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DNA damage and ageing: new-age ideas for an age-old problem

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Abstract

Loss of genome maintenance may causally contribute to ageing, as exemplified by the premature appearance of multiple symptoms of ageing in a growing family of human syndromes and in mice with genetic defects in genome maintenance pathways. Recent evidence revealed a similarity between such prematurely ageing mutants and long-lived mice harbouring mutations in growth signalling pathways. At first sight this seems paradoxical as they represent both extremes of ageing yet show a similar ‘survival’ response that is capable of delaying age-related pathology and extending lifespan. Understanding the mechanistic basis of this response and its connection with genome maintenance would open exciting possibilities for counteracting cancer or age-related diseases, and for promoting longevity.

In Greek mythology, Klotho, Lakhesis and Atropos, the three fates, spun, wove and snipped the thread of life, an unalterable process to which both gods and humans had to submit themselves. Human efforts over recent centuries have succeeded in substantially lengthening the thread, allowing ageing to become a common feature of society. However, despite intense research, the molecular basis of the processes that cause loss of bodily functions, and degeneration of cells and tissues is still unresolved. It is widely accepted that ageing is the consequence of stochastic damage accumulation[1]. Ageing is unique in that it does not seem to be subject to evolutionary selection, as it occurs after the reproductive phase, suggesting that it may occur by default[2]. Nevertheless, it is apparent from studies in many systems that

ageing is subject to regulation by evolutionarily highly conserved molecular pathways[3–5]. As such, damage drives functional decline with advancing age; however, the existence of universal mechanisms that are able to promote longevity may set the pace on how rapidly damage builds up and function is lost. We discuss the nature of the processes that determine the length and the quality of the thread of life woven by Lakhesis and ultimately snipped by Atropos.

Damage and ageing: the DNA perspective

Within the complex chemical machinery of each cell, all biomolecules (proteins, lipids and nucleic acids) are subject to indiscriminate damage caused by spontaneous reactions (mostly hydrolysis) and by numerous endogenous and exogenous reactive agents. It is therefore plausible that damage to multiple cellular constituents accounts for ageing[1]. However, damage to certain macromolecules may play a more prominent part than damage to others. The almost exclusive link between an extending class of syndromes with phenotypes resembling accelerated ageing in many, but not all, organs and tissues (segmental progeria), and inborn defects in DNA metabolism points to genomic damage as a major culprit in the ageing process (Table 1). In principle, all other macromolecules are renewable, whereas nuclear DNA, the blueprint of virtually all cellular RNA and proteins, is irreplaceable; any acquired error is permanent and may have irreversible consequences. In spite of its enormous length and explicit physicochemical vulnerability, cellular function relies on the integrity of the somatic genome, which must be preserved during the entire lifetime of an organism. This is why nature has invested heavily in an intricate genome maintenance apparatus, consisting of several sophisticated DNA damage repair, tolerance and checkpoint systems, as well as effector machinery that enables cell survival or triggers senescence or cell death when DNA is damaged[6–8]. This elaborate network also includes intricate machineries to maintain telomeres (the ends of chromosomes), systems to repair mitochondrial DNA and as yet largely unexplored processes that maintain the epigenetic code. These mechanisms ensure that genetic information remains functionally intact for extended periods and is faithfully transmitted. Besides exogenous sources of DNA damage, such as UV and ionizing radiation, and numerous chemicals, there are also inescapable enemies from within. The culprit is the organism’s own metabolism, which generates reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide and hydroxyl radicals and their numerous subsequent reaction products: lipid peroxidation products, oestrogen metabolites, reactive carbonyl species, endogenous alkylating agents, spontaneous hydrolysis and deamination products[9]. Besides the immense diversity of DNA lesions, the enormous size of the mammalian genome greatly increases its vulnerability to injury, further aggravating the DNA problem. It is estimated that thousands of single-stand breaks and spontaneous base losses occur daily in the nuclear genome of every cell[10,11]. Together with other types of spontaneous damage, the total may amount to about 100,000 lesions per cell per day[11]. It is likely that this number increases considerably under certain conditions; for example, a single day in the sun may induce up to 100,000 UV photoproducts in each keratinocyte.

