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Review article

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Translating cellular senescence research into clinical practice for metabolic disease

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Abstract

Translational research on cellular senescence has led to numerous early-phase clinical trials targeting senescent cells to treat, prevent or alleviate multiple disorders and diseases, including metabolic diseases and their comorbidities. Cellular senescence is a cell fate that occurs in response to stressors, including metabolic disruptions, and is one of the hallmarks (or pillars) of ageing. In their senescent state, cells cease proliferation and can develop a senescence-associated secretory and metabolic phenotype that contributes to the pathogenesis of metabolic dysfunction associated with obesity and ageing. Metabolic stress, which is central to the development of metabolic diseases, can trigger cellular senescence, thereby enabling a vicious cycle that exacerbates metabolic dysfunction. Therapies targeting senescent cells (senotherapeutics), either alone or in combination with other gerotherapies or lifestyle interventions, hold great promise for addressing the ongoing obesity epidemic and the need for improved therapies to prevent and treat metabolic diseases and their complications and comorbidities. In this Review, we discuss novel senotherapeutics, including challenges related to the translation of these therapies and the need to establish gerodiagnostic biomarkers to track the elimination of senescent cells, define eligibility and measure efficacy, as well as considerations for clinical trial design and execution.

Sections

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Key points

- Cellular senescence is a fundamental ageing process that seems to contribute to the pathogenesis of many chronic diseases, including metabolic diseases.
- Lifestyle and pharmacological interventions that affect metabolic disorders can prevent senescent cell accumulation or modulate their secretory phenotype.
- Elimination of senescent cells with senolytic drugs or inhibition of the senescence-associated secretory phenotype have shown promise for preventing, alleviating or delaying metabolic diseases and associated comorbidities in preclinical models.
- Senotherapies are a potentially viable intervention for treatment of metabolic diseases.
- Early-phase clinical trials are evaluating the safety and tolerability of senolytic drugs, along with monitoring target engagement (the clearance of senescent cells) across multiple age-related diseases.
- The development of gerodiagnostic biomarkers that target fundamental ageing processes will be critical for identifying individuals who will benefit the most from senolytic therapies and facilitate individualized approaches for treatment of metabolic diseases.

Introduction

Ageing is a major risk factor for multiple disorders and diseases, including cardiovascular diseases, neurodegeneration, renal dysfunction, cancers and metabolic disorders. The geroscience hypothesis postulates that interconnected molecular and cellular mechanisms of ageing, such as chronic sterile inflammation, macromolecular and organelle dysfunction, stem cell and/or progenitor dysfunction and cellular senescence, contribute to these disorders and diseases and present promising therapeutic targets to treat conditions collectively rather than individually.

In response to damaging stimuli, a cell can undergo cell death from necrosis, apoptosis or other causes. An alternative response is to cease proliferation, whereby damaged cells enter a senescent state that prevents further amplification. Although cellular senescence is a response to age-associated damaging processes, it can also accelerate other ageing mechanisms through its senescence-specific metabolic and secretory phenotypes[1,2]. The exact mechanisms leading to the accumulation of senescent cells with ageing are still elusive; however, preclinical and observational studies in humans suggest that metabolic stress is a key driver of the senescence programme, even independently of ageing[3,4]. Accumulation of aberrant metabolites, reactive oxygen species and mediators of inflammation in metabolic diseases can trigger cellular senescence[5]. Senescent cells develop a senescence-associated secretory phenotype (SASP), which can comprise cytokines, chemokines, extracellular matrix remodelling factors, bioactive lipids, reactive metabolites, nucleotides and exosomes, fostering a chronic low-grade inflammatory environment[6–8]. The SASP of senescent cells is highly heterogeneous, is specific to the cell type and context, and serves as the primary mediator of both detrimental and beneficial effects of senescent cells[6,8–11]. For instance, senescent cells have important roles during embryonic development[12,13], timing of parturition[14] and in tumour suppression[15].

Regarding the detrimental role of senescent cells, the SASP can exacerbate tissue dysfunction through paracrine and endocrine mechanisms and can itself induce senescence locally or in distant tissues[16,17]. Related to the damaging microenvironment that senescent cells can create, they also have upregulated prosurvival pathways and senescence-associated anti-apoptotic pathways (SCAPs), which enable the cells to persist[18–20]. These prosurvival pathways present targets that could be exploited for developing therapies to target senescent cells.

In ageing and obesity, compromised immune cell function might contribute to the accumulation of senescent cells[21–26]. It is thought that the burden of senescent cells needs to exceed a certain threshold, outpacing immune clearance of already present and newly formed senescent cells, in order to cause dysfunction[2,16,21]. Direct evidence for this threshold effect comes from transplantation experiments[16]. These experiments showed that transplanting a small number of senescent cells into old mice of a normal weight fed a chow diet, or old, obese mice fed a high-fat diet, was sufficient to induce adverse phenotypes. Furthermore, double that number of transplanted senescent cells was required to elicit similar phenotypic changes in younger, healthy mice with a lower pre-existing number of senescent cells and a better functioning immune system than in older mice. This finding suggests that vulnerability to senescent cell burden varies with age and health status, reinforcing the idea of a dynamic interplay between senescent cell load and immune-mediated senescent cell clearance. Senescent cell burden, particularly in metabolic tissues (for example, adipose tissue, liver and skeletal muscle), accelerates with ageing and obesity and can be pronounced at sites of pathology[16,27–31]. As in ageing-associated conditions and obesity[32–36], metabolic diseases have an earlier onset and a higher prevalence in populations with an elevated senescent cell load (such as survivors of childhood cancer and women with a history of preeclampsia) than in those with an average senescent load[37–42].

These observations, along with preclinical evidence linking senescent cells to metabolic diseases, have spurred substantial interest in senotherapeutic approaches for the treatment and prevention of metabolic diseases and their complications. Indeed, genetic or pharmacological approaches targeting senescent cells in preclinical models have shown promise for alleviating and preventing metabolic diseases and associated comorbidities[2,43,44]. The first generation of senolytics (drugs that selectively eliminate senescent cells[19]) has been tested in several early-phase clinical trials for different indications[28,45]. Lifestyle interventions, such as diet and exercise, and some compounds that inhibit the SASP (for example, ruxolitinib, resveratrol and metformin) can mitigate the damaging effects of the SASP in preclinical models and represent a possible alternative approach to directly eliminating senescent cells. Given the growing obesity epidemic, rapidly ageing population and wide-ranging effects of senescent cells on human health and disease, these therapeutic strategies could revolutionize disease prevention and treatment and have a considerable effect on human healthspan.

This Review explores the steps that are underway to translate senotherapeutics into clinical practice for metabolic disorders. We consider the relationship between metabolic disorders and cellular senescence, review current and emerging therapies, and address the challenges of translating senotherapeutics into clinical practice for metabolic disorders.

