its spectrum of roles under different conditions (TABLE 1). Developmental senescence and replicative senescence (which occurs secondary to telomere shortening) occur under physiological conditions during embryogenesis and ageing, respectively, whereas other types of senescence are often induced by pathological stressors, including tumorigenesis, diabetes mellitus, chemotherapy or radiation.

Embryogenesis and development. In 2006, a transcript of *INK4b*, which encodes a cyclin-dependent kinase (CDK) inhibitor that blocks progression of the cell cycle beyond the G1 phase, was detected in the roof plate of the developing chicken hindbrain[14], implicating senescence in the regulation of embryonic development. Subsequently, p66Shc, which regulates oxidative stress-induced senescence, was found to mediate early cleavage arrest in failed bovine embryonic development, suggesting that cellular senescence might fine-tune embryogenesis to prevent the continued development of poor-quality embryos[15].

In the mammalian embryo, senescence occurs at multiple locations, including the limbs, nervous system and gut endoderm[16]. In the developing kidney, accumulation of senescent cells signals immune cells to facilitate mesonephros regression through macrophage-mediated phagocytosis of these senescent cells[17]. Markers of senescence, including senescence-associated β-galactosidase (SABG), p21, p27 (encoded by *CDKN1B*) and p15 (encoded by *CDKN2B*), were detected in mouse mesonephros at embryonic day 12.5 to 14.5 (REF.[17]). Knocking down p21 in mouse embryos results in developmental abnormalities[16]. Senescence has also been shown to regulate the development of multiple tissues in zebrafish embryos[18].

Importantly, senescent decidual cells in the mammalian endometrium can secrete multiple canonical implantation factors and form a suitable environment for embryonic implantation[19]. Cellular senescence may therefore have roles in pruning and remodelling developing systems and modulating their microenvironment, and is thus required to ensure fetal integrity.

Wound healing. Wound healing is a physiological response for repairing tissue injury that involves inflammation, new tissue formation and tissue remodelling. Cellular senescence has an important role throughout the wound-healing process. In cutaneous wound healing, the matricellular protein CCN1 can induce fibroblast or myofibroblast senescence and thereby reduce fibrosis via activation of the DDR and ROS–p16 signalling[20]. Similarly, in corneal wound healing, fibroblast senescence manifests as an anti-fibrogenic phenotype, with reduced responses to fibroblast growth factor 2 (FGF2; also known as basic FGF) and platelet-derived growth factor-BB, and increased expression of MMP1, MMP3 and MMP13 (REF.[21]).

Conversely, cellular senescence can interfere with wound healing. For example, inflammation-mediated cellular senescence decreases fibroblast proliferation and migration, which is vital during new tissue formation[22]. Tenovin-1 treatment induced senescence of cultured astrocytes and thereby impaired their wound-healing activity[23]. Moreover, senescent lung fibroblasts induced G2/M cell-cycle arrest of alveolar epithelial cells, leading to aberrant wound repair and re-epithelialization[24]. Senescent mesenchymal stem cell (MSC)-derived extracellular vesicles also inhibit wound healing via a mechanism that involves downregulation of miR-146a[25]. In diabetes, oxidative stress activates caveolin 1–PTRF signalling, which leads to induction of cellular senescence via the p53–p21 pathway[26]. The resulting diabetes-induced senescence[26], together with a CXCR2-enriched SASP[27], impair wound healing. These findings indicate that although transient cellular senescence can promote tissue repair, the prolonged presence of senescent cells can hamper this process.

Cancer. Cellular senescence can have beneficial and detrimental effects in cancer (FIG. 2). Oncogene activation, loss of anti-oncogenes and irreparable DNA damage not only induce apoptosis but also elicit cellular senescence to prevent tumour initiation. Transient insults may result in cell-cycle arrest, which can prevent carcinogenic mutations from being passed on to the next generation of cells and accelerate immune clearance.

DDR signalling is the main mechanism of oncogene-induced senescence. Oncogene activation or irreparable DNA damage induce activation of ataxia telangiectasia

DREAM complex
A multisubunit complex formed by the assembly of p130 and p107 with their dimerization partner, E2F4/5, and a multi-vulva class-B core complex.

mutated (ATM) and checkpoint kinase 2 (CHK2), leading to phosphorylation of histone H2AX and p53 and activation of p53–p21 signalling[28]. Additional pathways, including NLRP6–NF-κB–p14^{ARF}–MDM2 and miR-203–ITPKA–MDM2, can also activate p53–p21 signalling. In breast carcinoma cells, overexpression of oncogenic ERBB2 elicits senescence by upregulating p21 independently of p53 (REF.[29]). Loss of anti-oncogenes such as PTEN can induce senescence through the Akt–mTOR–p53 and p19^{ARF}–MDM2–p53 signalling pathways[30].

Depletion of CSN5 induced senescence in p53-null cells, suggesting that alternative pathways of senescence exist[31]. Further studies demonstrated that the