The consequences of DNA injury are generally unfavourable and determined by various parameters, the first of which is the type of damage. Some lesions are primarily mutagenic,

greatly promoting cancer. Others are mainly cytotoxic or cytostatic, triggering cell death or senescence, causing degenerative changes such as those associated with ageing. One of the most common lesions induced by oxidative damage is the highly mutagenic DNA lesion 8-oxo-G, which pairs equally well with the correct cysteine base and the incorrect adenine base, causing high levels of GC to TA transversions. On the other hand, lesions that affect both DNA strands, such as double-strand breaks (induced by radiation or ROS) or interstrand crosslinks (caused by chemical agents such as cisplatin) are difficult to repair. Such lesions usually kill cells or cause senescence rather than mutagenesis (which can lead to tumour formation), possibly accelerating organismal ageing. Indeed, long-term survivors of chemo- or radiotherapy show evidence of premature ageing[12,13]. Apart from the type of damage, the frequency of lesions and their location in the genome also determine the outcome. Additional parameters are the systems engaged in repairing the damage, notably their fidelity and efficiency, which may vary with cell type and the stage in the cell cycle or differentiation when the damage occurs. As efficient as the genome maintenance machinery may be, it cannot cope with all of the insults inflicted on the genome, leading to a gradual accumulation of DNA damage and mutations[14]. Certain DNA lesions are poorly, if at all, recognized by the mammalian repair machinery, presumably because they closely resemble the normal DNA conformation. An example is the cyclobutane pyrimidine dimer, the most abundant UV-induced DNA injury, which is often overlooked by global genome repair mechanisms and persists in many parts of the genome[15]. As this type of damage constitutes a permanent block for the regular high-fidelity replication machinery, a specialized apparatus has developed to allow bypass of persisting damage. This includes a set of at least five translesion polymerases, each specialized in bypassing different types of DNA lesions. Consequently, there may be an elevation in the mutation rate[16]. Also, dedicated pathways have developed for transcription stalled by DNA damage (see below).

Depending on the type and severity of DNA injuries, failure to repair them, either because they are overlooked or bypassed, may lead to cellular malfunctioning, triggering cancer and senescence, or cell death and eventually loss of organismal homeostasis over time, which contributes to ageing. The wide variety of DNA lesions and their diverse effects have necessitated the development of several layers of protection, including a complementary network of DNA repair pathways, each selective for a specific subset of DNA lesions. The elaborate nature of the genome maintenance apparatus highlights the importance of preserving genome integrity. However, the more complex a system, the more sensitive it is to errors and deficiencies.

Insights from DNA repair-deficient progeroid human syndromes and mouse mutants

Important clues for the clinical effect of DNA damage come from the diverse phenotypes of a rapidly expanding family of rare human disorders associated with genetic defects in DNA repair and damage-response systems. Disorders affecting genome maintenance fall into three classes: 1) conditions in which specific types of cancer are enhanced; 2) conditions in which many (but never all) aspects of ageing are accelerated, but cancer is reduced; 3) conditions in which both cancer and certain aspects of ageing are increased (Table 1). The outcome

seems to be governed by the genome maintenance system that is affected. The notion that in none of these syndromes all aspects of cancer and degenerative ageing are equally enhanced is consistent with the idea that each genome stability pathway covers a specific subset of damage and that there are no genes or processes that counteract all forms of DNA damage and their consequences to the same extent.

As is apparent from cancer research over recent decades, analysis of cancer-prone conditions has provided valuable insight into highly relevant pathways for the aetiology of tumorigenesis in general. Similarly, it is expected that the study of progeroid syndromes will highlight molecular mechanisms that normally prevent ageing and age-related disorders[17,18]. For obvious reasons longevity research generally enjoys wide interest, but strong reservations exist with respect to the relevance of progeroid syndromes and corresponding mouse models of the ageing process[19,20]. This is largely due to the fact that there are many ways of shortening lifespan, suggesting that premature death alone can indeed be a misleading endpoint. Studies based on lifespan alone, be it extended or shortened, are sensitive to artefacts and it is essential to minimize genetic or environmental sources of variation but also to examine additional ageing parameters, such as evidence of age-related pathologies (as in progeroid models)[21]. Particularly when this criterion is taken into account, evidence is mounting that DNA damage is a prime, *bona fide* cause of ageing.

