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Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases

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Abstract

Ageing is the predominant risk factor for many common diseases. Human premature ageing diseases are powerful model systems to identify and characterize cellular mechanisms that underpin physiological ageing. Their study also leads to a better understanding of the causes, drivers and potential therapeutic strategies of common diseases associated with ageing, including neurological disorders, diabetes, cardiovascular diseases and cancer. Using the rare premature ageing disorder Hutchinson–Gilford progeria syndrome as a paradigm, we discuss here the shared mechanisms between premature ageing and ageing-associated diseases, including defects in genetic, epigenetic and metabolic pathways; mitochondrial and protein homeostasis; cell cycle; and stem cell-regenerative capacity.

Ageing is a process of gradual functional deterioration at the cellular and organismal level. About half of human deaths are attributed to chronic ageing-associated diseases (AADs), most prominently heart disease, diabetes, chronic obstructive pulmonary disease (COPD), stroke, Alzheimer disease, chronic kidney diseases (CKDs) and cancer[1,2] (BOX 1). Despite ageing being the biggest risk factor for the development of these illnesses, our understanding of how the ageing process contributes to their onset and progression is rudimentary.

The role of ageing in human disease is commonly studied in animal disease models by delaying the onset and progression of ageing-associated defects in the tissue that is primarily associated with the various ageing-related diseases (BOX 1). Although animal models are a useful surrogate to study the fundamentals of ageing, which may be conserved across species, these systems are not ideal to elucidate the effects of ageing on human disease owing to the much lower frequency at which chronic AADs occur in laboratory animals compared with humans[3–5].

A key contributor to AADs is the ageing-related decline of cell and tissue function[6,7]. Cellular ageing is characterized by increased genomic instability, altered metabolism and the loss of regenerative potential. Cellular ageing and deterioration as a driver in AADs explain

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the observation that in many AADs, not only the tissue primarily associated with the disease is affected, but other tissues simultaneously undergo functional decline[6,7]. The often overlooked functional decline across multiple organs in AADs is important for disease pathology and diagnosis, as non-primary tissue defects can be used as an independent disease predictor: for example, handgrip strength and hip fractures are indicators of CKD and preclinical Parkinson disease, respectively[8,9]. These observations indicate that cellular ageing is a universal principle underlying AADs.

The study of human ageing has been facilitated by the discovery of mutations that cause premature ageing syndromes (TABLE 1). Most prominent among them are Hutchinson–Gilford progeria syndrome (HGPS)[10–12] and atypical Werner syndrome, which are caused by genetic defects in nuclear envelope proteins, as well as classical Werner syndrome, Cockayne syndrome, Bloom syndrome, xeroderma pigmentosum, ataxia telangiectasia, trichothiodystrophy, dyskeratosis congenita (DKC) and mosaic variegated aneuploidy syndrome, which are caused by defects in DNA repair and maintenance proteins (TABLE 1). The cellular defects that are observed in these and other human premature ageing models, including genomic and proteomic instability, altered metabolism and loss of regenerative potential, overlap with defects that occur during physiological ageing in humans. Moreover, there are striking commonalities between organismal defects in several premature ageing diseases and AADs. However, as premature ageing syndromes only represent some aspects of the normal ageing process, it is not surprising that progeroid syndromes are typically only associated with a subset of AADs (TABLE 1). For example, HGPS involves extensive cardiovascular and osteoporotic pathology, whereas premature ageing disorders caused by mutations in DNA repair proteins are often characterized by cancer susceptibility and neurodegeneration. These parallels suggest common aetiologies between premature ageing syndromes and AADs.

In this Review, we discuss defects in cell and molecular mechanisms that are common between human premature ageing diseases and physiological ageing, and we highlight the role of these pathways in several human AADs. We use HGPS as a paradigm for the interplay between premature ageing, physiological ageing and AADs because it is one of the best characterized premature ageing diseases and exhibits a wide range of cellular, tissue and organismal defects that are shared with AADs.

HGPS as a Rosetta Stone for ageing mechanisms

HGPS is an ultra-rare premature ageing disease that affects 1 in 4–8 million newborns[13]. The clinical features of HGPS become overt shortly after birth and include full-body alopecia, loss of subcutaneous fat and skeletal muscle, nail dystrophy, joint stiffening, wrinkling of the skin, subcutaneous calcifications, weakening of the bone structure and loss of eyesight[13] (TABLE 1). HGPS is invariably fatal, with atherosclerosis-resembling progressive cardiovascular disease, myocardial infarction and stroke being the most common causes of death during the patient's mid-teens[14]. HGPS is predominantly caused by a heterozygous silent mutation (G608G) in the *LMNA* gene, which leads to the production of progerin, an aberrant form of the nuclear structural protein lamin A[10,11,15]. Wild-type lamin A is post-translationally processed: cleavage of the C terminus by CAAX prenyl protease 1

homologue (encoded by *ZMPSTE24*, also known as ZMPSTE24 in mice) releases mature lamin A, which then undergoes higher-order assembly into intermediate filaments that are incorporated in the nuclear lamina and the nuclear interior[16,17] (FIG. 1). In HGPS, the 1824C>T mutation (*LMNA*^{G608G}) activates a cryptic splice donor site, leading to the removal of a 50-amino-acid region containing the ZMPSTE24 recognition site. As a result, progerin accumulates at the nuclear periphery and disrupts the mechanochemical properties of the nuclear lamina, as indicated by the aberrant nuclear shape seen in cells from patients with HGPS[17] (FIG. 1). Similar cellular defects are caused by *LMNA* mutations that cause atypical HGPS, including *LMNA*^{G608S} and *LMNA*^{E145K} (REFS 16,18). Defects in mechanical properties and mechanotransduction at the nuclear lamina are thought to be relevant to the pathology of patients with HGPS, as many of the affected tissues, such as the vasculature, bone and joints, are exposed to mechanical forces[17,19].

HGPS differs from other human premature ageing syndromes by its early onset, severity of ageing symptoms and wide range of affected tissues[15,20] (TABLE 1). In contrast to HGPS, the classical adult progeria Werner syndrome is characterized by the onset of osteoporosis and cancer by the third decade of life. The early emergence of ageing defects in patients with HGPS can be partially attributed to the dominant-negative mode of action of progerin, whereas other progeroid syndromes are often associated with recessive genetic defects that result in a loss of function of DNA repair proteins, which might be partially compensated by alternative DNA repair pathways[20]. Consequently, patients with HGPS have a wider range of tissue defects, from osteoporosis to skeletal muscle- and cardiovascular-related ageing pathologies, whereas DNA repair-associated progeroid syndromes typically involve higher cancer predisposition and, in some cases, progressive neurodegeneration[20] (TABLE 1). Interestingly, for unknown reasons, patients with HGPS are not at increased risk of developing diabetes and chronic kidney failure. Moreover, they do not exhibit neurodegeneration, probably as a result of microRNA-9 (miR-9) repressing the neuronal expression of lamin A and progerin. Furthermore, despite the high levels of DNA damage, patients with HGPS do not develop childhood tumours, which could result from the altered composition of the extracellular matrix reducing the invasion of tumour-initiating cells[21,22] and progerin exhibiting a tumour-protective function[23].

Although several AAD symptoms are absent in HGPS (TABLE 1), many of the hallmarks of cellular ageing observed in tissues affected in AADs are also seen in patients with HGPS[24] (FIG. 1). This prominent display of cellular ageing defects in HGPS has been attributed to the detrimental effects of progerin on the nuclear lamina, which is a key organizer of the mammalian cell nucleus[25]. The lamina has been mechanistically linked to most of the universal hallmarks of ageing and AADs (FIG. 1), including loss of genomic and epigenetic integrity, shortened telomeres, reduced protein homeostasis (proteostasis), metabolic reprogramming, mitochondrial dysfunction, cellular senescence and reduced stem cell maintenance and regenerative capacity[26]. The expression of progerin is thus implicated in diverse pathways, whereas progeroid syndromes like Werner syndrome, Bloom syndrome and Cockayne syndrome have a more limited range of defects that originate mainly from defective DNA repair[27–34]. The importance of the nuclear lamina in ageing is further illustrated by the premature ageing syndrome Néstor–Guillermo progeria syndrome (NGPS), which is caused by a homozygous mutation in the nuclear lamina-localized protein barrier-

to-autointegration factor (BANF1)[35]. Similar to HGPS, NGPS is associated with joint stiffness, loss of subcutaneous fat and skeletal muscle, and growth retardation[35] (FIG. 1). The implication of nuclear lamina dysfunction in various hallmarks of cellular ageing makes HGPS a suitable model to discuss the parallels between premature ageing and AADs at the cellular and molecular level.

HGPS is especially relevant to normal ageing because physiologically aged individuals also generate small amounts of progerin owing to the spontaneous sporadic usage of the cryptic splice site that is activated in patients with HGPS[28,36]. Given the dominant-negative action of progerin, these low levels of progerin are thought to contribute to normal ageing[36]. This view is supported by extensive similarity of cellular and organismal defects in patients with HGPS and normally aged individuals[20,26]. In addition, genetic abrogation of progerin and lamin A expression extends the lifespan of mice[37], and the *LMNA* 1968G>A mutation, which results in lower activation of the cryptic splicing event of progerin, results in a milder ageing-related pathology[38].