Cellular senescence in metabolic disease

Metabolic dysfunction (which includes insulin resistance, hyperinsulinaemia, hyperglycaemia and hyperlipidaemia) often arises during ageing, is accelerated by obesity and can lead to the development of type 2 diabetes mellitus[27,46–49]. An accelerated onset of tissue dysfunction occurs in multiple organs in obesity and type 2 diabetes mellitus and is linked to aberrant activation of fundamental ageing mechanisms and the accumulation of senescent cells[50,51]. Age-related metabolic dysfunction and accumulation of senescent cells are shared risk factors for type 1 diabetes mellitus, type 2 diabetes mellitus, cardiovascular disease, chronic liver disease, renal dysfunction, peripheral neuropathy, retinopathy, osteoporosis, dementias and frailty, among other conditions[27,46,52,53].

Predispositions to metabolic dysfunction and to accumulation of senescent cells seem to be linked. Individuals with first-degree relatives with type 2 diabetes mellitus have a higher prevalence of the metabolic syndrome and also have an increased propensity for senescent cell formation in their adipose tissue compared with individuals who have no family history of diabetes mellitus[54,55]. Moreover, individuals who develop obesity during childhood exhibit more pronounced accumulation of senescent cells than adults who were lean during childhood, which reinforces the concept of obesity as a catalyst for accelerated ageing processes[56]. Perturbation of metabolic pathways, most notably insulin–insulin-like growth factor 1 signalling, affects lifespan in model organisms[57]. Furthermore, an increased senescent cell burden is found in metabolic tissues in states of disrupted metabolism and is thought to contribute to disease pathogenesis[55]. However, aberrant metabolic states themselves also promote formation of senescent cells, leading to a pathogenic loop[5] (Fig. 1). To understand this dynamic, it is essential to consider the specific cell types and molecular mechanisms within these tissues that contribute to and are affected by senescence, as they might offer therapeutic targets for breaking this pathogenic feedback loop.

Senescent cells in metabolic tissues

With ageing and obesity, accumulation of senescent cells in major metabolic organs, including adipose tissue, liver, pancreas and muscle, is associated with tissue dysfunction and dysregulation of metabolic homeostasis[46].

Adipose tissue

White adipose tissue is the largest endocrine organ and has an essential role in energy storage, nutrient sensing and metabolic health. Adipose progenitor cells, endothelial cells and even mature adipocytes can acquire a senescent phenotype[58]. Through their SASP, senescent cells in white adipose tissue can induce senescence both in neighbouring cells and systemically, cause inflammation and fibrosis, impair adipogenesis in surrounding cells, and contribute to adipocyte hyperplasia, increased lipolysis and ectopic adipose deposition in non-adipose tissues, thereby fostering insulin resistance[46]. Interestingly, transplantation of a small number of senescent cells into mice caused an accelerated ageing-like phenotype[16]. Genetic and pharmacological elimination of senescent cells can prevent adipocyte hyperplasia, visceral adipose tissue accumulation and insulin resistance in aged and obese mice, which suggests that senescent cells can be a causal factor underlying age-associated and obesity-associated metabolic dysfunction[8,46]. Furthermore, senolytics alleviated impaired insulin resistance caused by transplanting adipose tissue from humans with obesity into mice, and adipose tissue-specific targeting of highly p21-expressing senescent cells in obese mice alleviated insulin resistance[59].

Liver

The liver is a regulator of metabolism, producing 80–90% of the body's endogenous glucose through glycogenolysis and gluconeogenesis. The four primary cell types in the liver (hepatocytes, hepatic stellate cells, Kupffer cells and liver sinusoidal endothelial cells) are each susceptible to senescence[12]. In both ageing and obesity, the liver becomes a primary site for accumulation of senescent cells, which is associated with ectopic lipid accumulation that contributes to conditions such as hepatic steatosis, non-alcoholic fatty liver disease (also known as metabolic dysfunction-associated steatotic liver disease) and cancers[60,61]. In fact, the degree of hepatic steatosis correlates positively with the burden of senescent cells in the liver[60]. Additionally, elevated levels of hepatic senescence markers are associated with increased fasting levels of insulin and insulin resistance, indicating a potential role of hepatic senescence in metabolic phenotypes[62].

Pancreas

Pancreatic islets comprise intricate networks of endocrine cells, including α-cells, β-cells, δ-cells and pancreatic polypeptide cells. β-Cells are most often studied in the context of senescence owing to their central role in metabolic health as insulin-producing cells; however, features of senescence have also been identified in α-cells[63,64]. A study published in 2023 suggests that senescent β-cells contribute to the pathogenesis of both type 1 diabetes mellitus and type 2 diabetes mellitus[65]. In younger and older human islet samples and in aged mouse models, senescent β-cells impaired glucose homeostasis owing to their reduced ability to proliferate and respond to glucose[63]. However, more research is needed to determine the role of senescent β-cells in the age-related decline in β-cell mass or β-cell hypertrophy. In addition, a better understanding of the roles of and interactions among different pancreatic senescent cell types, and their paracrine and systemic effects in health and disease, might facilitate the development of cell type-specific senotherapies.

Skeletal muscle

Skeletal muscle serves as a primary site for glucose uptake and is crucial for fatty acid metabolism. Muscle mass and strength decline with ageing (which is mainly attributed to decreased physical activity), and intramuscular adipose tissue increases; this phenotype is also common in individuals with obesity at different ages (that is, sarcopenic obesity)[66]. Ageing is associated with cellular senescence and reduced regenerative capacity of progenitor satellite cells[67]. Although it is unclear whether cellular senescence in muscle directly contributes to age-related sarcopenia, studies indicate that removing senescent cells from progeroid mice can prevent progeria-related sarcopenia[68]. The exact role of senescent muscle cells in age-related and obesity-related metabolic dysfunction remains an area requiring further investigation.

Cardiovascular tissues

Accumulation of senescent cells is linked to cardiovascular complications of metabolic disorders. In both ageing and obesity, the abundance of endothelial and smooth muscle cells that are senescent increases, and this increase might contribute to atherosclerosis, hypertension and other cardiovascular disorders[69–71]. Senescent cells in the vasculature might have a key role in the development and progression of atherosclerotic disease, which is also linked to metabolic disorders such as type 1 diabetes mellitus, type 2 diabetes mellitus and dyslipidaemia[72,73]. Studies have suggested that senescent endothelial cells, vascular smooth muscle cells and macrophages contribute to plaque formation, chronic low-grade inflammation and impaired vascular repair through their

SASP[74–76]. These senescent cells not only effect local vascular dysfunction but might also promote systemic metabolic disturbances, which reinforces the vicious cycle between senescent cells and metabolic diseases[77]. Targeting senescent cells therefore might prove to be a therapeutic strategy for mitigating the progression of cardiometabolic complications associated with metabolic disorders[78].