The idea of a double-edged sword of DNA damage — damage-induced mutations causing cancer and damage-triggered cell death/senescence/ malfunction contributing to degenerative forms of ageing[22] — is consistent with the phenotypes of DNA repair/genome instability disorders and a growing list of mouse mutants deficient in DNA repair mechanisms. Detailed systematic analysis of these mice, compared with their littermate controls, have revealed the premature appearance of various symptoms of ageing indistinguishable from the same phenotypes normally occurring much later in life. In some cases, a mouse model even paved the way for identifying the parallel human syndrome[23–26], leaving no doubt that mouse models and human syndromes constitute valid ageing mutants. The overall picture emerging from these mutants is that genetic defects in DNA repair systems that mainly prevent mutagenesis are generally associated with a strong predisposition to specific types of cancer, with only minor symptoms of degenerative ageing phenotypes such as in xeroderma pigmentosum (XP) patients. On the other hand, deficiencies in repair and surveillance pathways that mainly protect from the cytotoxic and cytostatic effects of DNA damage tend to be characterized by a decrease in the incidence of cancer and the premature appearance of some, but not all degenerative ageing phenotypes, such as that of Cockayne syndrome (CS) patients. Impairment of genome stability processes that combat mutagenesis and cell death leads to susceptibility to both cancer and accelerated ageing, such as in patients with both XP and CS (XPCS; Table 1).

An informative example incorporating all aspects discussed above is the nucleotide excision repair (NER) pathway. This is a multi-step ‘detect-excise-and-patch’ repair system for a broad class of helix-distorting lesions such as UV-induced photoproducts and numerous bulky chemical adducts[8]. Such DNA damage is detected in two ways: 1) the global-genome NER (GG-NER) sub-pathway, which detects lesions with sufficient helix-opening properties anywhere in the genome, and 2) the transcription-coupled NER (TC-NER) sub-pathway,

which is selective for lesions that stall the transcription elongation machinery. Both processes detect lesions in a different manner, but the repair process uses the same toolbox, which opens the helix, excises a 22–30-base damage-containing oligonucleotide, fills in the single-strand gap by repair synthesis and ligates the final nick[27].

Apart from a common UV hypersensitivity, genetic defects in each of the two sub-pathways have virtually opposite consequences. Impairment of GG-NER in humans causes XP, characterized by an increase of more than 1000-fold in the susceptibility to sun-induced skin cancer[28]. This is explained by the fact that compromised GG-NER leads to accumulation of DNA lesions over the entire genome and with replication, which increases the risk of mutations. Consistent with this, an increase in the level of mutations is observed, as is apparent from mutagenesis reporter mice[29].

On the other hand, genetic defects in TC-NER are associated with the human progeroid disorder CS or the CS-like brittle hair disorder trichothiodystrophy (TTD) that also harbours a partial GG-NER defect. Both conditions and associated mouse models show many symptoms of premature ageing, including progressive neurodevelopmental delay, cachexia, kyphosis, retinal degeneration and deafness[28,30,31]. Remarkably, TTD mice as well as CS and TTD patients seem to be protected from cancer despite their DNA-repair defect[23,28]. This is explained by the fact that TC-NER repairs only a small but vital part of the genome, namely the transcribed strand of active genes, when lesions actually block RNA polymerase II[32,33]. As this system deals with only a tiny fraction of the genome, it is not crucial for preventing mutations and thus cancer. Yet, it is crucial for promoting cell survival after DNA damage, as it enables resumption of the essential process of transcription. Thus, a TC-NER defect increases damage-induced cell death, which prevents damaged cells from surviving and, in effect, this protects from cancer. In a TC-NER mutant, the balance between anti-ageing and anti-cancer genome maintenance responses is shifted to the latter, favouring cell death or senescence, which promotes ageing, while protecting from cancer. Mouse models for these syndromes reveal an absence of significantly elevated spontaneous mutations[29], but show markedly accelerated age-related pathology in a number of tissues and organs. This indicates that an increase in point mutations is not a prerequisite for progeria[29]. Combinations of XP and CS, showing both a predisposition to cancer as well as features of segmental premature ageing, are very rare in patients and are mimicked in the corresponding mouse models[34].