The single, well-defined genetic defect in patients with HGPS, the direct links between progerin and numerous cellular ageing hallmarks, the expression of the disease-causing protein during normal physiological ageing and the manifestation of ageing-related pathologies across multiple tissues make HGPS an attractive model to study the role of ageing mechanisms in AADs.

Genomic instability in ageing and AADs

The human genome is under continuous attack by DNA-damaging insults that threaten cellular homeostasis. These assaults are counteracted by mechanisms that repair DNA damage and protect chromosomal ends from shortening, which decline during human ageing[39–42] and in AADs, leading to cellular deterioration.

Defects in DNA repair pathways

Several DNA damage repair pathways maintain the integrity of the genome. Nucleotide excision repair (NER) pathways repair single-strand DNA damage[40–42], whereas double-strand breaks (DSBs), which promote large chromosomal rearrangements that threaten cell survival, are preferentially and faithfully repaired by homologous recombination but can also be repaired by error-prone non-homologous end joining (NHEJ). The efficiency of these pathways decreases during human ageing[39–42] (FIG. 2), resulting in increased chromosomal aberrations and permanent activation of DNA damage signalling with age[43].

DNA repair is impaired in HGPS.—In HGPS, chronic activation of DNA damage signalling results from an increased number of replication-induced DSBs and their defective repair[44]. DNA replication defects, including replication fork collapse, are a prominent source of DSBs and occur more frequently in HGPS because of reduced levels of the critical replication DNA clamp protein PCNA, disrupted interactions between lamin A and proliferating cell nuclear antigen (PCNA), and increased proteolytic degradation of the replication factor C1 (REFS 45–47) (FIG. 2). Homologous recombination and NHEJ-mediated repair of these DSBs is impaired by the delayed recruitment of the repair proteins

TP53-binding protein 1 (TP53BP1) and RAD51, inhibition of the poly(ADP-ribose) polymerase 1 (PARP1) DNA repair protein, and reduced levels of the NHEJ-associated proteins DNA-PKcs and X-ray repair cross-complementing protein 6 (XRCC6)[30,48,49]. Moreover, aberrant sequestration of the NER repair protein XPA at sites of DSBs further interferes with DSB repair and decreases NER[45] (FIG. 2).

Impaired DNA repair in other progeroid syndromes.—A causal role of NER and DSB repair in ageing and AADs is further suggested by the progeroid phenotypes in Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy, all of which are caused by defects in NER proteins, as well as in ataxia telangiectasia, Bloom syndrome and Werner syndrome, all of which are defective in DSB repair[20] (FIG. 2; TABLE 1). The increased prevalence of neuronal pathologies among patients with some of these progeroid syndromes indicates that postmitotic neurons crucially depend on DNA repair efficiency, probably because they accumulate DNA damage during the organismal lifespan as a result of high transcriptional activity and exposure to oxidative metabolic stress[50]. Paradoxically, the efficiency of the DNA repair system in the brain is low, and it is even lower in neurodegenerative diseases[50]. This observation is consistent with the increased incidence of aneuploid neurons in Alzheimer disease[50,51], which probably results from defective NHEJ-mediated repair and is consistent with the finding that mutations of the parkin protein in familial Parkinson disease[52] (BOX 1) directly inhibit NER. Moreover, both these diseases cause fibroblasts and lymphoblasts to become hypersensitive to X-ray-induced DNA damage[50,53]. These increased amounts of DNA damage may functionally impair neurons and promote an apoptosis-driven decline in neuronal mass[50].

DNA repair impairment in AADs.—Increased DNA damage is also seen in the specific cell types that are affected in AADs. Vascular smooth muscle cells (VSMCs), which become defective in atherosclerosis, have higher amounts of DNA damage after exposure to reactive oxygen species (ROS), owing to increased mechanical stress, lipoprotein accumulation and inflammatory responses. The subsequent reductions in the proliferation and apoptosis of VSMCs may promote atherosclerotic plaque rupture[54]. VSMCs become increasingly senescent in patients with HGPS in conjunction with defective homologous recombination repair[48]. Similarly, lymphocytes from patients with type 2 diabetes (T2D) have reduced capacity to repair ROS-induced DNA damage, and NHEJ deficiency impairs pancreatic β-cells[55,56]. Furthermore, differentiation of bone-forming osteoblasts is inhibited by DNA damage and contributes to weakened bone structure in a progeria mouse model[57]. In line with this evidence, defective NHEJ can result in osteopenia, a less severe ageing-related form of osteoporosis[58].

Decreased DNA repair efficiency leads to the accumulation of genomic mutations during ageing, which promotes tumorigenesis through activation of oncogenes or inactivation of tumour suppressor genes. This mechanism is exemplified by the increased incidence of tumours observed in most of the DNA repair pathway-associated progeroid syndromes[20] (TABLE 1).

The above examples suggest that DNA damage is a key factor in AADs, but a key question that remains open is whether the effect of DNA repair on genome integrity is stochastic or affects specific genome regions[59].

Reduced telomere length

Telomeres are repetitive sequences at the distal ends of chromosomes that are capped by the shelterin complex, which includes the telomeric repeat-binding factor 1 (TERF1) and TERF2 proteins, and protect chromosomal ends from being recognized as DSBs[60]. Telomeres shorten during cell division (a process known as telomere attrition) and can trigger DNA damage signalling and cellular senescence when they reach a critically short length. Telomerase, a complex consisting of telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC), which elongates telomeres at each cell cycle, is highly expressed in embryonic stem cells; however, it is undetectable in most other human cells[61].

Patients with HGPS show increased activation of DNA damage signalling at telomeres; their telomere length is reduced[62,63] and telomeric chromosomal aberrations increased owing to impaired homologous recombination[64]. Similarly, chromosomal end-to-end fusions occur in the progeroid *Terc*-knockout mouse model[20]. Progerin may further increase telomere damage by disrupting both endogenous lamin A and TERF2-dependent protective stabilization of telomere ends, which is also affected in patients with atypical Werner syndrome[65–68].

Telomere damage can trigger the synthesis of progerin in wild-type cells, and the loss of function of the telomerase complex causes the premature ageing syndrome DKC, which suggests a causal role for telomere shortening in AADs[20,69] (TABLE 1). Genetic ablation of *Terc* RNA in mice shortens telomeres to a critical length within a few generations, leading to cardiac myocyte hypertrophy, impaired left ventricular function and increased systolic blood pressure, all of which are normally associated with ageing[61]. Additionally, *Terf2*-knockout mice show increased apoptosis of cardiac myocytes[60]. A role for telomere shortening in cardiovascular disease is further supported by *Terc*-knockout mice presenting an atherosclerotic phenotype, and by vascular endothelial cells and VSMCs from human patients who have increased haemodynamic stress and atherosclerotic regions having shorter telomeres[60]. Increasing telomerase activity can be beneficial because it prolongs the lifespan of vascular endothelial cells, but it is also detrimental because it promotes neointimal VSMC and leukocyte proliferation, which aggravates the atherosclerotic phenotype[60].

Telomere attrition also promotes osteoporosis in patients with DKC. Chondrocytes and peripheral blood leukocytes in elderly individuals with osteoporosis have shorter telomeres, and restoring telomerase activity in osteoblasts increases bone deposition[70]. Mutations that result in TERT loss of function and telomere attrition also cause ageing-associated lung emphysema and fibrosis[71]. Studies in mouse models suggest that telomere attrition accelerates the development of ageing-related lung emphysema by reducing the ability of the lungs to withstand toxin-induced stress[72,73]. In CKD, telomere attrition was found to reduce cell viability and increase renal injury upon ischaemia–reperfusion[71]. The same relationship may hold for pancreatic β-cells, the survival and functionality of which are compromised under high blood sugar levels in *Tert*-knockout mice[71].

Although TERT expression in fibroblasts from patients with HGPS can rescue certain cellular ageing-associated defects, the observation that progerin and TERT-expressing human fibroblasts retain some ageing defects suggests that other cellular ageing mechanisms may either regulate the integrity of telomeres and other genomic regions or drive ageing[32,74].

Epigenetic defects

Chromatin structure is modulated by DNA methylation and histone post-translational modifications, which affect genomic integrity, gene expression and ultimately cellular health and disease[26,75].

Changes in histone methylation in ageing

Cells from aged individuals show a global loss of his-tones and a progressive loss of histone H3 trimethylation at lysines 9 and 27 (H3K9me3 and H3K27me3), which are repressive marks that promote chromatin compaction[26] (FIG. 3). Loss of heterochromatin is increased by ageing-associated downregulation of heterochromatin protein 1 homologue-α (HP1α; also known as CBX5), the nucleosome remodelling and deacetylase (NuRD) chromatin remodelling complex and Polycomb group (PCG) proteins, all of which are epigenetic silencers[20,32,76]. Global loss of heterochromatin, HP1α and NuRD complex protein members has also been reported in cells from patients with HGPS[28,77]. In these cells, loss of the NuRD complex and decreased expression of the H3K27-specific methyltransferase EZH2 results in the depletion of the repressive H3K27me3 heterochromatin mark[32,77] (FIG. 2). Interestingly, knockdown of the H3K27 demethylase UTX1 in *Caenorhabditis elegans* extends the lifespan by 30%[78]. Decreased activity of the Polycomb repressive complex 2 (PRC2) member EZH2 has been implicated in T2D, as conditional deletion of *EZH2* in pancreatic β-cells in juvenile mice reduces β-cell proliferation and mass through induced cellular senescence, resulting in a diabetic phenotype[79].