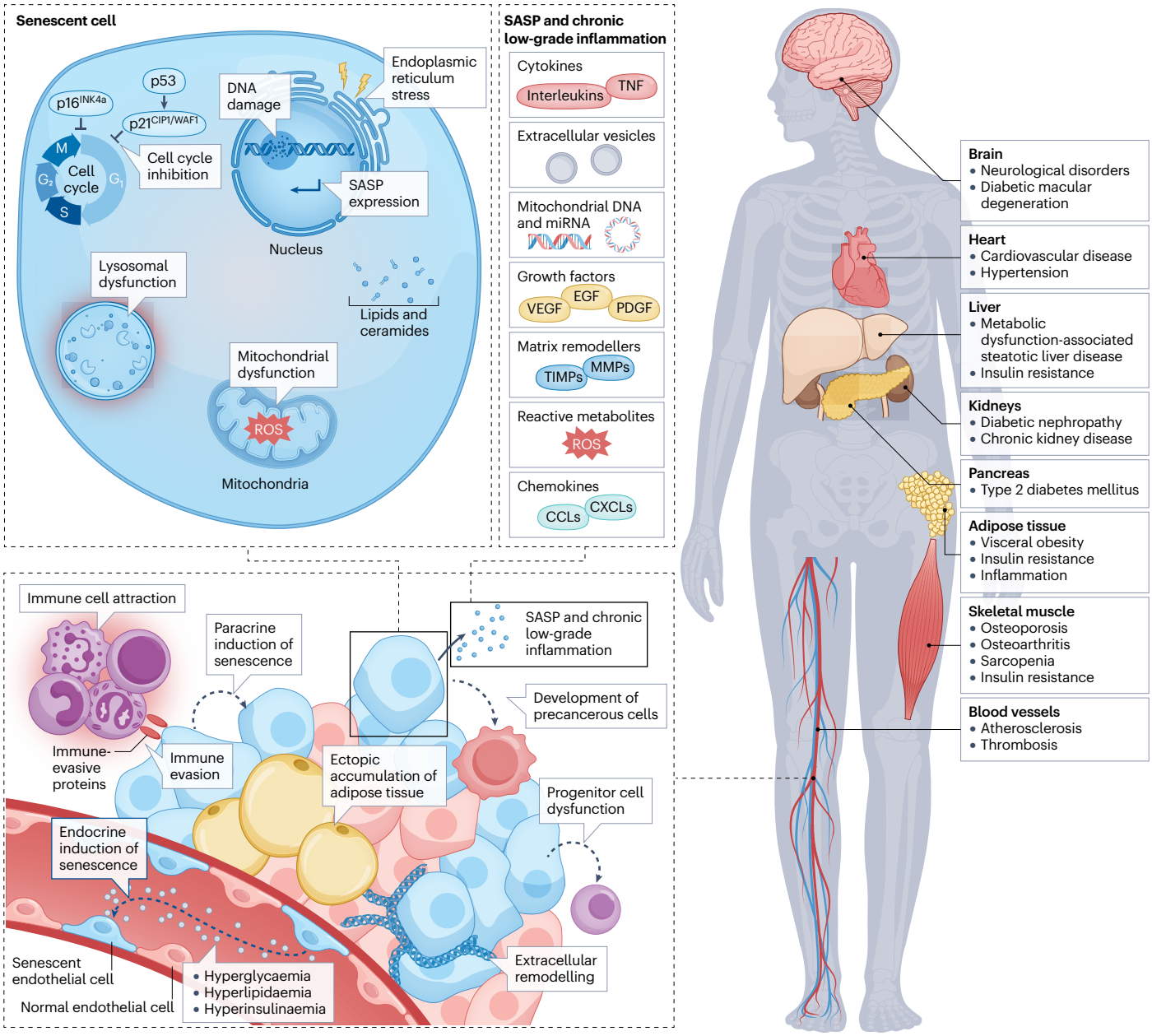

Fig. 1 | Pathogenic loop of metabolic insults and cellular senescence. The pathogenic loop depicts the interplay between senescent cells and metabolic dysfunction. Senescent cells develop a senescence-associated secretory phenotype (SASP), whereby they accumulate and secrete pro-inflammatory cytokines, chemokines, growth factors, extracellular vesicles, mitochondrial DNA, microRNAs (miRNAs), reactive metabolites and matrix remodelling enzymes. These factors attract, activate and anchor immune cells, disrupt tissue homeostasis, induce tissue damage, cause paracrine and endocrine spread of senescence, and impair organ function locally and at a distance. Tissue dysfunction and damage contribute to systemic metabolic dysregulation, including insulin resistance, chronic inflammation and altered energy homeostasis. The resulting metabolic dysregulation creates a permissive environment for the accumulation of additional senescent cells by promoting cellular stress, DNA damage and immune evasion. The increased burden of senescent cells exacerbates this pathogenic loop, further amplifying tissue dysfunction and metabolic impairment. By eliminating senescent cells, senolytics might break this cycle, restoring tissue function. CCLs, C-C chemokines; CXCLs, C-X-C chemokines; EGF, epidermal growth factor; MMPs, matrix metalloproteinases; p16, cyclin-dependent kinase inhibitor 2A; p21, cyclin-dependent kinase inhibitor 1A; p53, tumour protein p53; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TIMPs, tissue inhibitors of metalloproteinases; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

Other organs

Chronic metabolic stress can lead to the accumulation of senescent cells beyond metabolic organs. In the kidneys of people with diabetes mellitus, senescent cells contribute to fibrosis and chronic kidney disease[79]. In addition, senescent cells are associated with neuroinflammation that leads to neurodegeneration and psychological disorders, such as dementia and anxiety, respectively[80,81]. Importantly, metabolic stress can induce senescence of immune cells, weakening immune responses and potentially fuelling systemic low-grade inflammation, reducing resilience to infection and facilitating progression of diseases[82]. Thus, targeting senescent cells systemically might be an approach not only to improving metabolic health, but also to alleviating or even preventing associated comorbidities.

Effects of current interventions for metabolic disease

Lifestyle interventions

Lifestyle changes, such as weight loss, dietary interventions, regular exercise, reducing alcohol consumption and quitting smoking, improve metabolic health and promote healthy ageing[83]. Evidence indicates that these lifestyle interventions might also influence cellular senescence and the SASP. For instance, a high-fat diet induces senescence and SASP factor production in adipose tissue and other organs[27], as do alcohol and cigarette smoke[84–88], in mouse models. Conversely, reducing calorie intake, including through bariatric surgery, reduces the levels of pro-inflammatory SASP markers, such as plasminogen activator inhibitor 1 and IL-6, and leads to longer telomeres 2 years after surgery than before surgery[89]. In studies in aged rodents, monkeys and humans, dietary interventions such as calorie restriction without malnutrition and intermittent fasting, which are associated with extended healthspan and lifespan[90–92], have been linked with reductions in senescent cell numbers in the liver and colon, as well as a reduction in circulating levels of SASP factors[93–97]. Calorie restriction reduced the circulating levels of pro-inflammatory SASP factors in randomized controlled trials in middle-aged individuals with obesity and prediabetes, as well as in healthy young to middle-aged individuals[98,99].

Furthermore, aerobic exercise prevents the accumulation of senescent cells induced by high-fat feeding in mice[100]. In older humans (~67 years of age or older), an intervention that included endurance and resistance training reduced circulating levels of senescent T cells as well as the SASP[101]. It seems that chronic exposure to high-intensity exercise can be associated with a decrease in senescent cell burden, as has been noted in the colon[102]. In addition, senescent cell burden is inversely linked to physical function, such as grip strength and mobility in women with obesity or overweight, and in middle-aged and older humans with overweight[101–103]. More investigation is needed to determine whether lifestyle interventions have senolytic or SASP-inhibitory effects in humans and whether there is an inflexion point beyond which they might actually promote increased senescence.