XFE is a distinct progeroid syndrome caused by a defect in XPF–ERCC1, an endonuclease required for NER as well as for DNA interstrand crosslink (ICL) repair. ICLs covalently link both strands of DNA, preventing transcription and replication, and hence are extremely cytotoxic. Failing defence against such spontaneous lesions triggers cell death and senescence, culminating in accelerated ageing, as observed in both Ercc1 and Xpf mouse mutants and the human XFE[24]. Other repair systems, such as base excision repair (eliminating subtle base damages, abasic sites and single-strand breaks) and repair systems for double-strand breaks (homologous recombination and end-joining)[8], probably perform both roles; that is, they protect from cancer and ageing to different degrees[35,36]. Therefore, most defects in distinct DNA repair systems can trigger cancer, ageing or both[37], revealing a

fine-tuning among genome maintenance mechanisms that mainly protect from cancer, and those that predominantly prevent non-cancer, degenerative ageing phenotypes.

The link between DNA damage and longevity

Genetic crosses in mice have revealed a striking correlation between the severity and type of repair defect and the severity and age of onset of premature ageing features. Crossing progeroid TC-NER-deficient CS and TTD mouse mutants with cancer-prone GG-NER mice (for example, $Csb^{m/m}/Xpa^{-/-}$, $Csa^{-/-}/Xpc^{-/-}$ and $Xpd^{TTD}/Xpa^{-/-}$ mice) substantially aggravates the DNA repair defect (thus increasing the load of endogenous genotoxic stress), further compromising transcription and markedly hastening the onset of progeroid features, including a lifespan reduction from 1.5–2 years to only 3–4 weeks[30]. As mentioned, $Ercc1^{-/-}$ mice and the recently discovered corresponding human progeroid syndrome XFE[24], which are deficient in NER as well as ICL repair, show severe progeroid features that are, in part, different from TC-NER deficiencies (for example dramatic liver, kidney and bone marrow ageing, not observed in TC-NER mutants). Evidently, defects in distinct repair systems for cytotoxic lesions account for a bewildering but specific range of age-related pathologies, which may also explain the distinct segmental nature of progerias.

Recently, the onset of progeroid features in $Csb^{m/m}/Xpa^{-/-}$, $Xpd^{TTD}/Xpa^{-/-}$ and $Ercc1^{-/-}$ repair mutants was shown to be accompanied by marked changes in gene expression and physiological parameters, correlating with a systemic suppression of the growth hormone (GH)/insulin growth factor (IGF)-1 somatotroph axis, suppression of oxidative metabolism, as well as suppression of lactotroph and thyrotroph processes[24,30]. These changes are paralleled by reduced serum glucose and insulin levels, a consistent upregulation of antioxidant defence and stress responses, along with a marked propensity to store glycogen and fat, indicating an attempt to withhold their energy resources[24,30,38]. Paradoxically, however, most of these changes, including suppression of the GH/IGF1 hormonal pathway, as well as upregulation of antioxidant and defence responses, are associated with delayed ageing and longevity, as seen in dwarf mutant and calorie-restricted mice, rather than with the extremely short lifespan of NER-deficient progeroid animals[39,40].

Indeed, in organisms as evolutionarily diverse as worms and mice, constitutive defects in single genes that perturb endocrine signalling can considerably extend lifespan. Genetic suppression of insulin-signalling in worms prolongs lifespan by several-fold. Similarly, the most prominent pathway affected in long-lived, endocrine-disturbed and dietary-restricted mice is the GH/IGF1 pathway, often paralleled by alterations in thyrotroph and lactotroph functions[5,41]. For example, Ames and Snell dwarfs[42,43], the little mouse ($Ghrhr^{lit/lit}$)[44,45], the homozygous GH receptor/ binding protein ($Ghr/bp^{-/-}$)[46,47], as well as the heterozygous IGF1 receptor ($Igf1r^{+/-}$)[48,49] knockout mice and the Klotho-overexpressing mice[50], invariably demonstrate a suppression of the GH/IGF1 somatotroph axis, moderate to pronounced dwarfism and increased lifespan. Similarly, dietary restriction (the only well documented intervention that prolongs lifespan and delays the onset of several ageing-associated diseases in mammals) results in decreased insulin/IGF1 signalling with similar downstream events[51–56]. When dietary restriction and pituitary dwarfism are combined, an additive extension of lifespan is observed[57]. Thus, suppression of the GH/IGF1 axis is