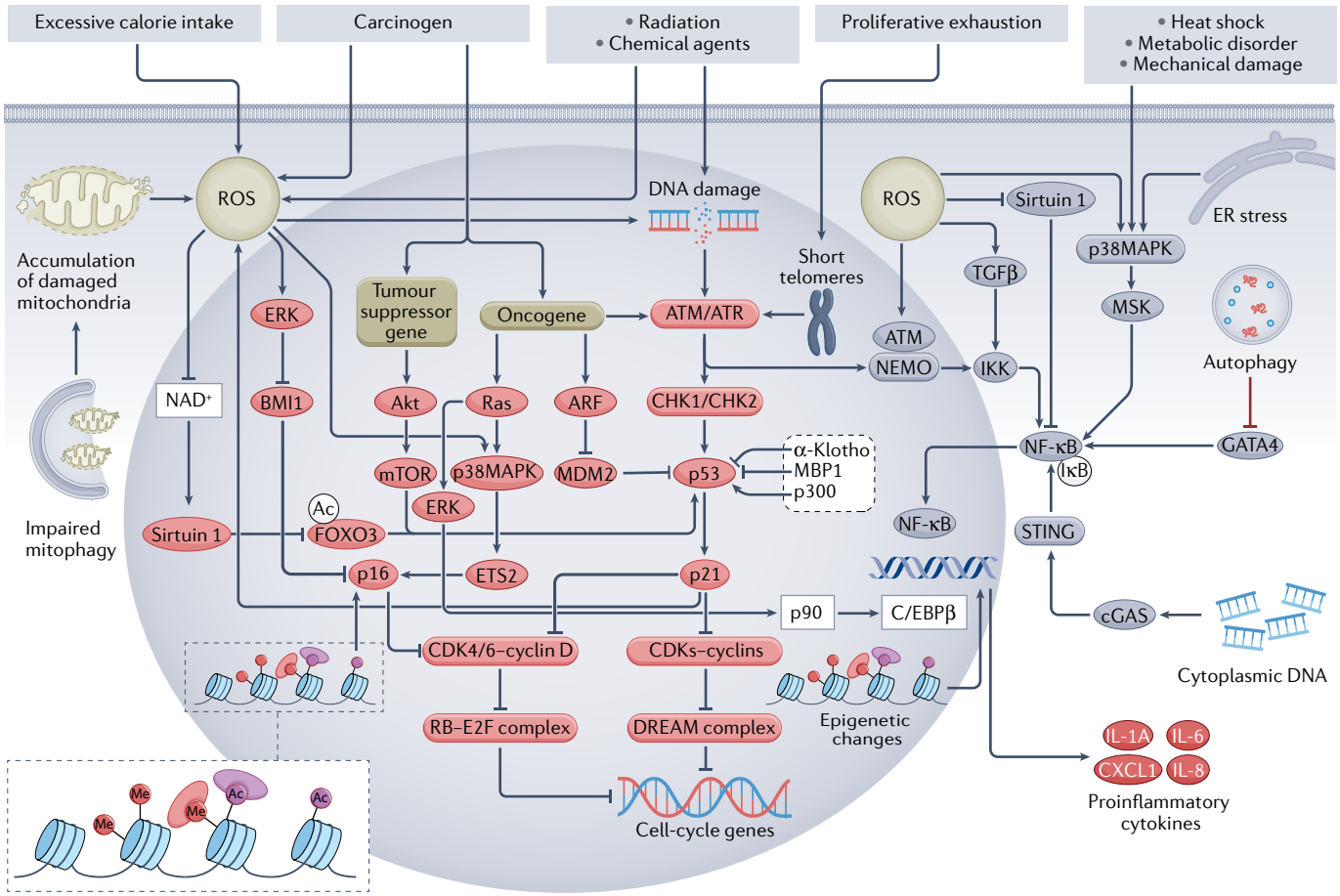

Fig. 1 | **Mechanisms of cellular senescence and the SASP.** DNA damage secondary to radiation, chemical agents or accumulation of reactive oxygen species (ROS) is the main cause of cellular senescence-inducing stress. Proliferation-induced telomere shortening can also activate the DNA damage response, which in turn leads to activation of the p53–p21 pathway, inhibition of cyclin-dependent kinase (CDK)–cyclin complexes and formation of the DREAM complex, which represses cell-cycle genes, leading to cell-cycle arrest and senescence. Activated p21 can also induce further ROS production, forming a vicious circle. In addition, impaired mitophagy can lead to mitochondrial dysfunction and excessive ROS production. ROS can induce senescence independently of the DNA damage response by activating the p16–RB pathway via activation of ERK, which inhibits BMI1 and thereby enables activation of p16, and by activating p38MAPK signalling, which upregulates ETS2 and in turn activates p16, and by inhibiting NAD^+, which leads to reduced expression of sirtuin 1 and activation of FOXO3, which activates p53. P16 inhibits the formation of CDK4/6–cyclin D complexes and thereby promotes formation of the RB–2F complex, which inhibits the transcription of cell-cycle genes. Oncogene activation can activate the p53–p21 pathway not only via the DNA damage response, but also via the ARF–MDM2 signalling. In addition, oncogene activation can activate the p16–RB pathway via p38MAPK signalling. Loss of tumour suppressor genes induces senescence via Akt–mTOR signalling, which activates p53. Other factors that regulate the p53–p21 pathway include α-Klotho, MBP1 and p300. Epigenetic alterations such as methylation (Me) and acetylation (Ac) can induce senescence through the p16–RB pathway. NF-κB signalling regulates the senescence-associated secretory phenotype (SASP) and together with the transcription factor C/EBPβ, co-activates promoters of SASP genes, such as those that encode pro-inflammatory cytokines. The DNA damage response protein ATM together with NEMO activates the NF-κB–C/EBPβ signalling pathway. ROS can activate the SASP not only by promoting nuclear translocation of NEMO and activation of ATM, but also by inhibiting sirtuin 1 and activating p38MAPK and TGFβ, which in turn activate NF-κB. Heat shock, metabolic disorders, mechanical damage and endoplasmic reticulum (ER) stress can also activate the NF-κB–C/EBPβ pathway via p38MAPK signalling. Cytoplasmic DNA accumulation can trigger aberrant activation of cGAS-STING cytoplasmic DNA sensors and promote the SASP via activation of NF-κB. Impairment of autophagy hampers degradation of the transcription factor GATA4, which activates NF-κB and leads to initiation of the SASP. Notably, oncogenic Ras can activate C/EBPβ via ERK–p90 signalling and histone epigenetic changes can regulate the SASP independently of the NF-κB–C/EBPβ pathway. ARF, ADP-ribosylation factor; BMI1, B lymphoma Mo-MLV insertion region 1 homologue; cGAS, cyclic GMP–AMP synthase; CHK, checkpoint kinase; ERK, extracellular regulated protein kinases; ETS2, E26 transformation-specific proto-oncogene 2; E2F, early 2 factor; FOXO3, forkhead box protein O3; IKK, IκB kinase; MDM, mouse double minute 2; MSK, mitogen- and stress-activated protein kinase; NEMO, NF-κB essential modulator; STING, stimulator of interferon genes.

Table 1 | **Inducers of cellular senescence**

Inducer	Senescence pathway
Replicative stress	Cell proliferation leads to telomere shortening, which hinders DNA copying and can activate the DNA damage response, resulting in replicative senescence.
Oncogene activation	Activation of oncogenes can directly induce the DNA damage response or activate MDM2–p53–p21 or p38AMPK–p16 signalling pathways, which lead to cellular senescence.
Loss of tumour suppressor gene	Loss of a tumour suppressor gene can induce cellular senescence via activation of Akt–mTOR–p53 signalling.
Development	Senescence markers can be observed in the limbs, nervous system, gut endoderm and mesonephros; p21 has an important role in development-associated senescence.
Epigenetic influences	Epigenetic modification of histones induces senescence by activating p16–RB signalling.
Mitochondrial dysfunction	Mitochondrial dysfunction leads to overproduction of reactive oxygen species, which cause DNA damage and activate the DNA damage response or ERK–p16–RB signalling.
Chemotherapeutic drugs or ionizing radiation	These therapies induce DNA damage and the DNA damage response, which lead to cellular senescence.

p16–RB and TAp63–p21–RB pathways are involved in oncogene-induced senescence and suppression of tumorigenesis[32,33]. In mice, inactivation of heat shock factor 4 (HSF4) enhanced senescence and suppressed tumorigenesis independently of p53 via a mechanism that is dependent on p21 and p27 (REF.[34]). Reactive oxygen species (ROS)-induced senescence in cancer cells is dependent on $p16^{INK4A}$, $p21^{Waf1/Cip1}$ and/or $p27^{Kip1}$, but does not require p53 (REF.[35]).

The high-mobility group box-containing protein 1 (HBP1) transcription factor is a novel activator of p21 (and thereby senescence) that acts by attenuating degradation of p53 or by regulating Wnt–β-catenin–EZH2 signalling independently of p53 (REF.[36]). Wnt signalling also has a role in inducing the senescence of thyroid cancer cells[37]. In Ras-induced breast cancer, the growth arrest and DNA damage 45a protein was found to suppress tumorigenesis by inducing senescence and apoptosis via p38 MAPK signalling[38]. Other mechanisms, including IL-6–STAT3 signalling and autophagy, also have roles in tumorigenesis and senescence, but how they contribute requires further investigation.

Although senescence can prevent cancer by inducing cell-cycle arrest, evidence suggests that the SASP-evoked chronic inflammatory microenvironment can promote tumorigenesis. For example, knockdown of polypyrimidine tract-binding protein 1 (PTBP1) in a mouse model inhibited the SASP and prevented the growth of inflammation-driven advanced liver tumours[39]. The Ras oncogene-activated chemokine growth-regulated alpha protein can reprogram the stromal microenvironment by inducing senescence of fibroblasts and thereby promote ovarian tumorigenesis[40]. p38–MAPK and p44–p42 MAPK–ERK signalling also foster a pro-inflammatory and growth-stimulatory microenvironment[41] by mediating post-transcriptional regulation of SASP mRNAs, including IL-6, IL-8, GM–CSF and CCL20 mRNA[42]. IL-6 induces increases in suppressive myeloid cells, which inhibit antitumour T cell responses[43]. In addition, the SASP factors CXCL1 and matrix metalloproteinase 14 (MMP14) stimulate ovarian and hepatocellular carcinoma by regulating p65 and facilitating invasion, respectively[44], whereas IL-6, MMP3, MMP9 and CXCL10 contribute to the development of squamous cell skin carcinoma[41]. The pro-tumorigenesis SASP factor osteopontin is regulated by C/EBPβ and the transcription factor Myb[45], and has roles in the regulation of processes that are critical for cancer progression, including immune responses, cell adhesion and cell migration. Moreover, colon tumour cells can secrete phospholipase-D2, which induces senescence of neighbouring fibroblasts[46]. Senescent fibroblasts in turn release the SASP factors HGF, MIF and CCL2, which activate Wnt signalling and increase the stem cell properties of colon tumour cells[46].

The metalloproteinase inhibitor TIMP1 is an important molecular switch that determines the effects of senescence in prostate cancer. TIMP1 inactivation promotes metastasis through the activation of MMPs, which leads to upregulation of secreted factors that promote tumour progression, including FGF1, growth/differentiation factor 15 and insulin-like growth factor-binding protein 5 (REF.[47]). Other factors such as COX2 also regulate the SASP composition and contribute to tumorigenesis[48].