Pharmacological interventions

Pharmacological interventions targeting metabolic disorders seem to have a pleiotropic effect on senescent cells. The antidiabetic drug metformin has long been used for the treatment of type 2 diabetes mellitus. Interestingly, metformin can also inhibit the SASP by affecting mitochondrial function and interfering with the NF-κB pathway[104], and is therefore considered a SASP inhibitor. It is through these mechanisms that metformin might exhibit gerotherapeutic effects on multiple age-related diseases[105,106]. Sodium–glucose transporter protein 2 inhibitors (a class of antidiabetic drugs that includes dapagliflozin or empagliflozin and that lowers blood levels of glucose by reducing glucose reabsorption in the kidney) reduced markers of senescent cells in kidney, adipose tissue and heart in a mouse model of diabetes mellitus[107–109]. In part, this effect was mediated by restoring immune surveillance of senescent cells by downregulating PDL1 (ref. 109).

Glucagon-like peptide 1 receptor (GLP1R) agonists, which have attracted much attention owing to their weight-lowering effects, decrease blood levels of glucose and appetite[110]. In vivo, GLP1 acts through the cAMP–PKA pathway to alleviate cellular senescence induced by oxidative stress[111]. However, GLP1R agonists exert their effect on insulin secretion by pancreatic β-cells in a glucose-dependent manner, which can lead to elevated insulin levels, particularly if glucose levels are not fully normalized[112]. It should be noted that high insulin levels can increase levels of senescence-associated β-galactosidase in mouse adipose tissue[109], and also induces expression of p53 and p21, and aggravates the SASP of already senescent cells in human hepatocytes[113]. However, the effects of administration of exogenous insulin as a treatment for diabetes mellitus on senescent cells are unknown. Similarly, the long-term effects of GLP1R agonists on senescent cell burden, as well as the effects of the rapid weight loss they cause, are currently unknown.

The effects on senescence of commonly used drugs that target the comorbidities of obesity are beginning to be understood. Hypertension, which is associated with metabolic dysfunction, induces cellular senescence in rat heart and kidney as well as in the human kidney; antihypertensive drugs, such as losartan (an angiotensin II type 1 receptor blocker), reduce senescent cell markers[114]. Furthermore, statins, such as simvastatin or atorvastatin, might have senolytic or SASP inhibitory effects, but can induce cellular senescence, depending on the experimental system used[115–117].

In general, existing therapies that target metabolic disease seem to have geroprotective effects, reducing morbidity across multiple organ systems, which might be partly through their effects on senescent cells. However, in some instances, such as the case of potential hyperinsulinaemia or sudden changes in glycaemic control with GLP1R agonists or insulin, this relationship is not linear and requires further investigation. It is also not clear whether effects on senescent cells resulting from these therapies persist, or whether a 'bounce-back' or 'yo-yo' phenomenon could occur after cessation of treatment.

First-generation senotherapeutics

Senolytics, the vanguard of senotherapeutics

First-generation senolytics (namely, quercetin and fisetin (natural flavonoids), dasatinib and navitoclax (ABT-263)) were developed following the discovery of a network of SCAPs[18–20] (Fig. 2). Targeting major nodes of these SCAPs enables apoptosis and allows the self-destruction of those senescent cells that have a pro-apoptotic SASP. These senotherapies have been widely tested in preclinical models and have entered early-phase clinical trials[2] (Tables 1 and 2). In mouse preclinical models of metabolic disorders, such as diet-induced obesity, dasatinib plus quercetin in combination or navitoclax reduced senescent cell burden in adipose tissue and liver, and also reduced inflammation, hepatic steatosis and metabolic dysfunction (including glucose intolerance and insulin resistance); however, navitoclax induced thrombocytopenia while the dasatinib plus quercetin combination did not[27,60,118]. Conversely, in other studies using mouse preclinical models of metabolic dysfunction-associated steatotic liver disease or non-alcoholic fatty liver disease, monthly dasatinib plus quercetin treatment did not lead