associated with delayed age-related morbidity and longevity, profound metabolic changes (including low serum glucose and insulin), enhanced antioxidant defences and stress resistance, and reduced frequency of somatic mutations[48,58,59]. Conversely, overexpression of GH causes pathology and markedly shortens lifespan[60]. The genome-wide expression parallels between long-lived mutant dwarf or CR mice and the NER progeroid mutants[40] explain the arrested growth and development of NER progeria, which are not caused by a defect in the hypothalamus or the pituitary of NER progeroid mutants[24].

Studies on dwarf mutants suggest that lifespan can, in principle, be genetically modulated by single gene mutations, although ageing is not abolished altogether by these mutations. CR interventions later in life demonstrate that longevity assurance mechanisms can be adaptive and to some extent reversible[61]. How does this relate to the irreversible, random damage theory of ageing[62]? Given the abundance of evidence for both models, is there a link between conserved pathways that promote longevity by suppressing the random accumulation of damage? According to the 'disposable soma' theory, ageing arises from the accumulation of macromolecular damage because of inherent limitations in somatic maintenance and repair[1]. As energy reserves that are engaged in one process are unavailable to contribute to another, it is conceivable that an organism can only maximize its Darwinian fitness by optimally allocating its metabolic needs between the maintenance and repair of its soma and physiological processes, such as reproduction and development. Under affluent conditions it would give preference to rapid reproduction, whereas in times of scarcity, reproduction would be postponed and a larger share of resources devoted to maintenance. The NER progeroid mice could resemble the stress condition normally associated with food restriction and elicit a very similar adaptive response. It is appealing to speculate that the progressive changes associated with the insulin/IGF1 pathway and metabolism are adaptive responses aimed at minimizing further damage, by shifting the energy equilibrium from growth and proliferation to preservation of somatic maintenance (Fig. 1). This adaptive 'survival' response is likely to be driven by intrinsic genome instability, but it can also be triggered by other emergency situations such as calorie restriction. In parallel, accumulation of DNA damage may trigger similar responses with normal ageing. Indeed, chronic exposure of wild-type mice to non-toxic doses of pro-oxidant or crosslinking agents elicits the same GH/IGF1 suppression[63]. Thus, the gradual accumulation of damage could also explain the known GH/IGF1 somatotroph attenuation in naturally aged mammals. In support of this, $Csb^{m/m}/Xpa^{-/-}$ and $Ercc1^{-/-}$ mice demonstrate significant, genome-wide expression parallels with naturally aged mice, indicating that stochastic accumulation of damage to macromolecules (including DNA) may cause the physiological decline in the GH/IGF1 axis and organismal deterioration with advancing age[24,30].

As yet we do not know the sequence of events leading from DNA damage to the activation of longevity assurance pathways. It is likely that there are other protective mechanisms that will postpone cancer as well as ageing. These include reduced or better controlled production of metabolic byproducts through regulation of metabolism and oxidative phosphorylation, as well as improved anti-oxidant/detoxification defences, which reduce the DNA damage load and its noxious sequelae. Many of these systems seem to be under the control of the highly conserved GH/IGF1 somatotroph axis and are triggered by the survival

response. In addition, improved overall repair pathways of both categories, that is, anti-cancer and anti-ageing, are predicted to extend lifespan next to other mechanisms, including epimutations and protein metabolism, which are relevant for both ageing and cancer. Presumably, gradual evolutionary improvements in these systems have enabled longer-lived species, such as humans, to achieve their long lifespan by combating cancer and ageing simultaneously. This model also holds the promise that we may find compounds that either trigger the protective survival response or diminish the oxidative (DNA) damage load by effectively scavenging deleterious ROS. Promising indications in these directions have already emerged, such as the design and synthesis of small dietary restriction mimetics that could potentially promote healthy and long lifespan in higher organisms[64].