The major function of the PRC2 complex is to establish H3K27me3 marks, to which the PRC1 complex binds, and to induce transcriptional silencing by promoting histone lysine *N*-methyltransferase SUV39H1-mediated H3K9me3 (REF. 80) (FIG. 3). Disruptions of the nuclear lamina affect PCG protein localization, resulting in genome-wide loss of H3K9me3 in HGPS; this loss seems to contribute to defective telomere maintenance and aberrant activation of pericentromeric satellite repeats, which are normally silent[32,77,81]. Progressive loss of HP1α, which binds to H3K9me3, may further contribute to hetero chromatin depletion, which cannot be compensated for by the globally increased levels of the H4K20me3 heterochromatin mark[77]. Progressive loss of H3K9me3 also occurs in human cells lacking the Werner protein, probably as a result of reduced SUV39H1 activity and HP1α binding[82]. Conversely, increased levels of H3K9me3 are observed in a progeria-like mouse model in which the gene for the prelamin A-processing enzyme ZMPSTE24 is deleted. In this mouse model, SUV39H1 depletion restores genomic integrity and increases lifespan[83]. Loss of H3K9 methylation has also been linked to several AADs, and H3K9me3 depletion activates a vascular inflammatory gene signature in CKD[84]. In familial Alzheimer disease, the accumulation of mutant tau protein reduces H3K9me2 and HP1α levels, which

results in upregulation of the neurotoxic piwi-like protein 1 (PIWIL1)[85]. Moreover, reduced expression of HP1α occurs in multiple cancers and correlates with poor prognosis[86].

Ageing affects histone acetylation

The global loss of histone methylation in HGPS is accompanied by hypoacetylation of histones H2B and H4, possibly owing to diminished association of the histone acetyltransferase KAT8 with the nuclear lamina[87]. Interestingly, either KAT8 overexpression or treatment with histone deacetylase (HDAC) inhibitors extends the lifespan of progeria-like *Zmpste24*-knockout mice[87]. The H4K16 acetylation (H4K16ac) mark, which is associated with both transcriptional activation and repression, promotes NHEJ and homologous recombination, and increased levels of H4K16ac are associated with an extended cellular lifespan[88,89]. Treatment with HDAC inhibitors can prevent ageing-associated cognitive decline and reduce the severity of ischaemic stroke, Parkinson disease and osteoporosis in mouse models of disease by altering the expression of disease-promoting and disease-repressing genes[90,91]. HDACs, including sirtuins, also regulate the acetylation of non-histone proteins, including master regulators of cell growth and metabolism, suggesting a direct role for epigenetic regulation in the metabolic control of ageing[26].

Cellular metabolism

Metabolic signalling is crucial for the maintenance of cellular homeostasis, as such signalling allocates energy to essential protective mechanisms that safeguard the integrity of the genome, epigenome, proteome and cellular organelles. Dysregulated metabolic signalling, which triggers a cascade of deleterious cellular events, is widely implicated in AADs.

Nutrient-sensing metabolic pathways

Maintaining a proper balance between catabolic and anabolic pathways is essential to maintaining adequate cellular energy levels. Disruption of this equilibrium perturbs cellular homeostasis, and drives cellular ageing and AADs[26]. Nutrient-sensing signalling pathways, including the insulin and insulin-like growth factor 1 (IGF1) signalling (IIS) pathway, and the sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK) pathways, regulate the metabolic status of cells and have prominent roles in physiological ageing[26].

Dysregulated IGF1 signalling causes ageing.—The IIS pathway is activated when there is an excess of nutrients, including insulin, IGF1 and free amino acids. This activity results in downstream activation of mTOR (FIG. 4) and, through various downstream effectors, increases protein synthesis and the promotion of other anabolic processes[92]. Reduced IIS signalling, either caused by genetic polymorphisms or following caloric restriction, promotes longevity and healthspan[26]. However, these effects of reduced IIS signalling are dependent on the age of the organism, the duration and the degree of repression, and the levels of cellular stressors such as inflammation. While short and moderate IIS repression may be beneficial by minimizing cellular growth to direct energy towards the repair of cellular damage, chronically increased attenuation is deleterious and

promotes ageing[92]. In the progeria-like *Zmpste24*-knockout mouse model, IGF1 levels are drastically reduced from a neonatal age throughout life, and IGF1 treatment extends lifespan and delays the manifestation of progeroid features[93]. Parkinson disease is characterized by prolonged attenuation of mTOR, which results in increased neuronal death; this activity in animal models can be partially prevented by mTOR activation[94].

Sustained IIS activation can also be detrimental to cellular health (FIG. 4). T2D-induced chronic mTOR activation deactivates insulin receptor substrate 1 (IRS1) through a feedback loop that uncouples insulin and IGF1 receptors from downstream signalling and causes insulin resistance[94]. This mechanism causes diabetes-associated symptoms in patients with Werner syndrome that can be alleviated with mTOR inhibitors[20,95]. Neurons are highly sensitive to alterations in IIS signalling because of their elevated metabolic rate and dependency on glucose[94]. In patients affected by Alzheimer disease, symptoms of diabetes — which result from uncoupling and inefficient IGF1 receptor signalling, and are aggravated by inhibiting insulin receptors with β-amyloids — precede cognitive decline by decades. Treatment with the mTOR inhibitor rapamycin partially restores insulin–mTOR signalling and alleviates neuronal defects in animal models of Alzheimer disease[94,96].

Decreased sirtuin and AMPK activity contributes to AADs.—The protein deacetylase SIRT1 stimulates pathways that increase cellular energy levels and promote cell survival under conditions of stress and increased levels of NAD^+ (REF. 26). During ageing, increased DNA damage signalling depletes NAD^+, reducing SIRT1 activity[97] (FIG. 4). The importance of decreased SIRT1 activity in ageing is supported by the finding that its restoration in progeria-like *Zmpste24*-knockout mice, resulting from treatment with the SIRT1 activator resveratrol, improves osteoporotic pathologies and extends lifespan[98]. SIRT1 activation also alleviates symptoms of Alzheimer disease, as it inhibits mTOR, which is hyper-activated in Alzheimer disease, and induces mTOR-independent anti-amyloidic cleavage and degradation of tau protein[92] (TABLE 1).

SIRT1 activation also increases healthspan through activation of AMPK. In response to elevated AMP:ATP ratios, AMPK inhibits mTOR, promotes lipid catabolism and gluconeogenesis and, through positive feedback, activates SIRT1 (REF. 99) (FIG. 4). Like SIRT1, AMPK activity decreases with age. Consistent with this decline, treatment with the AMPK activator metformin extends the lifespan of *C. elegans* and mice, reduces kidney fibrosis in individuals with CKD and exerts anti-diabetic effects[26,100]. T2D metabolic defects are also ameliorated by increased activation of SIRT6, possibly through suppression of IGF1 signalling[92]. SIRT6 levels are decreased in patients with HGPS, and SIRT6 over-expression partially rescues the senescent phenotype of fibroblasts from patients with HGPS and extends the lifespan of wild-type male mice[101,102].

Although it is evident that ageing is linked to IIS, AMPK and sirtuin-mediated metabolic signalling, how the downstream activators of these pathways affect cellular ageing in disease is only partially understood. An important factor that impacts cellular ageing in this context is the metabolic control of mitochondrial integrity.

Mitochondrial dysfunction and oxidative damage

Mitochondria produce ATP in an oxygen-dependent manner through oxidative phosphorylation (OXPHOS) by creating a proton gradient across the inner mitochondrial membrane (through electron transport chain protein complexes), which is then used by ATP synthase. In addition, mitochondria regulate gluconeogenesis, fatty acid oxidation, intracellular calcium levels and apoptosis[103].

Decreased OXPHOS activity in HGPS, physiological ageing and AADs.— Mitochondrial integrity becomes compromised during ageing, as indicated by decreased transmembrane potential, increased formation of ROS at the expense of ATP synthesis, calcium dysregulation, apoptosis induction and increased mutations in mitochondrial DNA (mtDNA, which encodes proteins in the OXPHOS system)[103]. The connection between mitochondrial integrity and ageing is demonstrated by knock-in mice that express a proofreading-deficient version of the mtDNA polymerase POLGα. In these mice, OXPHOS efficiency is reduced owing to the accumulation of mtDNA mutations, which causes accelerated ageing[104]. In HGPS, mitochondria are aberrantly swollen and fragmented[105], and OXPHOS activity progressively decreases from an early age[106]. *Wrn*-null mice have enlarged mitochondria, increased accumulation of mtDNA mutations and increased ROS formation at the expense of ATP generation[107].