Senescence also has important roles in the initiation, progression, chemoresistance and prognosis of kidney cancers. Repression of phospholipase A2 receptor (PLA2R1) by the oncogenic HIF2α–MYC pathway increases kidney cell resistance to senescence and accelerates the growth of renal cell carcinoma (RCC)[49]. Poly(C)-binding protein 4 (PCBP4) and p53-bound enhancer regions 2 (P53BER2) have been identified as renal tumour suppressors that induce senescence by upregulating p53 expression[50,51]. RCC is characterized by high expression of xeroderma pigmentosum complementation group-F (XPF) and endoglin, which increase its chemoresistance. Knockdown of XPF or endoglin increased the senescence and reduced the chemoresistance of renal cancer cells[52,53]. Conversely, inactivation of *TP53* (which encodes p53) increased senescence and promoted an inflammatory microenvironment, which facilitates RCC aggressiveness and metastasis[54]. The mechanisms that tip the balance between the pro-tumorigenic and anti-tumorigenic functions of senescence are unclear and likely cell type specific. Moreover, different levels of oncogene activation cause disparate senescence trajectories such that transient senescence might be tumour suppressive[55], whereas prolonged or permanent senescence might promote proliferation, stemness, migration and invasion of cancer cells[56]. Additional studies are needed to identify the stage at which senescence might become maladaptive and warrant inhibition.

Immunosenescence. In healthy individuals, immunosenescence begins at around the age of 50 years[57] and results in impaired vaccine responses and increased susceptibility to infection, autoimmunity and cancer, as well as chronic inflammation. A reduction in autophagy

Somatic hypermutation
A programmed process of adaptation to new foreign elements (such as microbes) whereby changes are introduced to the nucleotide sequences of immunoglobulin genes during B cell development.

Efferocytosis
The process by which apoptotic cells are removed by phagocytic cells.

is an important mechanism that contributes to immunosenescence. Impairment of autophagy hinders the degradation of damaged mitochondria, resulting in the accumulation of ROS and DNA damage[58].

Patients with CKD show accelerated immunosenescence that mimics that of elderly individuals[59]. The resulting chronic inflammation is associated with loss of kidney function[60] and complications such as cardiovascular disease and infections[61]. However, immunosenescence can be beneficial in settings where immune cell activation is undesirable. For example, immunosenescence of $CD4^+$ T cells in transplant recipients facilitates acceptance of kidney allografts[62].

In people aged >60 years, naive T cells decline, whereas memory T cells increase and show loss of CD28 and elevated expression of the senescence markers CD57 and KLRG1 (REF.[63]). Although age-related changes are more common in $CD8^+$ T cells, an increased frequency of highly differentiated $CD4^+$ T cells that express NKG2D has been reported in elderly people[64]. Senescent T cells express pro-inflammatory cytokines, exhibit shortened telomeres[63] and might negatively impact human longevity. The offspring of centenarians, who presumably carry longevity-favouring genes, have fewer senescent T cells than age-matched controls[65]. Increased expression of T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain is associated with T cell exhaustion and senescence[66].

Senescent B cells are also prevalent in the elderly. Memory B cells fill the immunological space, whereas naive B cells markedly decrease, resulting in a reduced ability to respond to new pathogens[67]. Senescent B cells also have a decreased capacity for somatic hypermutation[68] and thus show blunted antibody responses to infectious agents. The decrease in naive B cells is caused mainly by a decline of B cell lymphopoiesis, secondary to increased apoptosis of B cell precursors, impaired responsiveness to IL-7 and decreased potency of haematopoietic stem cells[69]. Moreover, senescent B cells, characterized by reduced expression of CD23, CD21 and CD35, accumulate in the bone marrow and suppress B cell lymphopoiesis in aged mice[70].

Although the number of natural killer (NK) cells does not necessarily decline with ageing, their function deteriorates owing to the altered expression of various cytokines[71], which reduces their ability to recognize infected and malignant target cells.

Senescent macrophages express high levels of the senescence-related markers $p16^{INK4a}$ and SABG[72]. They release pro-inflammatory cytokines that promote chronic inflammation and have an overabundance of ROS, which reduces their propensity for efferocytosis[73]. Expression of activating transcription factor 3 (REF.[74]) and bromodomain-containing protein 4 (REF.[75]) may contribute to macrophage senescence. Intriguingly, mature macrophages share inherent phenotypic similarities with senescent cells in terms of their signalling pathways, gene expression, metabolism and levels of organelles such as lysosomes[76]. The suitability of $p16^{INK4a}$ and SABG as markers for macrophage senescence has been questioned because these markers are also upregulated in response to stimuli that induce macrophage polarization to a M2 phenotype, such as IL-4 and IL-13 (REF.[77]). Furthermore, activated macrophages in atherosclerotic lesions resemble senescent cells and show lipid accumulation, SASP and a persistent DDR[75]. Hence, a senescence-like phenotype in macrophages might constitute a physiological activation state adopted in response to challenge rather than true senescence. Notably, cancer cells with chemotherapy-induced senescence undergo transcriptional changes linked to phagocytosis and can engulf adjacent cells[78]. Clearly, the interplay between truly senescent cells and senescent-like macrophages warrants additional studies.

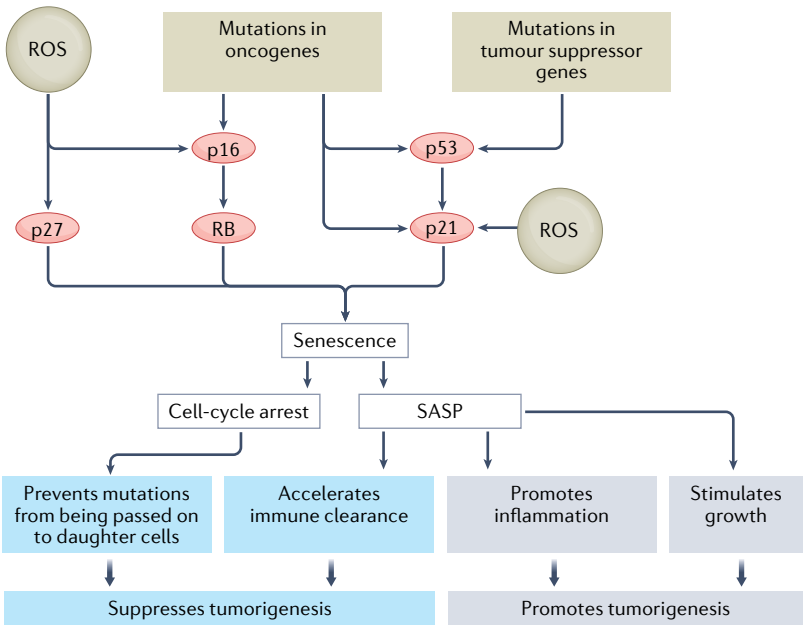

Fig. 2 | **Cellular senescence in cancer.** Most carcinogenic mutations induce senescence through the p53–p21 and p16–RB pathways, although some mutations activate p21 directly. Reactive oxygen species (ROS)-induced senescence in cancer cells is mainly dependent on p16, p21 and/or p27. Senescence-induced cell-cycle arrest can prevent mutations from being passed on to the next generation of cells and accelerate immune clearance, resulting in suppression of tumurigenesis. However, the senescence-associated secretory phenotype (SASP) also contributes to a pro-inflammatory and growth-stimulatory microenvironment that can promote tumour development.

Stem cell senescence. Stem cells can release paracrine factors to repair injured tissues and organs and have an important role in regeneration. However, risk factors such as ageing, irradiation, and metabolic disorders can induce stem cell senescence (SCS) and dysfunction, which contributes to age-related diseases[79]. For example, senescent $p16^{INK4a}$-positive MSCs contribute to osteoarthritis by secreting DKK1, which triggers premature bone remodelling and cartilage degradation[80]. Senescent MSCs also lose their cartilage regenerative properties.

The mechanisms that underlie SCS are complex. Stressors including ROS can promote MSC senescence induced by ageing, expansion and hypoxia[81], and transforming growth factor β1 (TGFβ1) can induce SCS by increasing ROS production and upregulating $p16^{INK4A}$ and p21 (REF.[82]). In addition, non-coding RNAs regulate SCS. For example, miR-152 induces human dental pulp SCS[83], whereas the long non-coding RNA Hnscr attenuates hypothalamic SCS[84]. Haematopoietic SCS is

regulated by the endogenous Ewing sarcoma gene[85]. Low mitochondrial NAD^+ levels contribute to bone-marrow MSC senescence, which may be associated with reduced expression of sirtuin 1 and sirtuin 3 (REFS.[86,87]). Notably, ageing is linked to compensatory overexpression of sirtuin 6 in bone marrow MSCs, which decreases SCS and confers oxidative stress resistance[88]. Several transcription factors also regulate SCS of different origins. NANOG delays senescence in hair follicle-derived MSCs[89], GATA6 and SOX11 regulate bone-marrow SCS[90], MDM2–p53 signalling has a vital role in epidermal SCS[91] and the ROR2–STK4–FOXO1–SMS1 pathway regulates dental pulp SCS[92]. Endometrial SCS, which is associated with recurrent pregnancy loss, may be mediated by SERPINB2–sonic hedgehog signalling[93].