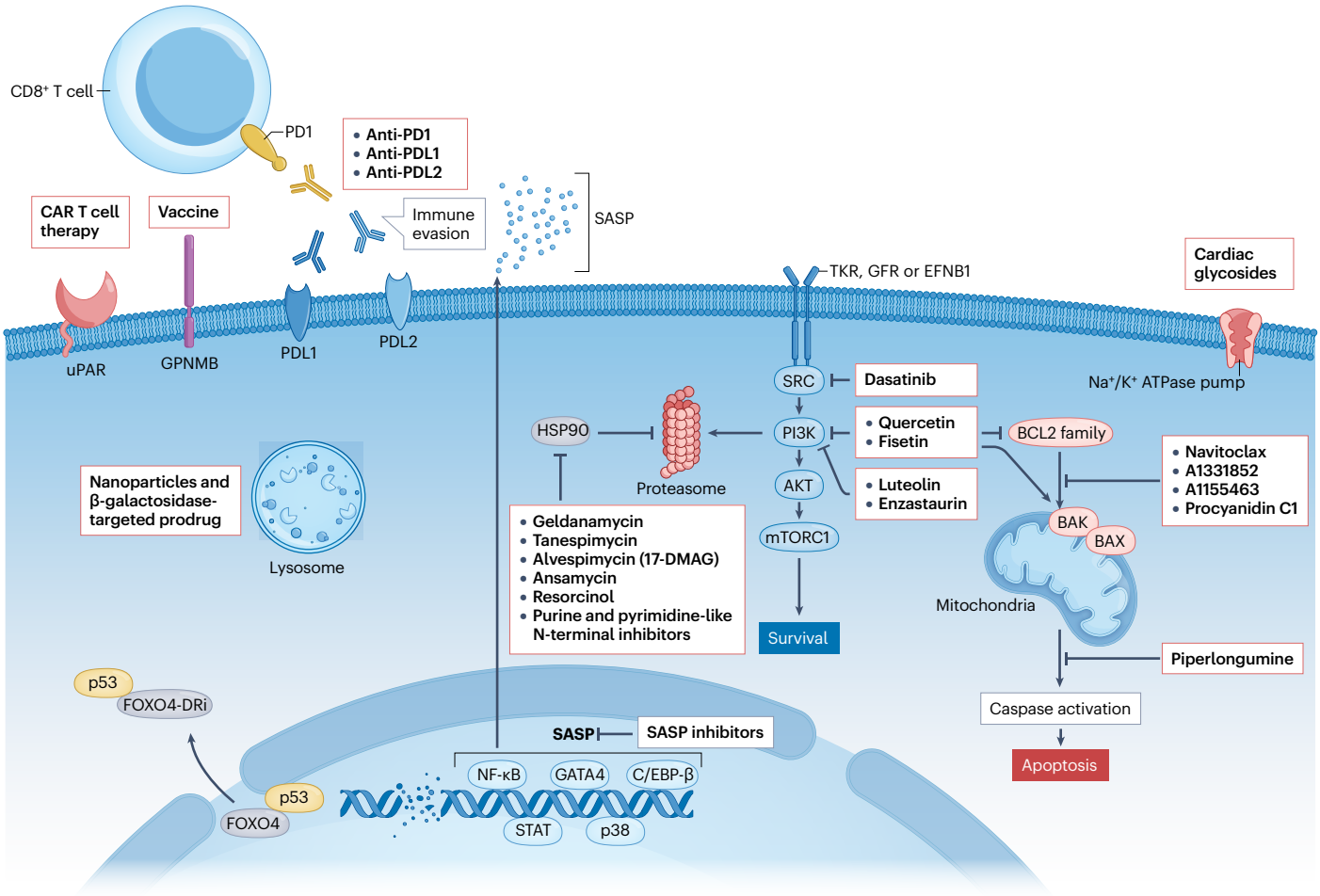

Fig. 2 | Senotherapeutic strategies and their targets. First-generation senolytics target different senescence-associated anti-apoptotic pathways, including tyrosine kinase receptors (TKR), growth factor receptors (GFR), ephrin receptor B1 (EFNB1), src-family kinases (SRC), phosphoinositide 3-kinase (PI3K)–AKT, heat shock protein 90 (HSP90), B cell lymphoma 2 (BCL2) family members, caspase inhibitors and p53 modulators. High-throughput library screens and other approaches have informed second-generation senolytic strategies, including lysosomal and senescence-associated β-galactosidase-activated prodrugs and nanoparticles, sodium–potassium pump (Na^+/K^+ ATPase)-dependent apoptosis, senescence-associated secretory phenotype (SASP) inhibition, depleting availability of glucose and increasing fatty acids to exploit the Warburg shift of senescent cells, and immune-mediated clearance by chimeric antigen receptor (CAR) T cells, immune checkpoint blockade, antibody–drug conjugates or vaccines. Anti-PD1, antibody that blocks PD1; anti-PDL1, antibody that blocks PDL1; anti-PDL2, antibody that blocks PDL2; BAK, BCL-2 homologous antagonist killer; BAX, BCL-2 associated X protein; C/EBP-β, CCAAT/enhancer-binding protein-β; DRi, D-retro-inverso-isoform; FOXO4, forkhead box O4; GATA4, GATA-binding factor 4; GPNMB, glycoprotein non-metastatic melanoma protein B; mTORC1, mammalian target of rapamycin complex 1; NF-κB, nuclear factor κB; p38, mitogen-activated protein kinase p38; STAT, signal transducer and activator of transcription; uPAR, urokinase plasminogen activator receptor. Adapted from ref. 2, Springer Nature Limited.

to a statistically significant reduction in senescent cell burden[119,120], whereas biweekly administration in a mouse preclinical hepatic steatosis model did reduce senescent cell burden[60]. Similarly, in a study assessing reproductive senescence, biweekly dasatinib plus quercetin treatment reduced senescent cell burden in the ovaries of obese mice[121]. However, in mice with chemically induced oestropause, monthly dasatinib plus quercetin treatment did not alter senescent cell burden[122]. These findings indicate that further research is required to test and optimize the selection of different senolytic agents and dosing regimens in different disease models.

The majority of senolytic drugs are cell type-specific, with their efficacy being dependent on which SCAPs are active in any particular cell type[20]. As senescent cells have lost proliferative capacity and might take many days or even weeks to re-accumulate, transiently targeting multiple SCAP nodes with senolytics that have short elimination half-lives might increase specificity for senescent cells, reduce off-target effects on non-senescent cells and reduce potential adverse effects compared with single molecule senolytics given continuously. For instance, navitoclax, which targets a restricted range of BCL2 anti-apoptotic family members and can effectively kill certain senescent cell types, can be toxic for non-senescent cells and can cause adverse effects such as unpredictable thrombocytopenia or neutropenia, limiting its use for systemic administration[18,19,123–126]. Repurposing drugs such as dasatinib, quercetin and fisetin as senolytics could be advantageous due to their

known safety profiles, making their application as senotherapeutics in clinical trials more feasible than for navitoclax.

Senolytics are typically administered intermittently, which also limits their potential adverse effects compared with drugs that require continuous administration[127–129]. A single dose of senolytics in a 'hit-and-run' approach can effectively disable SCAPs and kill senescent cells, typically with very short half-lives (dasatinib 4 h, quercetin 11 h and fisetin 3–4 h) in humans[130–132]. Intermittent dosing frequency varies between conditions and depends on the rate at which new senescent cells are generated. These drugs can be administered either orally or topically, increasing their potential applicability to clinical practice if they are shown to be safe, tolerated, efficacious and effective in randomized, placebo-controlled clinical trials.

It should be noted that in genetic models used to eliminate senescent cells ($p16^{Ink4a}$-based or $p21^{Cip1/Waf1}$-based), the suicide gene used results in the death of only those senescent cells that express higher levels of p16 or p21, whereas first-generation senolytics target the SCAP network of those senescent cells that destroy and damage tissue by allowing them to undergo cell death. Targeting all $p16^{high}$ expressing cells can lead to liver fibrosis in mice[133] or pulmonary hypertension in mice[134], which might explain some of the adverse effects of targeting subsets of senescent cells using these genetic models as these subsets might differ from the subsets of senescent cells targeted by SCAP-inhibiting senolytics.

SASP inhibitors

SASP inhibitors suppress the SASP without killing senescent cells (Fig. 2). Examples of SASP inhibitors include ruxolitinib, metformin and rapamycin. These inhibitors generally require more continuous administration than senolytics to suppress the SASP. However, some drugs (such as rapamycin) can have persistent effects, possibly through indirect effects on immune cell populations[135,136]. Ruxolitinib can also be used to block the SASP; it acts by inhibiting the JAK–STAT pathway, thereby decreasing the release of pro-inflammatory cytokines and chemokines, and was found to improve physical function in 24-month-old mice[8]. However, such continuous administration could also lead to off-target effects and suppress non-senescent immune cell function that might be needed for other homeostatic processes.

Emerging senotherapeutics

Heat shock protein 90 (HSP90) inhibitors have been identified as senolytic compounds against some senescent cells[137]. For instance, in a mouse model of hyperglycaemia and hyperlipidaemia using streptozotocin-induced diabetic apolipoprotein E-deficient mice or diabetic *db/db* mice, HSP90 inhibitors improved insulin sensitivity and renal function and reduced expression of pro-inflammatory cytokines[138,139].

Bisphosphonate derivatives such as zoledronic acid, which is used for the treatment of osteoporosis, have shown senolytic activity in cell culture and in ageing mouse models, in reducing senescent cell burden and improving physical function[140]. The flavonoid procyanidin C1 eliminates senescent cells in cell culture, improves physical dysfunction in aged mice and alleviates age-related retinal impairment and bleomycin-induced pulmonary dysfunction in mouse disease models[141–143]. The effects of bisphosphonate derivatives and procyanidin C1 on metabolic disorders need to be tested.