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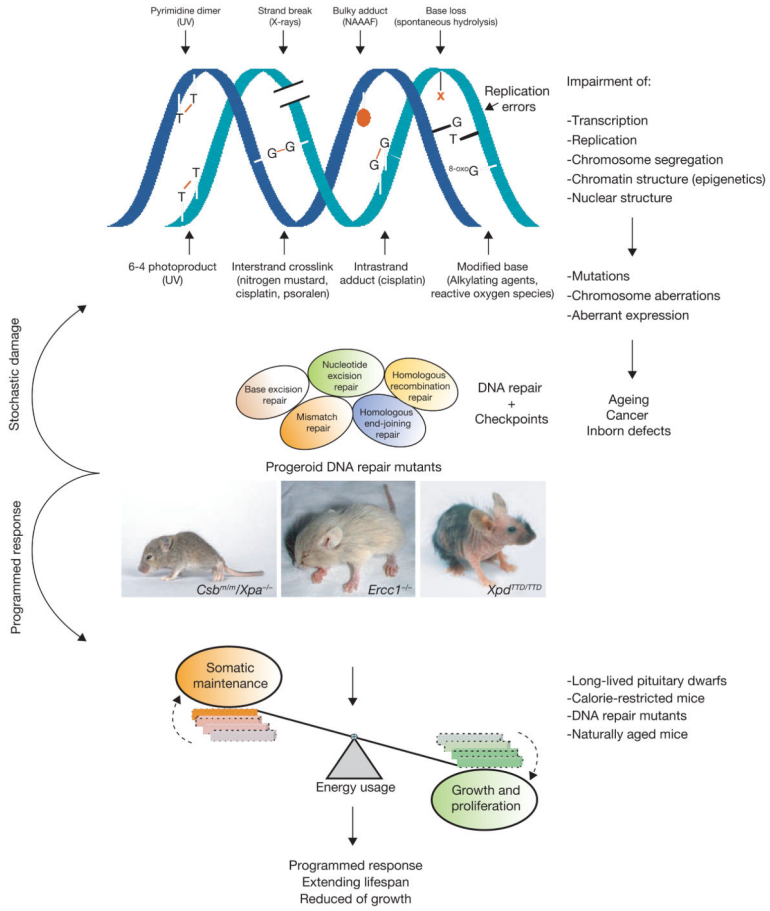

Figure 1.

Schematic representation of ‘stochastic damage’ and the connection with ageing and longevity assurance mechanisms. DNA is continually damaged by chemical alterations (such as spontaneous hydrolysis, deamination), by environmental agents as well as endogenous products (that is, ROS). Cells respond through a battery of DNA repair and genome surveillance systems that counteract DNA damage, thereby ensuring that their vital genetic information is preserved and faithfully transmitted to progeny. Nevertheless, a fraction of the damage escapes repair and accumulates, resulting in mutations, senescence or cell death and cellular dysfunction. Too much persisting DNA damage interferes with normal DNA metabolism, such as transcription, and triggers suppression of the growth hormone/IGF1 somatotropic axis, which is known to decline with age. Dampening of the insulin/IGF1 pathway and oxidative metabolism is thought to reduce the induction and effects of DNA damage by shifting the energy equilibrium from growth and proliferation to pathways that preserve somatic maintenance and thus attempt to extend lifespan (survival response). NER progeroid mice accumulate DNA damage much more rapidly than naturally ageing mice as a consequence of their repair defect, and onset of the life-extending ‘survival’ response is accelerated. Thus, studies in mice with inherited defects in genome maintenance seem to reconcile two apparently contrasting theories on ageing: the genetic basis of ageing and the stochastic damage accumulation. As random damage drives the age-

related functional decline, longevity assurance mechanisms determine the rate of damage accumulation and the functional decline with age.