The role of autophagy in hypoxia and D-galactose-induced SCS is controversial. Some studies have shown that autophagy inhibits MSC senescence[94]; however, high glucose-induced autophagy increases bone-marrow SCS[95]. Thus, the role of autophagy in SCS likely depends on the context. We found that fat-tissue-derived MSC senescence was elevated in patients with obesity[96] but not in patients with diabetic kidney disease compared with age-matched healthy individuals[97]. Hence, SCS is not necessarily a uniform finding in human disease.

Redox control of senescence. Oxidant stress caused by overproduction of ROS and/or deficiency of antioxidant defences can induce cellular senescence. Many factors can interrupt redox homeostasis and hence induce DNA damage, including high glucose, radiation and expression of oncogenes[98]. For example, autophagy-deficient melanocytes and keratinocytes with an overabundance of ROS become senescent[99,100] and lactose and fumarate can induce fibroblast and renal cancer cell senescence by inducing oxidative stress[101]. Downregulation of cathepsin-D not only increases ROS generation, but also inhibits the activity of nuclear factor erythroid 2-related factor 2 (NRF2)[102], which has an important role in antioxidant defence and prevention of senescence. The integral membrane protein caveolin 1 inhibits the activity of the antioxidant enzyme thioredoxin reductase 1, inducing ROS accumulation and cellular senescence[103]. In turn, oxidative stress has a positive feedback effect on caveolin 1 by activation of p38MAPK signalling, forming a vicious cycle[104]. Loss of the anti-apoptotic protein BCL-2 also disrupts redox homeostasis and impairs angiogenic function in senescent endothelial cells[105]. Interestingly, H_2 produced by gut bacteria can scavenge the hydroxyl radical and relieve oxidative stress, resulting in suppression of cellular senescence[106]. Many other factors also modulate the senescence process by regulating cellular redox status.

In addition to directly inducing DDR-mediated senescence signalling, ROS can regulate Akt signalling, an important pathway to cellular senescence, by modulating the expression of several microRNAs including miR-181a and miR-182 (REF.[107]). Redox homeostasis is also key to maintaining the integrity of telomeres[108]. Ultimately, telomere shortening and loss hinder DNA copying and lead to replicative cellular senescence.

Elevated oxidative stress can also induce senescence accompanied by nuclear shape alteration (and thereby DDR) through overexpression of lamin B1 (REF.[109]) and can modulate the SASP by regulating the homeostasis of the SASP initiators, IL-1α and Ca^{2+} (REFS.[110,111]). In patients with systemic sclerosis, oxidative stress induces fibroblast senescence and contributes to pro-fibrotic and pro-inflammatory phenotypes[112]. By contrast, senescent fibroblasts exhibit antifibrotic phenotypes during normal wound healing. This discrepancy might be the result of the intrinsic characteristics of dermal fibroblasts in patients with systemic sclerosis, which have high intracellular ROS levels, reduced proliferation rate, impaired bioenergetic functions and increased DNA damage and DDR compared with healthy fibroblasts[112]. Conceivably, differing features such as ROS levels may determine the propensity of fibroblast senescence to be linked to a pro-fibrogenic or anti-fibrogenic phenotype.

Clearly, increased oxidative stress has a key role in the development of cellular senescence. The ability of exogenous antioxidant strategies to attenuate senescence in selected cells without impairing fibroblast function remains to be explored.

Cellular alterations in senescence

Morphological alterations. Cellular senescence is characterized by morphological alterations that are controlled by molecular changes such as increased p53 expression and inhibition of RB phosphorylation. Generally, senescent cells have a larger and flatter body than healthy cells with a spread shape[113]. These changes might be due to cell-cycle arrest in the G_1/G_2 phase following the generation of intracellular content for cell division and its accumulation in the cytoplasm and nuclei. Enlarged and flat cells are associated with enhanced formation of actin stress fibres owing to upregulation of cofilin 1 (REF.[114]).

Senescent cells are also characterized by large nuclei, multi-nuclei[115] and chromatin reorganization, including chromosome condensation, redistribution and the formation of heterochromatic foci, possibly secondary to loss of lamin B1 from the inner surface of the nuclear envelope[116]. Vacuolization, granularity and intracellular debris in the cytoplasm of senescent cells have also been reported[117,118]. Some organelles show abnormal morphological changes, such as swollen mitochondria, increased lysosome numbers[119] and endoplasmic reticulum expansion, which is regulated by the transcription factor ATF6α[120]. Senescent morphology correlates with enhanced actin stress fibres and redistribution of focal adhesion plaques, which may permit the enlarged cells to adhere and spread and contribute to their capacity for tumour suppression[121].

In addition, specialized senescent cells may exhibit distinct morphological characteristics. For example, senescent auditory cells are ramified[122], senescent microglia have large bodies with a reduced number of processes[123] and senescent bone marrow-derived MSCs have a polygonal phenotype[124]. Kidney cells seem to share typical phenotypic characteristics of senescence. In aged kidneys, tubular cells, and to a lesser degree glomerular and interstitial cells, show as a diminished

Ramified
Used to describe cells that have long branch-like processes.

proliferative response that correlates with markers of cellular senescence, including $p16^{INK4a}$, SABG and telomere shortening[125]. Senescent glomerular endothelial cells drive podocyte injury, inducing reorganization of the F-actin cytoskeleton and a decreased number of focal adhesion processes[126]. Cellular morphological characteristics in different organ systems likely reflect prevailing local mechanisms of cellular damage.

Functional alterations. Senescent cells have abnormal function and are unable to proliferate owing to their stable cell-cycle arrest in the G1/G2 phase. Senescence thereby reduces the number of cells that are available to execute normal tissue functions. An increased rate of senescent cell production (due to increased exposure to stressors) and a reduced rate of senescent cell removal (due to deregulated immunosurveillance together with pro-survival signals and resistance to apoptosis) lead to the accumulation of these cells in organs with ageing[127]. In turn, senescent cells promote degeneration, ageing, systemic chronic inflammation — termed inflammaging — and age-related diseases due to the release of SASP factors and the resulting spread of senescence to previously non-senescent cells[128]. Congruently, senescent cells accumulate at the sites of age-related degenerative or preneoplastic pathology[129]. In addition to the SASP, the complement system contributes to inflammaging by recruiting macrophages and increasing the release of ROS, TNF and IL-6 (REF.[130]), which are important inducers of senescence.

SASP factors can exert both beneficial and deleterious functions. Beneficial effects of SASP factors include the roles of CXCL5 in embryonic development[131], PDGF-AA in tissue repair[132], IL-6 in cellular reprogramming[133], MMP1 and MMP33 in fibrosis resolution[20] and the anti-tumorigenic properties of CCL2 (REF.[134]). Notably, SASP factors also recruit immune cells to clear pre-malignant senescent cells. This process of senescence surveillance is an important contributor to the anti-tumorigenic properties of senescent cells[135]. Deleterious effects of SASP factors include the roles of IL-8, IL-10 and TNF in inflammation[136], PDGF-BB in fibrogenesis[137] and MMP1 and MMP3 in tumorigenesis[138]. Some SASP cytokines such as IL-6, IL-8 and CCL2 also promote vascular smooth muscle cell calcification and impair insulin sensitivity[139,140].

The SASP is regulated via complex DDR-dependent and DDR-independent mechanisms (FIG. 1). Activated NF-κB and the transcription factor, CCAAT/enhancer-binding protein-β (C/EBPβ) co-activate promoters of SASP genes[141]. However, NF-κB-independent SASP regulation mechanisms also exist. For example, cytoplasmic DNA accumulation can cause aberrant activation of cGAS-STING cytoplasmic DNA sensors and promote SASP by induction of interferon-β[142]. Downregulation of the lamin B receptor, which regulates heterochromatin organization, is necessary for the generation of cytoplasmic DNA[143]. Factors that are linked to infections, such as lipopolysaccharide and SARS-CoV-2 S antigen, can increase the release of pro-inflammatory, pro-fibrotic and pro-apoptotic SASP factors by senescent cells[144].