Other experimental strategies to target senescent cells include nanoparticles and β-galactosidase-activated prodrugs, which take advantage of elevated lysosomal mass and activity in many senescent cells[144–146]. The development of cell type-specific senolytic drugs is also underway, and it will be important to determine how this strategy compares to systemic pan-senolytics, especially in terms of potential adverse effects. For example, it might be advantageous to target senescent endothelial cells, as they are exposed to circulating factors in blood (such as damage-associated molecular pattern factors and pathogen-associated molecular pattern factors); endothelial cells are also subjected to mechanical sheer and flow stress, and are the first cell types to undergo cellular senescence in response to exogenous stressors[78].

Sirtuins are involved in DNA damage repair and mitochondrial function, using oxidized NAD (NAD^+). Senescent cells can diminish NAD^+ levels through their SASP, which activates the NAD-degrading enzyme CD38 that is expressed on macrophages[147,148]. Supplementation with nicotinamide mononucleotide, an NAD precursor,

Table 1 | Preclinical studies of senotherapeutics for metabolic disorders

Conditions	Intervention	Findings
Insulin resistance and obesity	Dasatinib + quercetin[27,118,181], navitoclax[118,182]	Improved metabolic and adipose tissue function[27,59,118,181–183]
		Reduced inflammation[27,181]
		Improved adipogenesis[27]
		Improved β-cell function[182]
Hepatic and renal disease	Dasatinib + quercetin[60,184], quercetin[185], FOXO4-DRI[186], navitoclax[187], A1331852[188]	Improved renal function[184,186,187]
		Reduced damage[185] and fibrosis[184,185,187]
		Reduced hepatic steatosis[60] and liver fibrosis[188]
Cardiovascular health	Quercetin[189], navitoclax[71,190–192], dasatinib + quercetin[19,69,193], navitoclax[69,194]	Activation of resident cardiac progenitor cells and cardiomyocyte formation[193]
		Alleviated myocardial hypertrophy and fibrosis[190,192]
		Improved left ventricular ejection fraction[19,190]
		Increased myocardial vascularization[190]
		Increased survival after myocardial infarction[191]
		Improved vasomotor function, reduced aortic calcification[69]
Frailty, cognitive function, and other age-related conditions	Navitoclax[195], fisetin[196], dasatinib + quercetin[16,19,172,197,198], procyanidin C1 (ref. 141)	Delayed age-associated physical dysfunction[16,19,172,195,199]
		Extended median and maximum lifespan[196]
		Improved muscle growth[197]
		Reduced inflammation and microbial dysbiosis[198]
		Delayed onset and progression of progeroid-related or age-related pathologies, reduced frailty[16,68,141,196]
		Increased maximum lifespan[196]

Selected references, but not all related publications, are cited. Adapted from ref. 2, Springer Nature Limited.

Table 2 | Clinical studies of senotherapeutics

Trial name	Intervention type	Status	NCT number	Key findings
Targeting cellular senescence with senolytics to improve skeletal health in older humans	Senolytic (dasatinib + quercetin, fisetin)	Completed	NCT04313634	Intermittent administration of senolytics increased radial bone mineral density Individuals with the highest senescent cell burden had a stronger response to the treatment[168]
Hematopoietic stem cell transplant survivors study	Senolytic (dasatinib + quercetin)	Completed	NCT02652052	Pending
Targeting pro-inflammatory cells in idiopathic pulmonary fibrosis: a human trial (IPF)	Senolytic (dasatinib + quercetin)	Completed	NCT02874989	Significant and clinically meaningful improvements in physical function The study confirmed the feasibility of administering senolytics in patients with idiopathic pulmonary fibrosis[45]
COVID-19 pilot study of fisetin to alleviate dysfunction and decrease complications (COVFIS-HOME)	Senolytic (fisetin)	Completed	NCT04771611	Pending
Pilot study in COVID-19 (SARS-CoV-2) of fisetin in older adults in nursing homes (COVID-FIS)	Senolytic (fisetin)	Completed	NCT04537299	Pending
Senolytic drugs attenuate osteoarthritis-related articular cartilage degeneration: a clinical trial	Senolytic (fisetin)	Completed	NCT04210986	Pending
A study to assess the safety and efficacy of a single or repeat doses of UBX0101 in patients with osteoarthritis of the knee	Senolytic (UBX0101, nutlin-3a or related)	Completed	NCT04229225, NCT04129944	Failed to achieve primary end point
Safety, tolerability and evidence study of UBX1325 in patients with diabetic macular oedema or neovascular age-related macular degeneration	Senolytic (UBX1325, BCLXL inhibitor)	Completed	NCT04537884, NCT04857996	No differences observed[200]
Exercise and low-dose rapamycin in older adults with CAD: cardiac rehabilitation and rapamycin in the elderly (CARE) trial	SASP inhibitor (rapamycin)	Completed	NCT01649960	Pending
Senolytic therapy to modulate the progression of Alzheimer disease	Senolytic (dasatinib + quercetin)	Pilot completed, ongoing	NCT04063124, NCT04685590	Central nervous system penetrance of dasatinib; provides preliminary support for the safety, tolerability and feasibility of the intervention and suggests that astrocytes and amyloid-β might be particularly responsive to the treatment
A study to assess the safety, tolerability and long-term follow-up of UBX0101 in patients with osteoarthritis of the knee	Senolytic (UBX0101, nutlin-3a or related)	Completed	NCT03513016, NCT04349956	Failed to achieve primary end point
An open-label intervention trial to reduce senescence and improve frailty in adult survivors of childhood cancer	Senolytic (dasatinib + quercetin, fisetin)	Ongoing	NCT04733534	Pending
ALSENLITE: senolytics for Alzheimer disease	Senolytic (dasatinib + quercetin)	Ongoing	NCT04785300	Pending
Dasatinib and quercetin to treat fibrotic non-alcoholic fatty liver disease	Senolytic (dasatinib + quercetin)	Ongoing	NCT05506488	Pending
Senescence in chronic kidney disease	Senolytic (dasatinib + quercetin)	Ongoing	NCT02848131	Pending
Alleviation by fisetin of frailty, inflammation, and related measures in older women and adults	Senolytic (fisetin)	Ongoing	NCT03430037, NCT03675724	Pending
COVID-FISETIN: pilot in SARS-CoV-2 of fisetin to alleviate dysfunction and inflammation	Senolytic (fisetin)	Ongoing	NCT04476953	Pending
Senolytic agent improves the benefit of platelet-rich plasma and losartan	Senolytic (fisetin)	Ongoing	NCT05025956	Pending
Use of senolytic and anti-fibrotic agents to improve the beneficial effect of bone marrow stem cells for osteoarthritis	Senolytic (fisetin)	Ongoing	NCT04815902	Pending
Quercetin in coronary artery by-pass surgery (Q-CABG)	Senolytic (quercetin)	Ongoing	NCT04907253	Pending
TAME (targeting aging with metformin)	SASP inhibitor (metformin)	Planned	To be determined	Pending

SASP, senescence-associated secretory phenotype. Adapted from ref. 2, Springer Nature.

hinders the development of cellular senescence in vitro by enhancing mitochondrial function, and extends healthspan in mice[149–152].