The OXPHOS system is a major producer of ROS[108]. Chronically elevated ROS levels lead to damage of cellular macromolecules, including OXPHOS complex proteins and mtDNA, creating a cycle in which ROS impairs mitochondrial integrity to further increase oxidative stress[109] (FIG. 4). In Alzheimer disease, elevated ROS levels precede and promote the formation of β-amyloid- and tau-containing plaques and neurofibrillary tangles[103], which further impair OXPHOS complexes[110]. A similar self-promoting loop occurs in familial Parkinson disease, in which disease-causing proteins increase ROS, impair OXPHOS and ultimately trigger neuronal death[103]. Genetic abrogation of the mtDNA surveillance factor TFAM similarly results in Parkinson disease in mice[103]. In atherosclerosis, chronic ROS promotes plaque formation by inhibiting OXPHOS and oxidizing low-density lipoprotein, which attracts monocytes and thereby has deleterious effects[103]. Mitochondrial dysfunction-induced inflammatory responses have also been reported in COPD[111]. ROS-induced loss of mitochondrial integrity further promotes vascular calcification, which is observed in individuals with HGPS, atherosclerosis, osteoporosis, CKD, T2D or Alzheimer disease[112,113].

Decreased antioxidative mechanisms and mitochondrial biogenesis in HGPS and AADs.—Cells can disrupt deleterious ROS-mitochondrial interplay by activating antioxidative mechanisms that decrease ROS levels (FIG. 4). Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcriptional master regulator of antioxidants, including thioredoxin-dependent peroxide reductase (PRDX3), which neutralizes most mitochondrially produced hydrogen peroxide[114,115]. NRF2 activity decreases with age[116]. Progerin aberrantly sequesters NRF2 and thereby inhibits its transcriptional activity, which results in chronic oxidative stress and drives the formation of cellular ageing in HGPS[27]. Defective antioxidative defence mechanisms also underlie Alzheimer disease and Parkinson

disease, possibly either through defective NRF2 activation or via direct inhibition of antioxidants by disease-causing proteins, such as PRDX3 inhibition via a Parkinson disease-causing *LRRK2* mutant[108,115,117]. Restoring mitochondrial integrity by overexpressing a mitochondria-targeted catalase antioxidant extends the lifespan of mice and protects against neurodegeneration, cardiac disease, cancer and insulin resistance[103,118].

Increased mitochondrial turnover and replacement of damaged mitochondria with intact ones also protects against oxidative damage. Peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α) promotes mitochondrial biogenesis while simultaneously activating the NRF2 antioxidative response[103] (FIG. 4). Activation of PGC1α alleviates mitochondrial dysfunction and other ageing defects in fibroblasts from patients with HGPS[105], although the beneficial effects of PCG1α activation *in vivo* appear to be tissue-specific and dependent on the duration and extent of activation[37]. Decreased PGC1α activity occurs in Alzheimer disease and Parkinson disease and is implicated in CKD-associated muscular dystrophy[110,119]. Diminished metabolic activation of the PGC1α upstream regulators SIRT1 and AMPK in HGPS, ageing and AADs likely underlies the observed decrease in PGC1α activity[26].

Overall, these observations indicate that metabolic signalling is coupled to mitochondrial integrity and ROS formation. The balance of this triad has major implications for the proteolytic autophagy system, which aids in the degradation of defective mitochondria, the recycling of amino acids required for mTOR-regulated protein synthesis and the removal of ROS-damaged macromolecules to maintain cellular homeostasis.

Proteostasis and proteolysis

Proteostasis is defined as the maintenance of a functional proteome through balanced regulation of protein synthesis, repair and proteolysis. The integrity of the proteome is dependent on continuous protein turnover, which ensures the degradation of damaged and misfolded proteins by autophagy and the ubiquitin–proteasome system (UPS), both of which are affected in human progeroid syndromes, physiological ageing and AADs.

Autophagy ameliorates ageing defects in HGPS

The metabolically driven build-up of damaged mitochondria and oxidized protein aggregates in ageing and disease indicates an imbalance between proteotoxic insults and the proteolytic pathways that remove damaged organelles and protein aggregates. Autophagy is a bulk degradative mechanism in which autophagosomes engulf damaged cellular components and promote their proteolytic degradation through fusion with hydrolase-containing lysosomes[120].

Interestingly, the IIS cascade impairs autophagy by activating mTOR[26] (FIG. 4). While temporary attenuation of autophagy by mTOR can be beneficial for cellular health by promoting anabolism, sustained autophagic impairment results in the toxic accumulation of protein aggregates in inclusion bodies called aggresomes, which fail to be degraded. Aggresomes contain both the autophagy adaptor protein p62 (also known as SQSTM1) and ubiquitin, which normally attract and promote proteolytic degradation of the aggregates[120].

In HGPS, ubiquitin- and p62-positive progerin aggregates have been identified[121]. Progerin aggregates are thought to be deleterious owing to the entrapment of normal cellular proteins, including NRF2 (REF. 27). Activation of autophagy through rapamycin-mediated mTOR inhibition promotes the solubilization and clearance of progerin and thereby alleviates cellular ageing defects[121]. Rapamycin treatment extends the lifespan of mice as well as that of *C. elegans*, where these lifespan-extending effects of IIS suppression are autophagy-dependent[26,122].

Proteostasis and autophagy defects in AADs

There is evidence of benefits of autophagic activation in AADs, and these effects can mostly be attributed to the increased clearance of disease-promoting toxic aggregates that form during chronic oxidative stress[120]. In Alzheimer disease, the levels of the lysosomal protease cathepsin D are reduced, impairing the clearance of β-amyloid and phosphorylated tau aggregates. Reducing the hyperactivated status of IIS–mTOR signalling increases autophagic clearance of these aggregates and rescues memory deficits in mouse models of Alzheimer disease[123,124]. Patients with Parkinson disease have decreased levels of lysosome-associated membrane glycoprotein 2 (LAMP2), which is thought to impair the clearance of α-synuclein aggregates and increase neuronal death[125]. In addition, genetic defects in the parkin and PTEN-induced putative kinase protein 1 (PINK1) proteins (BOX 1) impair autophagic clearance of damaged mitochondria in familial Parkinson disease[120].

LAMP2A and cathepsin D deficiencies are also known causes of cardiomyopathies, and impaired autophagy can promote atherosclerosis by promoting VSMC senescence and cell death[126,127]. Protein aggregation has also been implicated in T2D, as it has been found that amylin aggregates form in the pancreas in T2D mouse models; furthermore, aggregation is increased by genetic ablation of the autophagic protein ATG7 (REF. 128). Furthermore, an amylin mutation that increases the propensity of the protein to form aggregates is associated with T2D. Mutation-induced amylin aggregation precedes pancreatic β-cell dysfunction and is sufficient to induce a diabetic phenotype in wild-type rats[128].

Low proteasomal activity in ageing and AADs

The UPS clears damaged proteins through ATP-dependent proteolysis[126]. Patients with HGPS have decreased UPS activity[29] (FIG. 4), and proteasomal activity declines with ageing. In line with these findings, increased UPS activity extends the lifespan of *Drosophila melanogaster* and *C. elegans*[129].

Dopaminergic ablation of the P26S4 subunit of the UPS in mice increases α-synuclein aggregation and neuronal death in a manner similar to Parkinson disease[120]. In addition, reduced levels of the UPS activators PA700 and PA28 in the substantia nigra correlate with α-synuclein aggregation in patients with Parkinson disease[130]. Moderate repression of UPS activity by over expression of a dominant-negative proteasomal PSMB5 catalytic subunit mutant aggravates ischaemia–reperfusion-mediated cardiac defects, and pre-amyloid oligomer levels are increased in dilated and hyper-trophic cardiomyopathy[126]. Conversely, UPS activation is an emerging therapeutic strategy against cardiomyopathies[126]. Overall,

these findings indicate that autophagy and UPS play a crucial part in counteracting ageing-associated metabolically-induced stress.

Perturbation of cell fate

The accumulation of cellular damage in ageing triggers pathways that control cell proliferation and differentiation as well as stem cell-mediated regeneration to prevent the permanent collapse of cellular and tissue homeostasis. Of particular importance in ageing and AADs are cellular senescence and regenerative pathways.

Increased cell senescence in HGPS and AADs

The loss of genomic and proteomic integrity can induce cellular senescence, which is an irreversible state of proliferative arrest that is mainly dependent on chronic activation of the tumour suppressor RB–p16 and p53–p21 pathways[131,132] (FIG. 5). Temporary activation of these pathways can be beneficial, as it enables the repair of cellular damage before continuing proliferation. However, chronic activation of the RB–p16 and p53–p21 pathways has detrimental effects because it triggers self-sustaining inflammatory signalling driven by transforming growth factor β (TGFβ) and nuclear factor-κβ (NF-κB). This signalling is typified by the expression of interleukin-1 (IL-1) and 6 (IL-6), tumour necrosis factor-α (TNFα), cyclooxygenase 2 (COX2), and C-X-C motif chemokine 1 (CXCL1) and CXCL2 (REF. 131) (FIG. 5). This state is referred to as senescence-associated secretory phenotype (SASP), and its long-term activation can compromise the intercellular communication between senescent and immune-responsive cells, thereby preventing immune system-mediated clearance of senescent cells, which is normally promoted by SASP[131]. Failure to clear senescent cells can aggravate physiological decline during ageing by inducing cellular senescence in neighbouring cells via gap junction-mediated cell–cell contacts[26]. In line with this finding, artificially induced clearance of senescent cells extends the lifespan and healthspan of progeroid mice lacking the mitotic checkpoint protein BubR1 (TABLE 1), inhibits atherogenesis in low-density lipoprotein receptor-deficient mice and preserves renal and cardiac function in wild-type mice[6,7,133].