Hallmarks and markers of senescence

SABG activity is a widely used marker of senescence in tissues and cell cultures. The activity of SABG can be detected at pH 6 (the intra-lysosomal pH of senescent cells), whereas the activity of acidic β-galactosidase can be detected at pH 4 (the intralysosomal pH of non-senescent cells)[145]. However, SABG has some limitations as a marker of senescence. For example, many apoptotic non-senescent cells in developing limbs and healthy neurons during early embryonic development are SABG positive[146] and cell density might influence SABG staining regardless of cell proliferation status[147]. These findings suggest that SABG is not a sufficiently robust and specific marker of senescent cells.

Gene and protein components of senescence-related signalling pathways such as p16 and p21 are canonical markers of senescence[148,149]. Expression of Met is also considered to be a marker of cellular senescence[150] and the accumulation of nuclear globular actin accumulation has been reported to be a more sensitive marker of cellular senescence than SABG activity[151]. Other markers of senescence include telomere shortening[152], the DNA double-strand-break marker H2AX[153], typical chromatin changes such as senescence-associated heterochromatin foci[154], cytosolic double-stranded DNA and miR-146a[155,156]. Decreased cellular proliferation potential (which can be measured using BrdU or EdU incorporation assays) and increased apoptosis resistance (for example, as a result of upregulation of BCL proteins) also occur in some types of senescent cells[157].

Potential blood or urine biomarkers of senescence include plasma angiopoietin-like 2, growth/differentiation factor 15, stanniocalcin 1 and serine protease inhibitors, serum T-kininogen and urinary 8-oxoguanosine[11,158–160]. Activin A is normally only expressed during embryonic development, but is copiously expressed in injured and senescent kidneys and can be detected in the plasma and urine of patients with kidney disease[161]. SASP signatures enable the detection and characterization of cellular senescence in vivo but need to be defined in specific biological contexts as they might overlap with inflammatory profiles that are not associated with senescence. Extracellular vesicles can be isolated from urine or peripheral blood and analysed as an index of parent cell senescence; for example, increased levels of urinary $URAT1^{+}p16^{+}$ extracellular vesicles reflect increased proximal tubular cell senescence[162].

Several markers characterize specific senescent tissues or cells. For example, loss of EPC1 expression is a marker of senescence in human dermal fibroblasts[163]. In T cells, expression of NKG2D, KLRG1, CD57 and CD28 might reflect senescence[64,164,165]. NKG2D[166] and activin A[161] are potential markers of senescence in kidney tissue. Spectrin–phaemoglobin crosslinking is an important feature of senescence in red blood cells[167], SRSF1 has been postulated to be a key marker of endothelial senescence[168] and maspin is a marker of senescence in oral premalignant lesions[169].

Endogenous autofluorescence of MSCs is considered to be a useful marker to rapidly determine their senescent status in vitro[170]. However, the small number

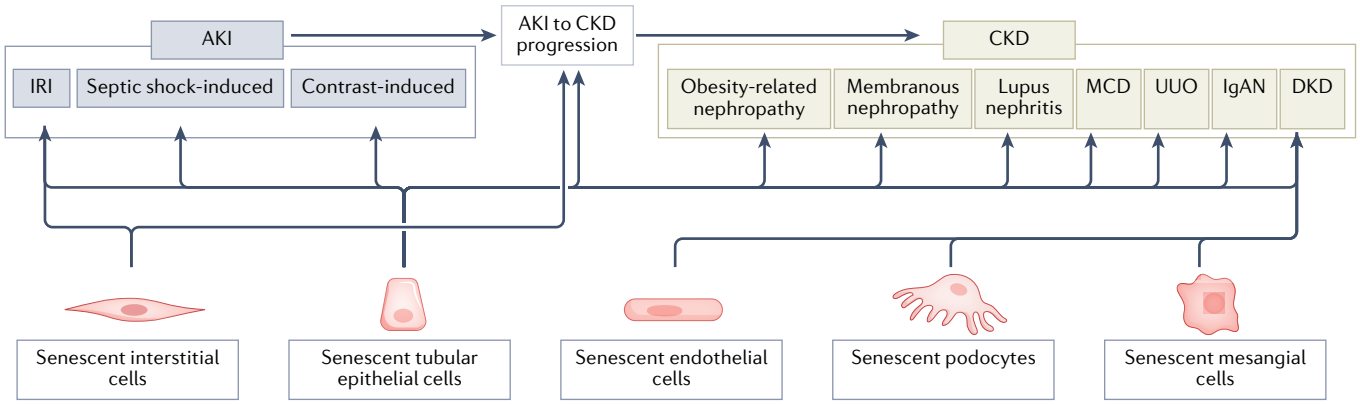

Fig. 3 | **Cellular senescence in kidney diseases.** Cellular senescence is involved in the pathogenesis of acute kidney injury (AKI) and many types of chronic kidney disease (CKD). Data from animal models suggest that senescent interstitial and tubular epithelial cells contribute to ischaemia–reperfusion injury (IRI), septic shock-induced AKI and contrast-induced AKI, as well as to AKI-to-CKD progression. Tubular epithelial cell senescence has also been detected in many forms of CKD, including obesity-related nephropathy, membranous nephropathy, lupus nephritis, minimal change disease (MCD), unilateral ureteral obstruction (UUO), IgA nephropathy (IgAN) and diabetic kidney disease (DKD). Endothelial cell, podocyte and mesangial cell senescence might also contribute to DKD.

of senescent cells relative to quiescent cells, robust tissue autofluorescence, and low penetration of fluorescence signals hamper the detection of senescent cells in vivo using fluorescence-based imaging. Near-infrared imaging methods are not clinically applicable because of the limited availability of high-performance second near-infrared region (NIR-II) fluorophores with high brightness and biocompatibility as well as the long-term health risks of using non-biodegradable quantum dots and lanthanide-doped nanoparticles. Positron emission tomography-based methods of detecting senescent cells are being investigated in animal studies but will require the development of sensitive clinical probes[171]. Advances in non-invasive imaging methods may enable the detection and spatial allocation of senescence-prone regions that warrant intervention.

Senescence in kidney diseases

Kidney cell senescence was first described in 1992 (REF.[172]). In addition to its role in physiological kidney ageing, senescence has important roles in the development of CKD and acute kidney injury (AKI) (FIG. 3). Interventions that clear senescent cells, including senolytic drugs, are therefore promising novel treatments for kidney diseases.

Acute kidney injury. Emerging evidence indicates that senescence contributes to the progression of AKI and that senescence inhibition can promote kidney recovery. For example, inhibition of tubular cell senescence using lipoxin A4 restored renal function in a rat model of septic shock-induced AKI[173]. Similarly, in a rat model of contrast-induced AKI, pre-treatment with paricalcitol before contrast medium administration reduced cellular senescence (that is, expression of SABG and $p16^{INK4A}$) and tissue damage and prevented kidney dysfunction[174]. Notably, patients aged over 70 years have a 3.5-fold higher incidence of AKI than younger individuals[175]. This increased incidence has been linked to immunosenescence, amplification of the SASP[176], and/or downregulation of the geroprotective protein α-Klotho[177]. Urine and plasma levels of p21 correlate with renal cortical expression of this protein and could be a useful non-invasive biomarker of AKI and kidney ageing[178].

The complement system (C5a), DNA methylation, Wnt4–β-catenin signalling and ROS have been implicated in the development of cellular senescence in AKI[179,180]. Senescence has been shown to reduce the regenerative capacity of tubular, glomerular and interstitial cells[181] and to delay recovery from AKI induced by ischaemia–reperfusion injury (IRI) in mice[182]. Following IRI, markers of kidney cell senescence (Bax and p16 mRNA) peaked at day 12, suggesting an increase in senescent cells in the chronic phase after AKI that might contribute to maladaptive repair and progression to CKD[183]. Treatment with nicotinamide mononucleotide reduced tubular cell DNA damage and senescence and attenuated renal fibrosis in mouse models of ischaemic AKI[184]. Increasing evidence suggests that cellular senescence might also have beneficial effects in AKI. A small-molecule inhibitor of CDK4 and CDK6 induced proximal tubule cell-cycle arrest and ameliorated kidney injury in a mouse IRI model[185]. Moreover, we found that inhibition of senescence within the first week after induction of renal ischaemia in a mouse model impeded functional recovery (measured using renal perfusion and plasma cystatin-c levels)[186], suggesting a protective role early in the process of AKI. Delineating the time course of kidney injury and the role of cellular senescence during each phase might identify a therapeutic time window to target senescence and interrupt the development of AKI.