Alternative experimental strategies for targeting senescent cells are being developed (Fig. 2). Senescent cells seem to be enriched in some proteins located at the cellular membrane, which can be used to target senescent cells[21,23,153–157]. Urokinase-type plasminogen activator receptor is upregulated in some senescent cells, such as human primary melanocytes and cancer cells, and in mouse models of liver fibrosis and ageing[153,154]. Chimeric antigen receptor (CAR) T cells targeting cells expressing urokinase-type plasminogen activator receptor reduced senescent cell burden in liver and improved glucose homeostasis and physical dysfunction in preclinical mouse models of diet-induced obesity and ageing (based on findings published in peer-reviewed papers and in a preprint)[153,154,158]. It should be noted that CAR T cells might persist for an extended period of time, and thus might lead to adverse effects involving processes for which certain types of senescent cells are beneficial, such as wound healing[9,11,159]. Clearing senescent cells with high p21 expression accelerates wound closure, partially through NF-κB inhibition, which suggests senescence has multifaceted functions in tissue remodelling[9]. In addition, like cancer cells, senescent cells seem to depend more on glucose than fatty acids as an energy source (that is, a Warburg shift)[160]. Hence, agents that alter the balance between glucose and fatty acids as energy sources (for example, SGLT agonists to reduce glucose availability or agents that alter NAD to NADPH ratios) might hold promise.

Glycoprotein non-metastatic melanoma protein B is upregulated in senescent vascular endothelial cells and in tissues of 25-month-old mice or mice fed a high-fat diet[155]. Vaccination against glycoprotein non-metastatic melanoma protein B during high-fat diet feeding led to a reduction in the level of senescent cells in visceral adipose tissue and improved glucose tolerance and insulin sensitivity[155]. Furthermore, senescent cells can express PDL1 and PDL2, which are immune-evasive ligands[23,26,161]. Blocking PD1, the receptor for PDL1 and PDL2, using neutralizing antibodies facilitated senescent cell clearance in the lung, liver and kidney in aged animals[26]. It should be noted that patients with cancer receiving anti-PDL1 and anti-PD1 immunotherapy can develop metabolic dysfunction, such as insulin resistance, due to dysfunctional systemic maintenance of peripheral tolerance[162–164]. In a mouse model of high-fat diet-induced obesity, blocking PDL1 function genetically in dendritic cells or using anti-PDL1 blocking antibodies exacerbated the disease phenotype, including increased T cell polarization towards T helper 1, adipose tissue inflammation and metabolic dysfunction[165]. These points suggest that PDL1 expression limits the chronic low-grade inflammation in obesity. Much more research is needed to determine if anti-PDL1, anti-PDL2 or anti-PD1 interventions have distinct effects on senescent cells and on metabolic health in ageing and in preclinical models of metabolic dysfunction.

In conclusion, current interventions targeting senescent cells have potential for preventing, delaying, alleviating or treating metabolic disorders, including insulin resistance, type 1 diabetes mellitus, type 2 diabetes mellitus and obesity. We emphasize that, before they are considered for use in routine clinical practice, the safety, tolerability, efficacy and effectiveness of senolytics for metabolic diseases must be demonstrated in carefully conducted randomized, placebo-controlled clinical trials. Additionally, although alternative strategies offer novel approaches for reducing senescent cell burden, further investigation into the distinct effects of these interventions on metabolic disorders is needed. Testing combinations of senolytic drugs with disease-specific treatments or in combination with drugs targeting other fundamental ageing mechanisms might be informative to optimize therapies that are guided by geroscience.

Considerations for clinical trials

Several early-phase clinical trials using senolytic drugs have been completed, are underway or are about to start (Table 2). The first clinical trial results were published within just 4 years of the first report of senolytics. In patients with idiopathic pulmonary fibrosis, oral administration of a total of nine doses of dasatinib plus quercetin over a 3-week period in a phase I open-label study seemed to improve physical function[45,166]. In patients with diabetic kidney disease, a single round of dasatinib plus quercetin led to a reduction in senescence markers in adipose tissue and a decrease in a composite score of nine circulating SASP factors in plasma[28]. In a pilot study testing dasatinib plus quercetin in patients with Alzheimer disease, senescence biomarkers were affected in plasma and cerebrospinal fluid, indicating possible clearance of senescent cells in the brain[81]. There were also promising results in a phase I trial of dasatinib plus quercetin in a small number of people with late-phase mild cognitive impairment or early Alzheimer disease, especially in the tertile of participants with the highest abundance of senescent cells in blood before senolytics were administered[167]. A randomized, controlled phase II trial of intermittent administration of dasatinib plus quercetin for osteoporosis in older women (60–90 years old) gave promising results, with increases in a bone formation marker and a trend for a reduction in a bone resorption marker, as well as an increase in radial bone mineral density in the subset of participants with the highest pretreatment senescent cell burden, all without serious drug-related adverse events[168].

Box 1 | Challenges for geroscience-based and senescence-targeting clinical trials

- No consensus has been reached on the definition of senescent cells or markers to demonstrate senescent cell burden and any subsequent reduction by senotherapeutic interventions.
- The dynamics of senescent cell accumulation are unknown, which hampers the development of senotherapeutic regimens.
- There is a lack of clinical investigators trained in ageing biology.
- Systemic versus local (or topical) application. The efficacy of senolytics might differ depending on whether they are administered systemically or locally, which requires further investigation.
- Timing and outcome measures for preventive trials need to be defined for each indication and overall healthspan.
- Sex differences in effects of senotherapeutic interventions are not clear and require further research.
- There is a lack of standard operating procedures for collecting, assaying and analysing outcome measures, which would facilitate the comparison of different clinical trials.
- There is a need to proceed cautiously and introduce senotherapeutics into clinical practice only after rigorous demonstration of safety, tolerability, efficacy and effectiveness, and with the approval of regulatory authorities and the medical community.

Box 2 | Gerodiagnostics for interconnected fundamental ageing processes

Promising results from preclinical studies have prompted the initiation of early-phase clinical trials. The adverse effects of many senolytic agents are not yet fully known in populations with senescence-associated disorders. To maximize risk to benefit ratios, the first clinical trials are being conducted in patients with serious health conditions. Early data suggest that senolytics reduce senescent cell burden[45] and lead to improvements in a composite score of senescence-associated secretory phenotype factors in humans[28], warranting evaluation of senolytics in larger randomized, double-blind, placebo-controlled trials to ensure safety, tolerability, target engagement and clinical efficacy and effectiveness.