In HGPS, increased cellular damage hyperactivates the RB–p16, p53–p21 and NF-κB pathways, causing cellular senescence and SASP, which is accompanied by increased levels of IL6, TNFα, CXCL1 and CXCL2 in progeria mouse models[34,134,135]. NF-κB hyperactivation is partially detrimental owing to its epigenetics-altering effects via activation of the histone methyltransferase DOT1L[136]. Conversely, genetic disruption of NF-κB or p53 signalling improves the lifespan and healthspan of HGPS mouse models[34,134].

In Alzheimer disease, neuron-supporting astrocytes, which have naturally high basal NF-κB activity and are implicated in the disease's pathology, show increased p16 and IL-6 expression levels[137]. Hyperactivation of canonical NF-κB signalling is detrimental to astrocytes and is believed to promote β-amyloid aggregation, which reversibly drives TNFα-, IL-1β- and COX2-mediated inflammatory signalling[138]. Like Alzheimer disease, Parkinson disease leads to increased NF-κB activity and COX2 levels[139]. Treatment of wild-type mice with COX2 inhibitors attenuates the neurotoxic effects of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which induces Parkinson disease via the inhibition of

OXPHOS[139]. Increased IL-1β exposure further aggravates the progression of Parkinson disease by inducing α-synuclein expression[139].

In ageing-associated idiopathic lung fibrosis, increased IL-1β levels may promote the differentiation of lung fibroblasts into myofibroblasts, thereby promoting fibrosis[140]. SASP-regulated changes in cellular identity also play a part in cancer, as IL-6 and IL-8 promote tumorigenesis by increasing epithelial-to-mesenchymal transition (EMT)[131]. SASP-suppressing TGFβ inhibitors have been shown to attenuate the progression of some tumours and are currently being evaluated in clinical trials[141]. Finally, TGFβ- and NF-κB-driven inflammatory processes leading to SASP underlie CKD, and repression of both pathways with angiotensin-converting enzyme inhibitors slows the progression of CKD[141].

Overall, irreversible growth arrest and perpetual hyperactivation of inflammatory secretory pathways can lead to a permanent state of cellular senescence that underlies ageing and AADs. The accumulation of senescent cells can be counteracted by stem cell-mediated regeneration.

Compromised stem cell regenerative capacity

Stem cells, which are capable of self-renewal and multi-lineage differentiation, reside in specific niches throughout the human body. Human mesenchymal stem cells (hMSCs) are present in virtually all tissues and differentiate into osteocytes, chondrocytes and adipocytes, whereas VSMCs are non-terminally differentiated cells of the vascular wall and only have limited differentiation plasticity[142,143]. Cellular ageing defects in fibroblasts isolated from patients with HGPS can be reversed upon generation of induced pluripotent stem cells (iPSCs), which do not express progerin because of the naturally occurring transcriptional repression of the *LMNA* gene that occurs in iPSCs[30,31]. Upon re-differentiation of HGPS-iPSCs into hMSCs and VSMCs, the transcriptional reactivation of the *LMNA* gene and the concomitant induction of progerin expression results in the emergence of the typical genomic, proteomic and senescent cellular ageing defects associated with HGPS[30,31] (FIGS 1–4) and decreases survival rates under stress conditions, such as hypoxia. This relationship may explain the loss of VSMCs in patients with HGPS owing to exposure to haemodynamic stress as well as the reduced ability of HGPS-hMSCs to prevent ischaemia–reperfusion damage in a hindlimb muscle model[31]. The viability and capacity of HGPS-hMSCs to withstand chronic oxidative stress can be restored through re-activation of NRF2, which is impaired by progerin[27].

In addition to stem cell exhaustion, which can also be observed for dermal stem cells in an HGPS mouse model, the accumulation of ageing defects may compromise the regenerative capacity of stem cells by altering their differentiation potential[144]. In that regard, progerin delays the differentiation of VSMCs and increases the osteogenic differentiation of hMSCs at the expense of adipocyte generation, which may contribute to the calcification of tissues (such as the skin and vascular walls) observed in patients with HGPS[48,145].

The observed accumulation of low levels of progerin and decreased levels of Werner protein in wild-type VSMCs and hMSCs, respectively, from elderly individuals may also explain the impaired regenerative capacity of stem cells during physiological ageing[82,146]. Indeed, one

or more of the typical cellular ageing hallmarks, such as oxidative stress or activation of DNA damage, senescence and SASP pathways, has been reported to occur with ageing in hMSCs, VSMCs, haematopoietic stem cells (HSCs), skeletal muscle cells and neuronal stem cells[143,147]. The detrimental effects of these hallmarks on stem cells is demonstrated by the decreased regrowth of lung and pancreatic tissues, which have naturally high regenerative potential, upon partial resection in aged humans compared with that in young adults[148,149]. Conversely, silencing p16, activating SIRT1, blocking SASP effects by overexpressing an IL-1 receptor antagonist or reducing ROS by overexpressing the anti-oxidant superoxide dismutase 2 improves the regenerative capacity of hMSCs and HSCs as well as neuronal, intestinal and muscle stem cells[143,147].

Adult stem cells may be particularly prone to ageing defects, as they mostly exist in quiescence, that is, a state of non-permanent growth arrest, which has been reported to coincide with decreased levels of DNA repair proteins and the postponement of DNA repair until re-entry into the cell cycle[147]. It is conceivable that the accumulation of DNA damage during this quiescent state may exceed a threshold that impairs subsequent stem cell function.

Decreased regenerative capacity of stem cells is important in several AADs. For example, VSMC senescence promotes the formation of atherosclerotic plaques[150]. In T2D, hMSCs may have diminished proliferative and differentiation capacity, and hMSC- and pancreatic-specific stem cell activity is beneficial to pancreatic β-cell mass and function[148]. Furthermore, the differentiation potential of lung-specific stem cells is dysregulated in ageing-associated idiopathic pulmonary fibrosis, and functional hMSCs aid in the repair of osteoporotic bone fractures[143,149]. Although the contribution of cardiac and neuronal stem cells to the turnover of terminally differentiated myocytes and neurons remains unclear[147,151], their beneficial immunoregulatory secretory effects have been established and shown to alleviate cognitive defects in mouse models of Alzheimer disease upon injection of hMSCs[147,151].

Overall, these observations in premature ageing disorders, natural ageing and AADs suggest that premature ageing and AADs are driven by genetic, metabolic and senescence-associated cellular-ageing defects that perturb the fate of stem cells.

Perspective

Here, we have explored the interplay between premature ageing, normal ageing and AADs. We discuss how individual cellular defects in the regulation of genomic, telomeric, epigenetic, metabolic, mitochondrial, proteolytic and cell cycle integrity contribute to cellular ageing and AADs (FIG. 1). The picture that emerges is one of extensive connections between these hallmarks of ageing; consequently, disrupting one of these processes induces other defects, which ultimately lead to a collapse of cell homeostasis that drives disease. Although this cascade reduces healthspan and drives ageing, the interconnected nature of these events may also provide a therapeutic opportunity in that amelioration of one or more of these hallmarks of ageing may be sufficient to alleviate the process as a whole.

Observations made in studies of premature ageing systems, normal ageing and AADs are complementary to each other. Premature ageing diseases only reflect some aspects of ageing, but they offer the benefit of well-defined genetics and controllable experimental approaches. Physiological ageing and AADs reflect the true ageing process, but their study is complicated by the confounding effects of their physiological and environmental context. Further unravelling the intricacies of the cellular ageing network will require the development of novel experimental model systems that are not hampered by the traditionally slow stochastic accumulation and low penetrance of ageing defects. Premature ageing diseases in humans provide such an opportunity because the associated cellular ageing defects recapitulate, to a large extent, those observed in physiological ageing and AADs. Furthermore, the accelerated nature of premature ageing syndromes, their defined single genetic cause and their strong phenotypic penetrance enables the development of robust cellular ageing assays.

The generation of iPSCs from patients with these and other premature ageing diseases is an exciting new strategy that enables the temporal dissection of the formation of prominent ageing defects[152]. Alternatively, inducible expression of mutant proteins linked to progeroid syndromes in wild-type cells can similarly address these questions, and both strategies have the additional benefit of being easily combined with available RNAi and CRISPR high-throughput screening approaches. CRISPR-Cas9 gene editing can further accelerate the characterization of newly identified ageing mechanisms by facilitating the generation of novel *in vivo* ageing and AAD models.