Chronic kidney disease. CKD is increasingly recognized to mimic age-related diseases and senescence and the SASP are important drivers of CKD progression[187] (FIG. 4). CKD can accelerate the senescence of immune, endothelial and vascular smooth muscle cells via a process known as uraemia-associated ageing[188,189], potentially constituting a feed-forward mechanism of

Geroprotective protein
A protein that has anti-ageing effects.

cellular damage. Immunosenescence in CKD manifests as an increased proportion of terminally differentiated T cells, telomere shortening of mononuclear cells, low thymic output[189] and reduced immune-mediated clearance of senescent kidney cells, which promotes CKD progression.

The mechanisms that underlie CKD-induced senescence include hyperphosphataemia, a common complication of CKD that elicits senescence in myoblasts[190], endothelial cells[191] and aorta smooth muscle cells[192] and contributes to sarcopenia and vascular calcification. Furthermore, uraemic toxins have been implicated in the senescence of proximal tubular cells[193]. Tubular epithelial cell senescence can be induced by inhibition of AMPK–mTOR signalling[194], activation of the Wnt–β-catenin pathway[195] or overexpression of Wnt9a[196], and promotes epithelial to mesenchymal transition and consequent fibrosis. α-Klotho, an endogenous antagonist of Wnt–β-catenin signalling, was downregulated in unilateral ureteral obstruction, adriamycin nephropathy, and IRI models of fibrotic kidney disease[197]. Senolytic combination therapy with dasatinib and quercetin alleviated kidney fibrosis in mouse models of chronic renal ischaemia[186] and abrogated the progression of AKI to CKD in mouse models of IRI and cisplatin-induced injury[198].

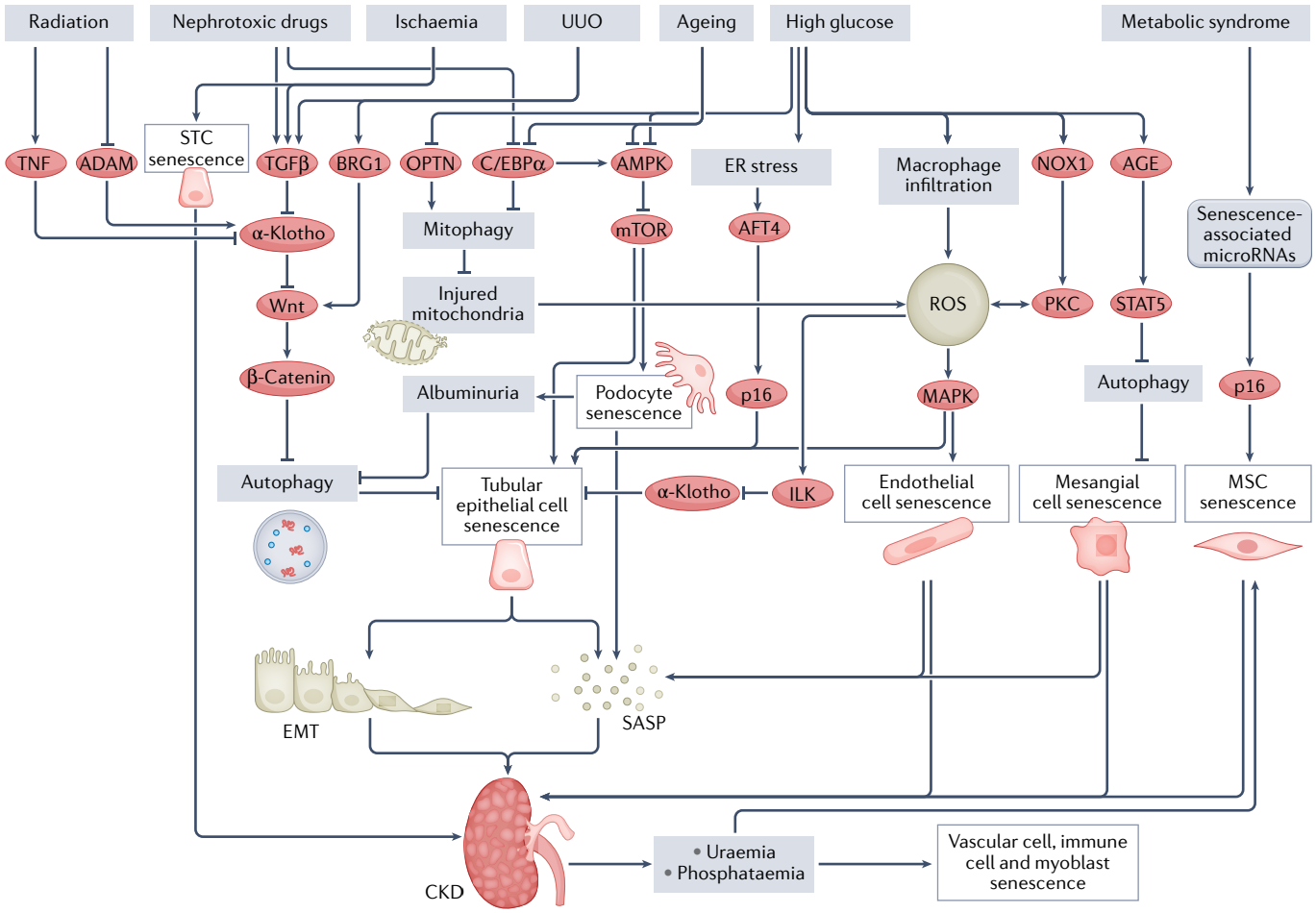

Fig. 4 | **Mechanisms of cellular senescence in chronic kidney disease.** Several stimuli can trigger the senescence of various kidney cell types through different pathways. High glucose levels result in macrophage infiltration into the kidney, mitochondrial dysfunction and activation of NOX1–PKC signalling, which lead to an increase in reactive oxygen species (ROS) and senescence of tubular epithelial cells and endothelial cells. High glucose can also induce senescence of tubular epithelial cells by provoking endoplasmic reticulum (ER) stress, which activates ATF4–p16 signalling. In addition, high glucose induces mesangial cell senescence via AGE–STAT5 signalling, which leads to the inhibition of autophagy and therefore results in the accumulation of injured mitochondrial and ROS (not shown). Nephrotoxic drugs and ageing can induce podocyte and tubular epithelial cell senescence via inhibition of C/EBPα, which leads to a reduction in AMPK–mTOR signalling. Ageing and high glucose can also induce tubular epithelial cell senescence by inhibiting AMPK. Nephrotoxic drugs, ischaemia, radiation and unilateral ureteral obstruction (UUO) activate Wnt–β-catenin signalling, which inhibits autophagy and therefore induces the senescence of tubular epithelial cells. Notably, ischaemia and metabolic syndrome can induce the senescence of kidney scattered tubule-like cells (STCs) and mesenchymal stem cells (MSCs), respectively, resulting in impairment of kidney repair, which promotes progression to chronic kidney disease (CKD). Chronic kidney cell senescence promotes epithelial-to-mesenchymal transition (EMT) and results in the senescence-associated secretory phenotype (SASP), which increases inflammation, eventually leading to the development of fibrosis and CKD. Furthermore, CKD can lead to uraemia-induced senescence of immune cells, endothelial cells, vascular smooth muscle cells and MSCs. CKD is also associated with hyperphosphataemia, which induces senescence in myoblasts, endothelial cells and vascular smooth muscle cells and thereby contributes to sarcopenia and vascular calcification. ADAM, A-disintegrin and metalloproteinase; ATF4, activating transcription factor 4; BRG1, brahma-related gene 1; ILK, integrin-linked protein kinase; NOX1, NADPH oxidase 1; OPTN, optineurin.