A remaining challenge is to develop analytical methods and standardize protocols to monitor target engagement across clinical trials. Over 80 clinical trials are either ongoing or planned that will assess different gerotherapeutics in various age-related diseases targeting different interconnected fundamental ageing processes[201]. Further research is needed to identify individuals who will benefit most from senolytic or other gerotherapies and to develop gerodiagnostic markers to guide the integration of gerotherapeutics into the clinic. The following factors should be considered in developing gerodiagnostic markers:

- Individual or composite markers should be more than mere 'ageing clocks'
- Should allow measurement of the extent of progression of fundamental ageing processes
- Can be assayed in human body fluids and/or non-invasive tests
- Should be reproducible, reliable, scalable and inexpensive
- Should be applicable across ethnic groups, sexes, socioeconomic groups and regions
- Should be diagnostic for multiple conditions, disabilities and diseases across the lifespan
- Can predict the incidence and/or progression of one or more diseases
- Should be responsive to interventions
- Can help guide selection of the best gerotherapeutic interventions or combinations in a personalized manner
- Should fit practical and regulatory parameters for broad adoption as clinical trial primary or secondary outcomes and, eventually, for broad clinical use
- Should allow the establishment of future biomarker composite scores that might be of use in determining if and how often administering gerotherapeutics is indicated

Although systemic administration of senolytics might prove to be beneficial for treating senescence-associated diseases due to senescent cell accumulation across various organs, in certain circumstances, local delivery of a high concentration of senolytics to the affected organ might be advantageous. Topical application might be beneficial for skin conditions, including non-healing diabetic wounds or focal alopecia[9,169,170]. The results of these initial studies are promising; however, much larger randomized, double-blind, placebo-controlled trials are necessary.

Given that the accumulation of senescent cells affects various tissues simultaneously and contributes to multimorbidity with ageing, defining trial outcomes that fully capture system-wide and organ-specific benefits remains challenging. These broad benefits might not be observed when senolytics are administered locally. Furthermore, given the potentially high senescent cell burden in other parts of the body, the re-emergence of senescent cells could be accelerated, necessitating a regimen with more frequent treatment for local applications than for systemic applications. A preventive trial design might also need to be explored to determine whether senolytics can prevent or delay the onset of a second disease in at-risk populations. In this regard, identifying reliable biomarkers that not only track the elimination of senescent cells, but also identify people who could benefit most from senotherapeutic interventions is of importance. Indeed, results from a clinical trial in fairly healthy women with osteoporosis suggested that study participants with the highest senescent cell burden benefited the most from senolytic therapy and had improvement in bone turnover markers[168].

It is also important to acknowledge the overlap between prevention and treatment in the context of chronic and progressive conditions such as metabolic disorders and ageing. In preclinical studies, interventions are initiated at different stages of disease development, making it difficult to draw a clear line between preventive and therapeutic approaches. This variability might influence therapeutic efficacy and outcomes. It will be important to better define these therapeutic windows and assess how disease stage at the time of initiation influences the effectiveness of senotherapeutic strategies.

Currently, no consensus exists regarding the definition of cellular senescence owing to the heterogeneity of senescent cell features across different cell and tissue types. Few tissue assays are highly sensitive or specific for senescent cells. A combination of assays might be best for estimating senescent cell burden in tissue samples, including such assays as the number of senescence-associated β-galactosidase-positive cells, expression of $p16^{INK4a}$, $p21^{CIP1}$, SASP factors, DNA damage foci (for example, γH2.AX), damage-associated molecular pattern molecules (such as HMGB-1 localization) and cells with senescence-associated distension of satellites or telomere-associated foci. It is also unknown if senescent cell abundance in biopsy samples of skin, adipose tissue or other tissues, or cheek swabs and blood cells reliably reflect systemic senescent cell abundance or only the senescence-associated diseases being investigated in a specific tissue[171]. Given that biopsy samples are not easily accessible for many tissues of interest, the development of non-invasive assays measuring SASP factors that are sensitive to intervention across different trials is attractive. There is a need to establish, optimize and validate such assays. Novel assays, for example of microvesicles shed into blood or urine, senescent cell surface markers and imaging methods to detect senescent cells need to be developed to identify and monitor senescent cells in clinical trials (based on findings published in peer-reviewed papers and in a preprint)[172–174].

In addition to the need to refine senescent cell detection in clinical trials, improved understanding of the dynamics of senescent cell formation across different physiological and pathophysiological states is needed to guide dosing regimens for senotherapeutics. The rates of senescent cell formation and accumulation are probably

heterogeneous among individuals, disease conditions and tissues, and might be affected by other patient-specific factors, such as level of physical activity, diet and medications. Therefore, much work remains to be done to investigate the rate of senescent cell formation in different physiological states to facilitate the tailoring of personalized dosing regimens for senotherapeutics, as has been done in the case of chemotherapy. It is imperative to harmonize the selection of biomarkers and assays across clinical trials that can be reliably and reproducibly measured in body fluids and tissues and reflect senescent cell burden so outcomes across trials can be compared.

Various tools have emerged to assess the rate of progression of ageing processes and predict mortality, such as the epigenetic clock, DNA methylation (DNAm) GrimAge[175–178], which can predict the development of cardiovascular diseases, cancer and type 2 diabetes mellitus. Notably, DNAm GrimAge correlates highly with the blood biomarkers plasminogen activator inhibitor 1, tissue inhibitor metalloproteinase 1 and growth differentiation factor 15, which are also part of the SASP and are produced by senescent cells[6,7,172,175,179,180]. It is unknown whether tools such as DNAm GrimAge can reliably identify individuals with a high senescent cell burden or those who would benefit from senotherapeutics.

The growing public interest in senotherapeutics and the possibility that they might be approved for use in clinical practice also highlights the need for clinicians trained in geroscience. Clinicians leading trials of senotherapeutics must be educated on how ageing processes and hallmarks contribute to disease pathologies and how senotherapeutics might specifically target these processes.

Conclusions

Although early results from clinical trials targeting senescent cells are promising, and while the understanding of commonly used therapies for metabolic disease grows, considerable challenges remain for translating these findings into the clinic (Box 1). Encouraging results from pilot trials have shown that senescent cells can be cleared in humans both in tissues and systemically[28], senolytics are well tolerated (as shown in multiple trials) and, most importantly, individuals with high senescent cell burden seem to benefit the most from senolytic therapies[81,167,168]. Therefore, key areas of research include identification and validation of biomarkers and development of composite scores across clinical trials to detect senescent cell burden (Box 2), possibly even making such scores an eligibility criterion for large-scale studies, to predict therapeutic responses for patient stratification, to monitor treatment and to assess long-term outcomes. Moreover, determining dosing regimens for senotherapeutics to ensure effective clearance of senescent cells while taking into account senescent cell re-accumulation and potential adverse effects remains a challenge.

The development of robust clinical trial designs requires refinement to ensure translation from preclinical models to humans, including large-scale randomized controlled designs and long-term follow-up. Understanding how senotherapies interact and affect existing interventions targeting metabolic disorders is crucial to translate senotherapies to clinical practice. With continued research and clinical validation, senotherapeutics have the potential to considerably affect metabolic disease and other age-related conditions. If clinical trials are successful, senotherapies might become a part of individualized care.

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S.C. and A.K.P. contributed to all aspects of the article. S.P.W. and N.M. contributed to writing the article and to reviewing and/or editing the manuscript before submission. J.L.K. and T.T. contributed to discussion of the content, writing the article and to reviewing and/or editing the manuscript before submission.

Competing interests
T.T., A.K.P. and J.L.K. have a financial interest related to this article, including patents and pending patents covering senolytic drugs and their uses. S.C. holds patents or pending patents on PDL2 at Mayo Clinic and Spanish National Cancer Research Center, some of which have been licensed to Rejuveron Senescence Therapeutics. The other authors declare no competing interests.

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