We anticipate that the development of new experimental approaches for the study of human premature ageing diseases will begin to resolve key questions on how cellular ageing defects are linked and how they are counteracted by anti-ageing pathways. Such studies will increase our understanding of the ageing process and will facilitate the detection and treatment of chronic ageing-associated and leading diseases, such as Alzheimer disease, Parkinson disease, atherosclerosis, diabetes and cancer.

Glossary

Nucleotide excision repair
(NER). A DNA repair pathway specialized in the removal of bulky DNA adducts, including ultraviolet damage-induced thymidine dimers

Non-homologous end joining
(NHEJ). A DNA repair pathway that repairs double-strand breaks through direct ligation of the broken ends without the need of a homologous template

Oxidative phosphorylation
(OXPHOS). A process by which electrons are transferred from electron donors to electron acceptors, thereby releasing energy in the form of ATP. In prokaryotes, this process takes place in the inner mitochondrial membrane at the site of the electron transport chain

Ubiquitin–proteasome system

(UPS). A system that degrades proteins marked by degradation-specific ubiquitin marks in an ATP-dependent manner

Epithelial-to-mesenchymal transition
(EMT). A process by which epithelial cells undergo various molecular changes related to cell–cell adhesion, polarity and invasive properties, in order to become mesenchymal cells. EMT has beneficial roles in wound healing but exerts detrimental effects in organ fibrosis and the initiation of tumour metastasis

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Box 1 | Chronic ageing-associated diseases

Alzheimer disease

A chronic neurodegenerative disease characterized by dementia, disorientation, mood swings, loss of appetite, jumbled speech and an inability to coordinate movements; this disease is also associated with an increased risk for osteoporosis and muscle wasting. Familial forms of Alzheimer disease are mostly caused by a mutation in amyloid precursor protein (APP) and presenilins 1 and 2, which increase the production of a cleaved APP product called β−amyloid (typically deposited in senile plaques). Furthermore, neurofibrillary tangles, consisting predominantly of hyperphosphorylated tau protein, are a hallmark of Alzheimer disease.

Atherosclerosis

A vascular disease characterized by arteries that are stiffened and calcified owing to a build−up of cholesterol−loaded plaques, which cause an obstruction of blood flow. Unstable plaques typically have decreased numbers of vascular smooth muscle cells and are more prone to rupture, which may cause heart attack or stroke.

Cancer

A group of diseases involving abnormal cell growth that manifests in either an invasive (malign) or a non−invasive (benign) form as a result of accumulation of genetic mutations that either inhibit the activity of tumour suppressor genes, or activate or overexpress oncogenes.

Chronic kidney disease

A chronic condition typified by a gradual loss of kidney function over time, which can result in high blood pressure, anaemia, loss of bone mass and neuronal damage.

Chronic obstructive pulmonary disease

A group of lung diseases that reduce airflow, cause difficulty breathing and predominantly result from either increased mucus production and inflammation (bronchitis) or the destruction and enlargement of the air spaces (emphysema). Idiopathic pulmonary fibrosis is characterized by a thickening and scarring of the lung, which reduces the exchange of oxygen with the bloodstream. Patients with chronic obstructive pulmonary disease (COPD) are at increased risk for the development of Parkinson disease.

Heart failure

A permanent state of insufficient cardiac output owing to the failure of the heart to properly contract or relax as a result of stretching/thinning or hypertrophy/stiffening, respectively, of the ventricular walls.

Osteoporosis

A loss of bone mass owing to an imbalance between the bone formation and bone resorption processes.

Parkinson disease

A long−term neurodegenerative disorder affecting motor system function that results in shaking, rigidity, difficulty walking and, in many cases, dementia and depression. Hereditary forms of Parkinson disease include mutations in α−synuclein, parkin, leucine−rich repeat serine/threonine−protein kinase 2 (LRRK2), PTEN−induced putative kinase protein 1 (PINK1), DJ1 and ATP13A2. A typical hallmark of Parkinson disease includes the accumulation of α−synuclein in the form of Lewy bodies, which contribute to cell death in the dopaminergic−innervated substantia nigra.

Sarcopenia

A degenerative loss of muscle mass and quality with ageing. Patients with COPD, heart failure, cancer or chronic kidney disease have an increased occurrence of sarcopenia.

Type 2 diabetes

A metabolic disorder in which insulin is not used properly, which is initially compensated for by increased production of insulin by pancreatic β−islet cells. Ultimately, the β−islet cells fail. Patients with type 2 diabetes are at risk for the development of Alzheimer disease as well as for chronic kidney failure.

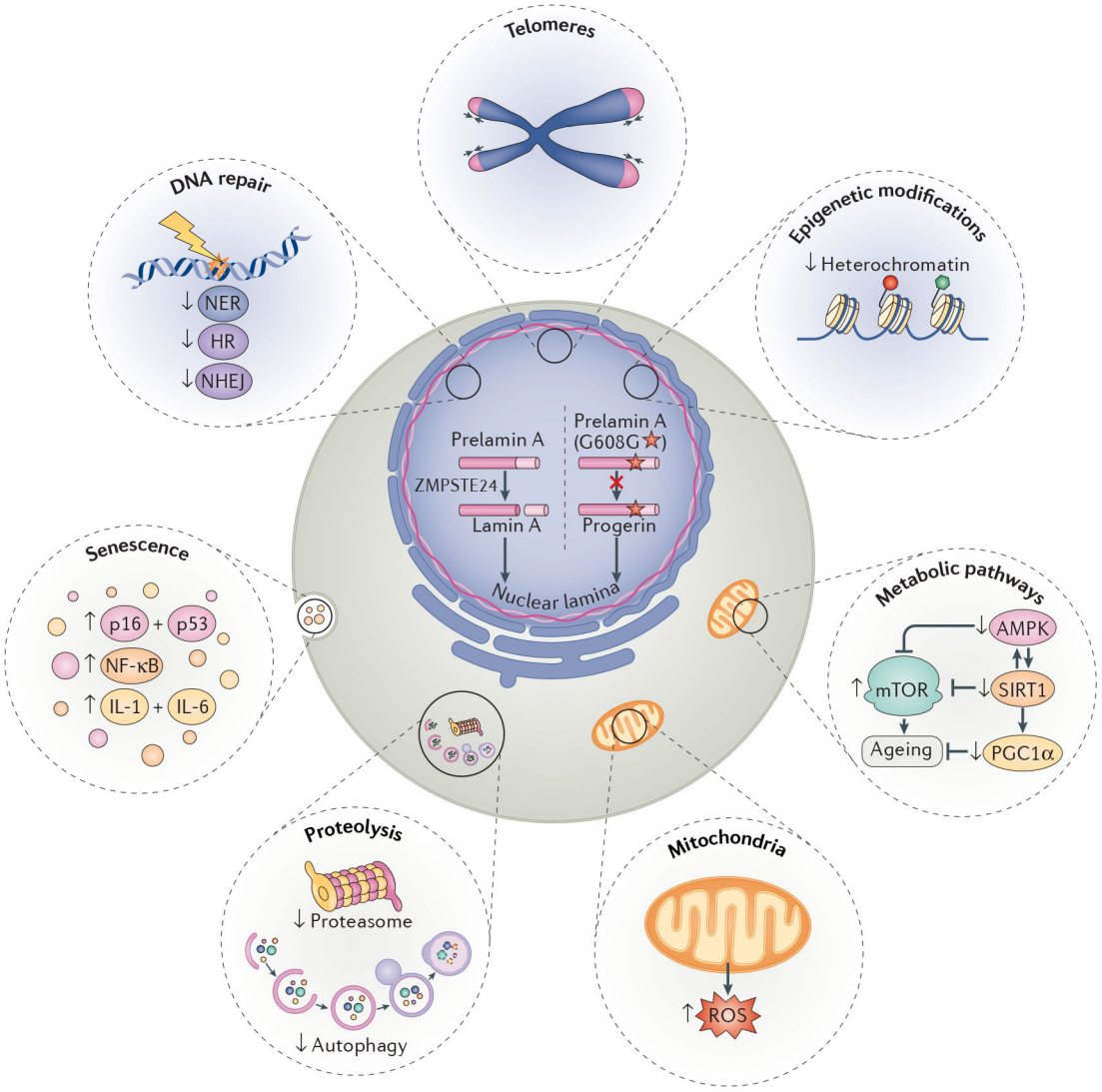

Figure 1 |. Cellular ageing defects.