Podocyte senescence induces glomerulosclerosis in the ageing kidney via AMPK–mTOR signalling[199], whereas DKD or overfeeding can induce renal cellular senescence by decreasing sirtuin 1 expression[200]. In patients with DKD, the circulating senescence marker activin A is elevated[161] and p16 is upregulated in tubular epithelial cells[201]. In mice with streptozotocin-induced diabetes, glomerular endothelial senescence is driven by M1 macrophages and largely dependent on intracellular ROS[202]. High blood glucose also induces mesangial cell senescence by activating RAGE–STAT5 signalling, which inhibits autophagy[203] and therefore leads to accumulation of injured mitochondria and ROS, which are important inducers of senescence.

We detected cellular senescence (upregulation of p16, p19 and p21) in the kidneys of mice[186], pigs[204] and patients[186] with renal artery stenosis and observed that ischaemic renovascular disease induces senescence of renal scattered tubular-like cells, which impairs their reparative capacity[205]. Senescence of renal tubular epithelial cells promotes progression of immunoglobulin A (IgA) nephropathy[206] and the presence of $p16^{INK4a}$-positive cells in kidney biopsy samples from patients with lupus nephritis is associated with renal injury and a worse prognosis[207]. Elevated gene expression of the senescence markers *Tp16*, *Tp19* and *Tp53* was also observed in mice with obesity-induced kidney injury[208] and p16 expression was strikingly increased in biopsy samples from patients with glomerular disease[209]. Exposure of kidney cells to nephrotoxic factors including radiation[125], TNF[210], hypoxia or glucose oxidase[211,212] can induce cell-cycle arrest in vitro. Replicative senescence is also involved in the development of chronic allograft nephropathy[213]. The complement factor H-related genes *CFHR1* and *CFHR3* have been implicated in tubular cell senescence in allografts in transplant recipients with IgA nephropathy[214].

Extensive basic and clinical studies are required to elucidate the complex mechanisms of cellular senescence in CKD. Although these mechanisms are shared across many forms of kidney disease, the extent and unique features of cellular senescence likely vary with the severity and underlying aetiology of CKD.

Interventions targeting senescence

As cellular senescence has key roles in many age-related diseases, interventions targeting senescence, known as senotherapeutics, are potential therapies for these diseases (TABLE 2). The promise of such approaches is underscored by the observation that genetic animal models of senescent cell deficiency show improved recovery from kidney injury[215] and extended lifespan[128]. Existing senotherapeutic approaches include drugs that selectively eliminate senescent cells, known as senolytics, drugs that inhibit the SASP, known as senomorphics, exogenous cell-based products and non-pharmacological therapies.

Senolytic interventions. Senolytic drugs were developed to overcome the characteristic resistance to apoptosis of senescent cells by inducing pre-programmed cell death[216]. Quercetin, a natural flavonoid found in some fruit and vegetables, has been shown to eliminate senescent vascular smooth muscle and endothelial cells in animal models by inducing apoptosis through activation of AMPK[217,218], sirtuin 1–PINK1-mediated mitophagy[219] and NRF2–NF-κB[220] signalling. We found that quercetin blunted the expression of senescence markers in the kidneys of obese mice[208] and had beneficial, senescence-independent effects on cardiac function in mice fed a high-fat diet owing to pro-angiogenic activity[221], highlighting the multiple modes of action of senolytic drugs.

The plant flavonoid fisetin[222,223] and procyanidin C1, which is a flavonoid found in grape seeds, are also senolytics[224]. Herbal extracts can also have senolytic activity. For example, one of the best-known anti-ageing drugs, ginsenoside, is an extract of ginseng that prevents senescence of bone marrow MSCs by activating NRF2 and PI3K–Akt signalling[225]. Ginsenoside can also modulate the SASP, reduce inflammation, balance redox status and attenuate organ ageing[226,227]. These observations suggest that selected dietary interventions with senolytic effects could potentially halt the progression of senescence-associated CKD.

AP20187, an FK1012 analogue, selectively induced apoptosis of $p16^{Ink4a}$-expressing senescent cells in various mouse models, resulting in improvements in age-related brain inflammation, cognitive function and stenotic kidney function[186,228]. Navitoclax (also known as ABT-263) is an inhibitor of anti-apoptotic BCL-2 family proteins that induces apoptosis and exerts potent senolytic effects in ageing animal models and in some types of senescent cells in vitro[229,230]. Other BCL-2 family inhibitors, including A-1331852, A-1155463, EF24 and venetoclax, are also effective senolytics[6,231,232]. In addition, heat shock protein 90 inhibitors have senolytic activity[233] and radio-electric asymmetric conveyer technology was shown to be effective in reducing the senescence of cultured stem cells[234]. Notably, these interventions do not selectively target senescent cells, and thus can be associated with off-target adverse effects, such as abnormal embryo development, dysregulated wound healing and tumorigenesis.

Organ-targeted or cell-targeted approaches using protein-based or peptide-based carriers, nanoparticles, extracellular vesicles or other vehicles could increase the specificity, decrease the off-target effects and facilitate the clinical translation of senolytic interventions. Current strategies to selectively target senescent cells include conjugating toxic drugs to antibodies against the senescent membrane marker β2-microglobulin[235], which is upregulated via a p53-dependent mechanism, suggesting that it is a marker of stress-induced senescence. Another strategy involves activation of invariant NK T cells to improve immunosurveillance and removal of senescent cells[236]. Moreover, chimeric antigen receptor T cells that were engineered to specifically recognize the urokinase-type plasminogen activator receptor on the surface of senescent cells had senolytic effects in vitro and in vivo[237]. Finally, anti-ageing vaccines have been developed to target $CD153^+$ senescent T cells or $GPNMB^+$ senescent endothelial cells with promising results in obese mouse models[238].

Radio-electric asymmetric conveyer technology
A technology delivering very low-intensity radio-electric emission to generate microcurrents in tissues or culture media and thereby produce biological effects.

Table 2 | **Senotherapeutic approaches**

Senotherapeutic approach	Type	Examples	Refs.
Senolytic interventions	Apoptosis inducers	Quercetin, AP20187, navitoclax, A-1331852, A-1155463, EF24 and venetoclax, antibody-engineered toxic drugs, ginsenoside	6,186,217,225,230,231,235
	Immunotherapies	Chimeric antigen receptor T cells, activator of invariant natural killer T cells, vaccines targeting GPNMB (which is overexpressed in senescent cells)	236–238
Senomorphic drugs	SASP regulators	Metformin, ruxolitinib, rapamycin, resveratrol, melatonin, androgen, oestrogen, oestradiol, glucocorticoids	239,243,244,247,250,254–257
Stem cells and their products	Stem cells	Bone marrow MSCs, pluripotent stem cells, umbilical cord-derived MSCs	258,259,261
	Stem cell-derived extracellular vesicles	MSC-derived extracellular vesicles, dental pulp stem cell-derived extracellular vesicles, antler stem cell-derived extracellular vesicles	262,264,282
Non-pharmacological therapies	Lifestyle interventions	Habitual moderate exercise, healthy diet, calorie restriction	268,269,271,273
	Others	Fractional micro-needling radiofrequency treatment, radio-electric asymmetric conveyer technology	234,275

MSC, mesenchymal stem cell; SASP, senescence-associated secretory phenotype.

Senomorphic drugs. One of the best-studied senomorphic drugs is metformin, which reduces the incidence of age-related diseases and expands the lifespan of *Caenorhabditis elegans*, mice and patients with type 2 diabetes mellitus[239]. Metformin also enhances the anticancer efficacy of CDK4 and CDK6 inhibitors by modulating the SASP[240], inhibits endothelial senescence caused by high glucose-induced metabolic memory by regulating the sirtuin 1–p300–p53–p21 pathway[241], triggers immune-mediated clearance of senescent cells and restores tumour immunosurveillance[242].

Other senomorphic drugs include ruxolitinib, a JAK inhibitor that reduces inflammation and alleviates frailty in aged mice by suppressing inflammatory SASP factors[243]. mTOR inhibitors, such as rapamycin, inhibit senescence and suppress the SASP in endothelial cells[244] and fibroblasts[245] by inducing autophagy, thereby reducing the accumulation of damaged organelles. Activation of mTOR leads to peroxisome proliferator-activated receptor-γ coactivator 1β-dependent mitochondrial biogenesis, ROS production and persistent activation of the DDR[246]. Thus, inhibition of mTOR ameliorates cellular senescence.