Table 1

A list of syndromes carrying defects in genome maintenance

Progeria			
Syndrome	**Mutated genes**	**Affected processes**	**Mouse models**
Cockayne syndrome (CS)	*CSA, CSB*	TC-NER	*Csa*$^{-/-}$
			Csb$^{m/m}$
		TC-NER; GG-NER	*Csb*$^{m/m}$*Xpa*$^{-/-}$; *Csb*$^{m/m}$*/Xpc*$^{-/-}$
			Csa$^{-/-}$*Xpa*$^{-/-}$; *Csa*$^{-/-}$*Xpc*$^{-/-}$
Trichothiodystrophy (TTD)	*XPB, XPD, TTDA*	Partial GG/TC-NER	*Xpd*^{ttd}
COFS	*CSB, XPD, XPG*	GG-NER; TC-NER	*Xpg*$^{-/-}$
XPE	*XPF/ERCC1*	GG/TC-NER, ICL repair, HR	*Ercc1*$^{-/-}$
Rothmund-Thomson (RTS)	*RECQL4*	Oxidative DNA damage repair	*Recql4*$^{-/-}$
Dyskeratosis congenita	*DKC1, TERC1*	Telomere maintenance	*Dkc1*^{m}
			mTR$^{-/-}$
Hutchison-Gilford progeria syndrome (HGPS)	*LMNA*	Nuclear lamina function	*Zmpste24*$^{-/-}$
Atypical Werner syndrome			*Lmna*$^{L530P/L530P}$
Restrictive dermopathy (RD)	*LMNA, ZMPSTE24*		
Mandibuloacral dysplasia (MAD)			

Cancer			
Syndrome	**Mutated genes**	**Affected processes**	**Mouse models**
Breast cancer 1, early onset	*BRCA1*	DSB repair (HR)	*Brca1*$^{-/-}$*; early lethality*
Breast cancer 2, early onset	*BRAC2*		*Brca2*$^{-/-}$*; early lethality*
Li-Fraumeni	*P53*	Checkpoint control	*p53*$^{-/-}$
Chk2	*CHK2*	G1 checkpoint control	*Chk2*$^{-/-}$
von Hippel-Lindau syndrome	*VHL*	Cell-cycle regulation	*Vhl*$^{-/-}$
Hereditary non-polyposis colorectal cancer	*Msh2;Mlh1*	Mismatch repair	*Msh2*$^{-/-}$
XP	*XPC*	GG-NER	*Xpc*$^{-/-}$

Progeria + cancer			
Syndrome	**Mutated genes**	**Affected processes**	**Mouse models**
Fanconi anaemia (FA)	*FANC, BRCA2*	DNA crosslink repair	*Fancc; Fanca; Fancg; Fancd2;Brca2*
Xeroderma pigmentosum (XP) combined with CS (XPCS)	*XPB, XPF, XPD, XPG*	NER	*Xpd*^{xpcs}
Xeroderma pigmentosum (XP)+DeSanctis-Cacchione syndrome (DSC)	*XPA, XPD*	NER	*Xpg*$^{-/-}$
Ataxia telangiectasia (AT)	*ATM*	DSB repair	*Atm*$^{-/-}$ *mTR*$^{-/-}$
Ataxia telangiectasia-like disorder (ATLD)	*MRE11*	DSB repair	*Mre11*$^{-/-}$
Nijmegen breakage syndrome (NBS)	*NBS1*	DSB and telomere maintenance	*Nbs1*^{p70}
Bloom syndrome (BLS)	*BLM*	Mitotic recombination	*Blm*$^{-/-}$

Progeria + cancer			
Syndrome	**Mutated genes**	**Affected processes**	**Mouse models**
Werner syndrome (WS)	*WRN*	Telomere maintenance, DNA recombination and repair	$Wrn^{-/-}$ $mTR^{-/-}$

Most of the conditions with inborn errors in genome maintenance fall into three classes: 1) those in which many attributes of ageing are accelerated but cancer incidence is reduced, 2) those in which specific cancer types are enhanced and 3) those in which incidence of both cancer and segmental progeria is increased. Mitochondrial heteroplasmic disorders are not shown but should also be considered to belong to the 'progeria + cancer' group. Abbreviations: TC-NER: transcription-coupled nucleotide excision repair, COFS: cerebro-oculo-facio-skeletal syndrome, HR: homologous recombination, ICL: interstrand crosslinks, DSB: double-strand break, XFE: Xpf-Errcc1 syndrome.