An overview of the cellular ageing defects that underlie premature ageing disorders, regular ageing and ageing-associated disease. These ageing defects are interconnected and include reduced DNA repair pathway efficiency, loss of genomic integrity, a global loss of heterochromatin, alterations in metabolic signalling, increased formation of reactive oxygen species (ROS) by mitochondria, reduced activity of proteostasis-promoting proteolytic pathways and activation of senescence pathways. Post-translational processing of wild-type prelamin A by the zinc metalloproteinase ZMPSTE24 releases mature wild-type lamin A that is incorporated in the nuclear lamina (indicated in the left half of the cell nucleus). In the premature ageing disease Hutchinson–Gilford progeria syndrome (HGPS), the *LMNA*^{G608G} mutation activates a cryptic splice site that results in the formation of a prelamin A isoform lacking 50 amino acids, including the ZMPSTE24 cleavage site, and is named progerin (indicated in the right half of the cell nucleus). Incorporation of this mutant isoform into the nuclear lamina distorts the nuclear shape and further contributes to other ageing defects shown in the figure (thin arrows indicate dysregulated pathways and

mechanisms). AMPK, AMP-activated protein kinase; HR, homologous recombination; IL-1, interleukin-1; NER, nucleotide excision repair; NHEJ, non-homologous end joining; NF-κB, nuclear factor-κB; PGC1α, proliferator-activated receptor-γ co-activator 1α; SIRT1, sirtuin 1.

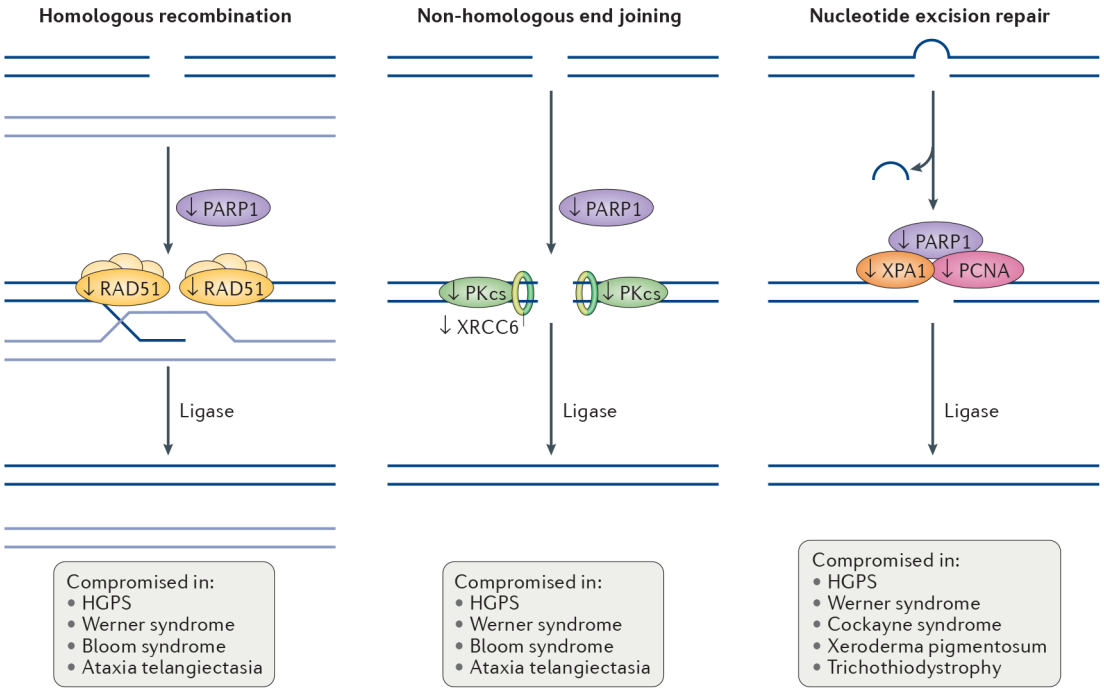

Figure 2 |. Defects in DNA damage repair associated with ageing.

An overview of DNA repair pathways that are impaired in premature ageing syndromes, ageing and ageing-associated diseases. Thin arrows indicate the DNA repair proteins that are impaired specifically in Hutchinson–Gilford progeria syndrome (HGPS). Double-strand breaks are either repaired by homologous recombination through RAD51-mediated repair using the sister chromosome as a template, or X-ray repair cross-complementing protein 6 (XRCC6)- and DNA protein kinase catalytic subunit (PKcs)-mediated non-homologous end joining of the broken ends. Poly(ADP-ribose) polymerase 1 (PARP1) promotes ataxia telangiectasia mutated (ATM)-dependent DNA damage signalling activation. In nucleotide excision repair, bulky DNA adducts are excised, and the resulting single-strand DNA breaks are repaired by the indicated proteins. The final step of repair for each repair pathway includes DNA ligase-mediated joining of the DNA strands at the breakage point. PCNA, proliferating cell nuclear antigen.

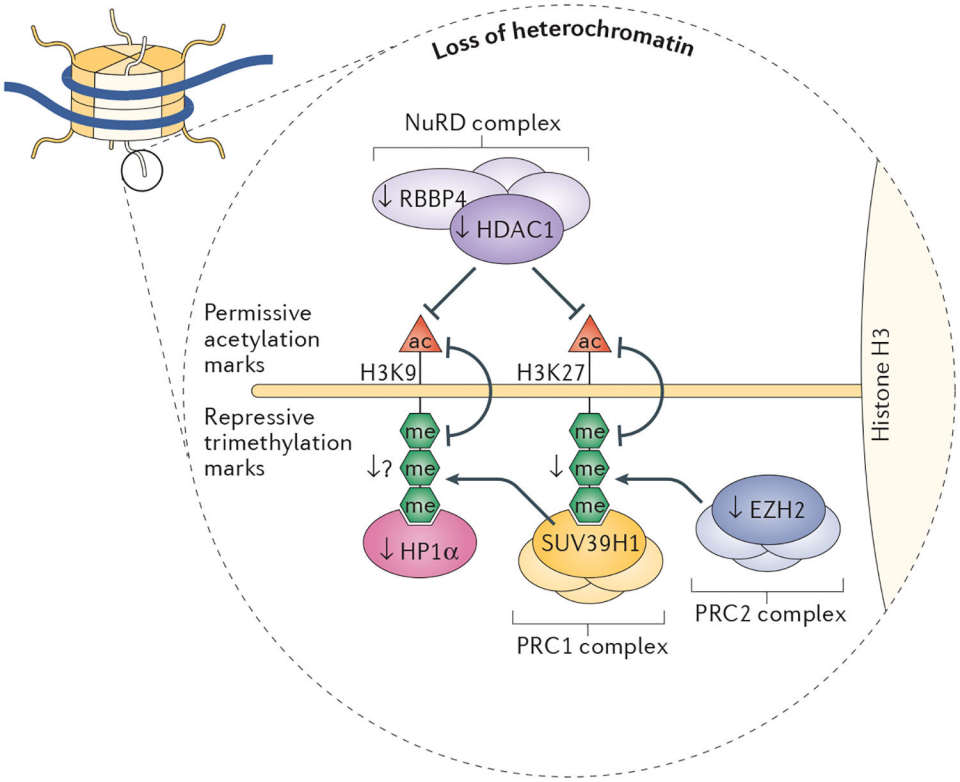

Figure 3 |. Epigenetic defects associated with ageing.

An overview of the epigenetic alterations (indicated by thin arrows) on the histone H3 tail that contribute to global loss of heterochromatin in Hutchinson–Gilford progeria syndrome (HGPS) and are associated with ageing and ageing-associated diseases. Decreased levels of EZH2 reduce the trimethylation (indicated by the 3 green hexagons) of histone H3 at lysine 27 (H3K27) by the Polycomb repressive complex 2 (PRC2) Polycomb group (PCG) protein complex[77], which is a repressive chromatin mark that enables binding of the PRC1 PcG complex and the subsequent trimethylation (H3K9me3), which can bind heterochromatin protein 1 homologue-α (HP1α); these methylation levels are decreased in HGPS[28]. H3K9me3 has been reported to be downregulated in cells from patients with HGPS but was conversely found to be upregulated in a *Zmpste24*-knockout progeria-like mouse model[28,83]. Various proteins within the nucleosome remodelling and deacetylase (NuRD) complex have decreased expression levels in HGPS[32], which reduces the histone deacetylation activity of this complex. H3K9 and H3K27 acetylation (indicated by red triangles) are expression-permissive chromatin marks that are thought to be mutually exclusive to the repressive trimethylation marks on the same lysines. HDAC1, histone deacetylase 1; RBB4, RB-binding protein 4.

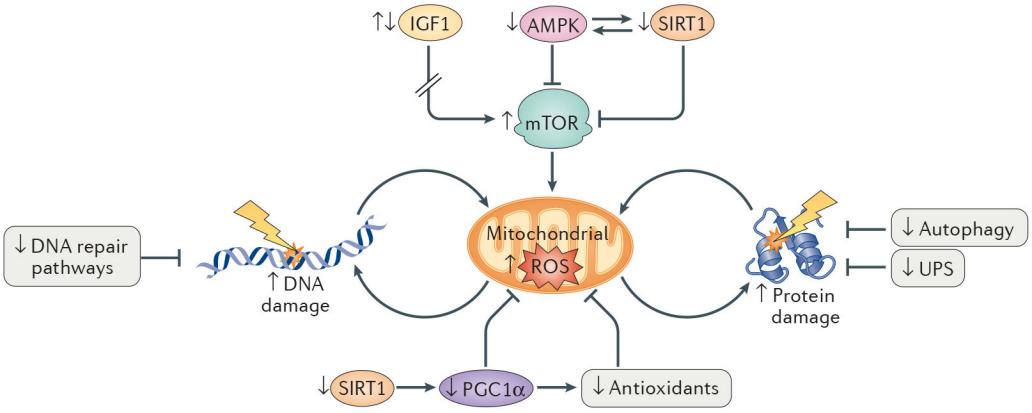

Figure 4 |. Mitochondrial ROS-driven ageing defects.