Several herb extracts, such as resveratrol[247], also show anti-SASP activity. Furthermore, the small molecule ML324 that inhibits KDM4, which is involved in the epigenetic regulation of SASP genes, was shown to decrease the SASP in senescent tumour stromal cells[248]. However, this approach needs to be used cautiously to avoid adverse effects given the sometimes incongruent behaviours of tumour and stromal microenvironments[249] and possibly other cellular niches.

Some hormones also have senomorphic effects. For example, melatonin suppresses SASP gene expression by interrupting the recruitment of CREB-binding protein (CBP) by poly-(ADP-ribose) polymerase 1 (PARP1), which is a sensor of DNA damage[250]. Melatonin improves senescent T cell activity[251], alleviated cardiac mitochondrial dysfunction in a mouse model of accelerated senescence[252], and rescued MSCs from uraemic toxin-induced senescence in CKD[253]. Other hormones, including androgens[254], oestrogens[255], oestradiol[256] and glucocorticoids[257], can also modulate the release of inflammatory cytokines. However, glucocorticoids need to be used with caution as they can induce senescence in primary human tenocytes[257].

Stem cells and extracellular vesicles. In addition to many other salutary effects, stem cells and their extracellular vesicles can exert senolytic activity. For example, bone-marrow-derived MSCs decreased senescence and improved cardiac function in aged mice[258], pluripotent stem cells prevented stress-induced senescence in cardiomyocyte-derived cells[259] and human umbilical cord-derived MSCs protected rat kidneys from AKI-induced senescence[180]. We observed relatively modest senolytic efficacy of adipose-derived MSCs in post-stenotic mouse and human kidneys[260]. In contrast to these senolytic effects, human umbilical cord-derived MSCs increased splenic $CD4^+$ T cell senescence and alleviated symptoms of lupus in mice[261]. These differing findings suggest that the effects of MSCs are likely cell type and context dependent.

Stem cell extracellular vesicles have robust anti-senescence activity and might be less prone to rejection or tumour formation than their parent stem cells. MSC-derived extracellular vesicles inhibited oxidative stress-induced senescence in endothelial cells, promoted wound closure in ageing diabetic mice[262] and decreased myocardial senescence, possibly by improving the systemic inflammatory profile, in a pig model of metabolic renovascular disease[263]. Dental pulp stem cell-derived extracellular vesicles prevented irradiation-induced senescence in submandibular cells by reducing

Metabolic memory
The durable effect of prior hyperglycaemia on the initiation and progression of diabetic complications.

Tenocytes
Elongated fibroblasts and fibrocytes that reside between collagen fibres.

inflammation and oxidative stress[264] and extracellular vesicles from antler progenitor cells alleviated MSC senescence in aged mice[265].

The anti-senescence functions of stem cells and extracellular vesicles have been mainly attributed to their contents, which can regulate the SASP, repair damaged organelles and rescue the function of senescent cells. However, stem cells and their extracellular vesicles likely also have indirect effects on senescence as a result of restoring the tissue microcirculation, parenchymal cells and cellular functions and/or inhibiting immune cell activation. Their application as primary anti-senescence interventions might therefore be premature. To date, clinical trials using stem cells or their extracellular vesicles to target senescence have not been reported.

Lifestyle interventions. Several lifestyle factors might accelerate senescence. For example, sleep deprivation activates the DDR and promotes the SASP in humans[266], whereas a healthy lifestyle, such as habitual exercise and caloric restriction, retards ageing. Animal and human studies have shown that lifelong exercise or habitual moderate exercise in aged individuals have beneficial effects on immunosenescence and age-related diseases (for example, metabolic disorders and liver steatosis) by modulating mitochondrial function, inflammation, the SASP and lipolysis[267–269]. Overfeeding accelerates senescence in mice[270], whereas caloric restriction alleviates senescence in dogs[271] and in murine white adipose tissue[272]. These findings might constitute a key mechanism by which caloric restriction extends lifespan and retards age-related chronic diseases. Dietary interventions can also influence age-related health through epigenetic alterations and modification of the gut microbiota. For example, nutrients such as betaine, choline and folate promote epigenetic changes that blunt age-related changes and CKD by targeting methylome or chromatin, whereas excessive intake of sugar promotes progression of age-related diseases by decreasing microbial diversity in animal models[273].

Cumulative lifetime exposure to external stressors, such as temperature, oxygen levels and inadequate nutrition, elicit adaptive homeostatic mechanisms, including antioxidant and anti-inflammatory responses, by activating the NRF2–KEAP1 signalling pathway[274]. Modifying these exposures might offer new strategies for improving the health span and combatting CKD and could potentially have beneficial effects on cellular senescence.

Clinical trials. Clinical studies of senolytic therapies are relatively scarce compared with the numerous animal and in vitro studies, but have shown some success. For example, fractional micro-needling radiofrequency treatment effectively removed senescent keratinocytes and improved hyperpigmentation of aged skin[275] and treatment with dasatinib and quercetin reduced the levels of circulating SASP factors and the abundance of senescent cells in adipose tissue and skin in patients with diabetic kidney disease[276]. Raltegravir[277] decreased senescent T lymphocytes in treatment-suppressed people with HIV. A psychosocial intervention with horticultural therapy involving park visits and gardening activities over a 6-month period alleviated immunosenescence and chronic inflammation in older adults (aged 61–77 years), assessed as having reduced IL-6 levels and T cell exhaustion[278]. Hence, non-invasive and cost-effective strategies for improving well-being should be vigorously pursued.

Importantly, senotherapeutic approaches can have adverse effects. Some senolytic drugs, such as navitoclax, can induce neutropenia, trabecular bone loss and osteoprogenitor dysfunction[279,280]. Moreover, as SASP factors have many physiological roles, including immunosurveillance in tumorigenesis, the potential adverse effects of senomorphic drugs might outweigh their benefits and reduce the success of clinical trials. Furthermore, genes may dictate traits that provide survival benefits in one stage of life but become maladaptive in another phase, a phenomenon known as antagonistic pleiotropy. The effect of senolytic drugs on tumorigenesis might therefore be age-dependent and, given the role of cellular senescence in development, the effects of senolytic drugs might differ between early and later stages of life[281]. Notably, we found that premature delivery reduced the efficacy of senolytic drugs in a renal artery stenosis model[186], consistent with temporal (rather than trait dependent) antagonistic pleiotropy. Thus, administration of these drugs needs to be carefully timed relative to both the instigating insult and the developmental stage of the patient, as these factors might dictate potential sequelae.

Given that chronic conditions continually generate new senescent cells, the frequency of senotherapy also requires further exploration. A mouse study suggested that intermittent administration of senolytics could be particularly effective at alleviating physical dysfunction and increasing survival[128]. Combination approaches that use senolytics and anti-SASP interventions to target a broad range of cell types might be particularly powerful.

Finally, the success of clinical trials of senotherapeutics could potentially be maximized by screening participants prior to enrolment to enable selection of those showing evidence of cellular senescence. However, sensitive screening tools need to be developed and validated to enable selection of those participants who are most likely to benefit from the intervention.

Conclusions

Cellular senescence drives various pathological processes but also has important roles in physiology and homeostasis, particularly in embryonic development and wound healing. Although senescence contributes to the development of age-related diseases, immune system dysfunction and tumour progression, it is also an important mechanism that protects against tumorigenesis. Evidently, cellular senescence is a double-edged sword, emphasizing the importance of discerning physiological from pathological senescence and developing therapies together with context and time-dependent treatment strategies to suppress its harmful effects while permitting its beneficial functions. Targeted delivery of senolytic compounds to senescent cells might also help to minimize their adverse effects and enhance their

benefits. Although many senolytic therapies have been investigated in animal models and in vitro, clinical trials of targeted treatment strategies are needed to assess their safety and efficacy in patients.

As existing senescence indices may differ among conditions and organs, non-invasive methods of detecting senescence with high sensitivity and specificity are needed. Many inflammatory factors are also SASP components; therefore, their expression is not sufficient to identify cellular senescence. Urinary exosomes bearing specific markers are useful for detecting kidney senescence[162], but methods for their harvesting and characterization require standardization. Clinical end-points and indices of the therapeutic success of senotherapeutics are required for clinical trials. In the future, novel biomarkers of senescence could potentially be used to direct the management of patients who might benefit from attenuation of cellular senescence.

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