Mitochondrial oxidative phosphorylation in ageing and ageing-associated diseases (AADs) is driven by a decrease in insulin-like growth factor 1 (IGF1) signalling, or uncoupling of IGF1 and mTOR signalling resulting from chronic activation of the IGF-1 pathway (indicated by interruption of arrow), and increased activation of mTOR, resulting from impaired AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) signalling[26]. Increased formation of reactive oxygen species (ROS) due to increased mitochondrial activity, decreased levels of antioxidants and decreased PCG1α (peroxisome proliferator-activated receptor-γ co-activator 1α) activity, resulting in impaired mitochondrial biogenesis and turnover, causes damage to DNA, proteins and other macromolecules[27]. Decreased efficiency of DNA repair pathways and proteostasis pathways, including autophagy and ubiquitin–proteasome system (UPS)-mediated degradation of damaged proteins, during (premature) ageing and in AADs further contributes to the deleterious effects of ROS on mitochondrial integrity and cellular homeostasis[26].

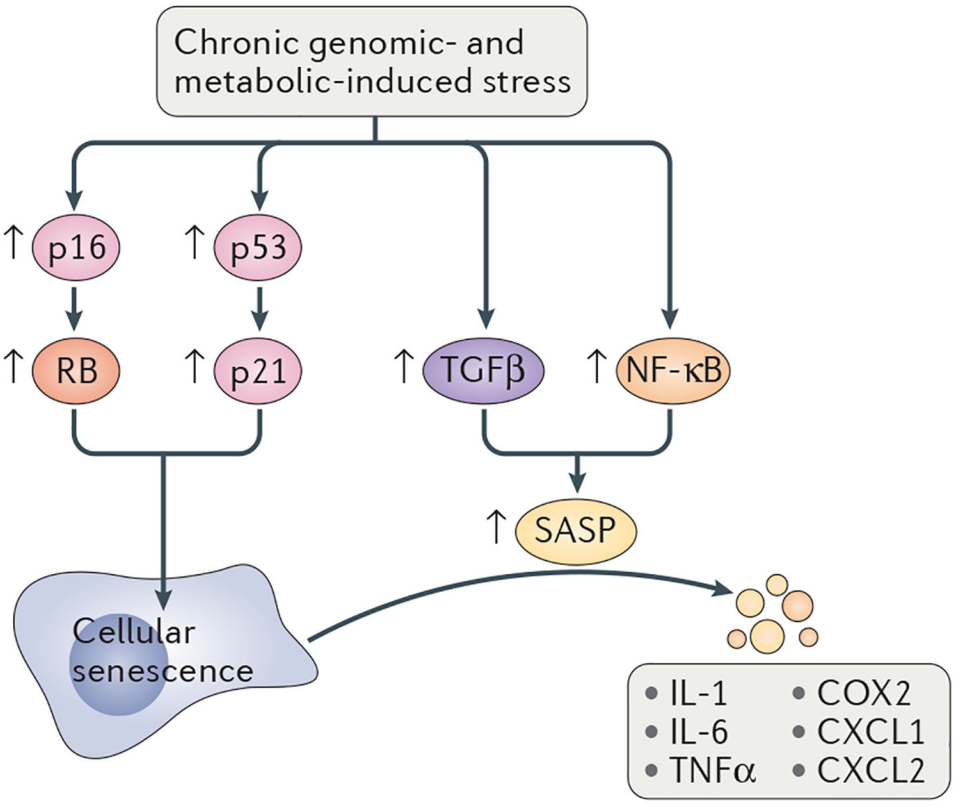

Figure 5 |. Cellular senescence pathways.

Chronic levels of elevated DNA damage and metabolic-induced cellular stress trigger the activation of p16 and p53 in Hutchinson–Gilford progeria syndrome (HGPS), ageing and ageing-associated diseases (indicated by arrows), through which activation of RB and p21 results in permanent senescent growth arrest[26]. Increased activation of transforming growth factor β (TGFβ) and nuclear factor-κβ (NF-κB) drive the senescent-associated secretory phenotype (SASP), which is characterized by the indicated inflammatory regulators. COX2, cyclooxygenase 2; CXCL1, C-X-C motif chemokine 1; TNFα, tumour necrosis factor-α.

Table 1 |

Progeroid syndromes

Progeroid syndrome	Gene	Main function of gene	Symptoms	Non-represented chronic ageing diseases (BOX 1)	Parallel with leading chronic ageing diseases (BOX 1)
Hutchinson-Gilford progeria syndrome	*LMNA*	Nuclear envelope architectural protein, heterochromatin organization	Alopecia, atherosclerosis, growth retardation, loss of subcutaneous fat, skeletal muscle wasting, nail dystrophy, stiff joints, tight skin, subcutaneous calcifications, osteoporosis, loss of eyesight, kidney failure	Cancer, CKD, COPD, diabetes, neurodegenerative diseases	Atherosclerosis, heart failure, skeletal muscle wasting, osteoporosis
Nestor-Guillermo progeria syndrome	*BANF1*	Nuclear envelope architectural protein, heterochromatin organization	Alopecia, growth retardation, loss of subcutaneous fat, skeletal muscle wasting, stiff joints, osteoporosis	Atherosclerosis, cancer, CKD, COPD, diabetes, heart failure, neurodegenerative diseases	Osteoporosis, skeletal muscle wasting
Werner syndrome	*WRN* (classical), *LMNA* (atypical)	*WRN:* DNA repair (NER, BER, NHEJ, HR), telomere maintenance	Growth retardation, tight skin, skin ulcers, osteoporosis, cataract, cardiac valve and soft tissue calcification, loss of subcutaneous fat, decreased fertility, increased risk for cancer	Cancer, CKD, COPD, diabetes, neurodegenerative diseases, skeletal muscle wasting, diabetes	Atherosclerosis, increased risk for cancer, heart failure, osteoporosis
Cockayne syndrome	*ERCC6, ERCC8*	DNA repair (NER)	Growth retardation, impaired development of the nervous system and progressive neurodegeneration, photosensitivity, cataracts	Atherosclerosis, cancer, CKD, COPD, diabetes, heart failure, osteoporosis, skeletal muscle wasting	Progressive neurodegeneration
Bloom syndrome	*BLM*	Double-strand break DNA repair	Growth retardation, photosensitivity, micrognathism, skin rash, dilated blood vessels, moderate immune deficiency, cancer, increased risk diabetes and COPD	Atherosclerosis, CKD, heart failure, osteoporosis, neurodegenerative diseases, skeletal muscle wasting	Cancer, increased risk for diabetes and COPD
Xeroderma pigmentosum	*XPA, XPB, XPC, XPD, XPG, ERCC4, ERCC6, DDB2, POLH, RAD2*	DNA repair (NER)	Photosensitivity, cancer, dilated blood vessels	Atherosclerosis, CKD, COPD, diabetes, heart failure, osteoporosis, neurodegenerative diseases, skeletal muscle wasting	Cancer
Ataxia telangiectasia	*ATM*	DNA damage signaling activator	Growth retardation, weakened immune system, cancer, degeneration of cerebellum, dilated blood vessels, diabetes	Atherosclerosis, CKD, COPD, diabetes, heart failure, osteoporosis, skeletal muscle wasting	Cancer, diabetes, neuronal degeneration
Trichothiodystrophy	*XPB, XPD, TFB5*	DNA repair (NER)	Growth retardation, brittle hair, nail dystrophy, intellectual impairment, neuronal degeneration, reduced fertility	Atherosclerosis, cancer, CKD, COPD, diabetes, heart failure, osteoporosis, skeletal muscle wasting, diabetes	Neuronal degeneration

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Progeroid syndrome	Gene	Main function of gene	Symptoms	Non-represented chronic ageing diseases (BOX 1)	Parallel with leading chronic ageing diseases (BOX 1)
Dyskeratosis congenita	*TERC, TERT, CTC1, WRAP53*	Components of telomerase and telomere maintenance complex	Nail dystrophy, leukoplakia of oral mucosa, bone marrow failure, hyperpigmentation of skin, premature greying of hairs, testicular atrophy, cancer, osteoporosis, pulmonary fibrosis	Atherosclerosis, CKD, diabetes, heart failure, neurodegenerative diseases, skeletal muscle wasting	Cancer, osteoporosis, pulmonary fibrosis
Mosaic variegated aneuploidy syndrome	*BUB1B, CEP57*	Mitotic non-disjunction	Short stature, central nervous system and brain abnormalities, intellectual disability, aneuploidy, increased cancer risk, cataracts	Atherosclerosis, CKD, COPD, diabetes, heart failure, osteoporosis, neurodegenerative diseases, skeletal muscle wasting	Cancer

BER, base excision repair; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, homologous recombination; NER, nucleotide excision repair; NHEJ, non-homologous end joining.