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Comparison of mice with accelerated aging caused by distinct mechanisms

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Abstract

Aging is the primary risk factor for numerous chronic, debilitating diseases. These diseases impact quality of life of the elderly and consume a large portion of health care costs. The cost of age-related diseases will only increase as the world's population continues to live longer. Thus it would be advantageous to consider aging itself as a therapeutic target, potentially stemming multiple age-related diseases simultaneously. While logical, this is extremely challenging as the molecular mechanisms that drive aging are still unknown. Furthermore, clinical trials to treat aging are impractical. Even in preclinical models, testing interventions to extend healthspan in old age is lengthy and therefore costly. One approach to expedite aging studies is to take advantage of mouse strains that are engineered to age rapidly. These strains are genetically and phenotypically quite diverse. This review aims to offer a comparison of several of these strains to highlight their relative strengths and weaknesses as models of mammalian and more specifically human aging. Additionally, careful identification of commonalities amongst the strains may lead to the identification of fundamental pathways of aging.

Introduction

Aging is a complex process that leads to a gradual, progressive and irreversible functional decline and loss of physiologic integrity with time (Kirkwood 2005). As a consequence of this loss in physiological reserve, old age is the leading risk factor for numerous chronic debilitating diseases including diabetes, osteoporosis, arthritis, cataracts, sarcopenia, cardiovascular and neurodegenerative disease (NCoA 2011). By 2050, the number of persons >60 years of age will double globally to reach >2 billion or >20% of the population (UN 2013). More than 90% of persons 65 and older have at least one chronic disease, while >75% have at least two diseases (NCoA 2011). Age-related diseases consume three quarters of our healthcare dollars and this cost is anticipated to double in the next 50 years as our population ages (Goldman and Olshansky 2013). Thus the concept of finding interventions

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to delay aging is gaining traction. This creates a need for preclinical models and clinical trial paradigms.

Because of its complexity, as well as the time involved, aging is difficult to study in humans. Diseases exist in which individuals age more rapidly than normal. Progeria and progeroid syndromes are heritable human disorders characterized by the early onset of complex age-related phenotypes. The majority of human progeroid syndromes are caused by defects in genome maintenance (Table 1). Because these diseases show significant phenotypic overlap with normal aging but do not recapitulate all features, they are sometimes referred to as "segmental progeroid syndromes" (Dolle and others 2011; Hasty and others 2003). These rare diseases can be recapitulated in model organisms to create rapid preclinical models for aging studies.

The time-dependent accumulation of random molecular and cellular damage is thought to contribute to aging-related degeneration (Kirkwood 2005). Damage to DNA is the only type of molecular damage that is directly repaired in the cell, illustrating the vital importance of maintaining genomic integrity. DNA repair mechanisms are therefore essential for somatic maintenance and staving off age-related decline. This is dramatically illustrated by the fact that inherited defects in genome maintenance mechanisms can lead to accelerated aging of one or more tissues (Hasty and others 2003) and the drastic acceleration of skin aging that occurs in sun-exposed areas of skin compared to protected areas (Gilchrest 2013).

Aging is caused by a combination of environmental and genetic factors approximated at a 70% to 30% ratio (Park 2010). This interplay is illustrated strikingly with DNA damage and repair. The environment drives DNA damage (e.g., our dependence on atmospheric oxygen for aerobic metabolism and ultraviolet radiation damage to the skin both drive accumulation of DNA damage). Without the environmental component, age-related decline is significantly reduced (e.g. skin never exposed to UV shows reduced aging). Genetics determine our ability to repair this DNA damage. Alterations in DNA repair genes can significantly exacerbate aging (Hasty and others 2003). Genetic variability in DNA repair capacity between individuals as well as differences in environmental exposures help explain why humans age differently.

Reactive oxygen species (ROS), the by-products of oxidative energy metabolism occurring in the mitochondria, are considered a ubiquitous cause of damage driving age-related decline in several organs and species (Harman 1956). ROS can directly or indirectly damage DNA, resulting in a wide variety of oxidative DNA lesions including small or large base modifications, single- and double-strand breaks, and interstrand crosslinks (Dizdaroglu and others 2002). These lesions accumulate in a variety of tissues with age and mutations affecting DNA repair lead to accelerated accumulation of these lesions and premature aging (Wang and others 2012).

Unrepaired DNA damage triggers a cellular response that arrests cell cycle progression so that DNA repair can occur before replication, in order to prevent mutations in the nuclear and mitochondrial genomes. If repair is not timely or complete, the DNA damage response culminates in signaling events that trigger apoptosis or cellular senescence. Senescent cells

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accumulate in mammals with age (Herbig and others 2006). Furthermore, senescent cells have been demonstrated to play a causal role in aging (Baker and others 2011). Senescent cells are thought to promote aging passively due to their inability to contribute to organ function and also actively by secreting pro-inflammatory factors (Coppe and others 2010).

Much of the recent progress in defining molecular pathways contributing to aging has been gained by the use of genetically tractable model systems, ranging from yeast, to flies and nematodes, to mice. The mouse is an attractive model system for lifespan and healthspan studies due to its relatively short lifespan and low cost of housing, genetic similarity to humans, availability of inbred and outbred strains, and genetic tractability. Additionally, as they age, mice develop cataracts, muscle weakness, immune abnormalities, impaired fertility, joint problems, central obesity, skin atrophy and many other aspects of normal mammalian aging (Maronpot 1999).

Murine models of progeroid syndromes are invaluable experimental systems for investigating the molecular mechanisms by which constant cellular, organelle or molecular stress drives rapid aging. They also have been valuable for accelerating the pace of interventional studies aimed at expanding healthspan (Baker and others 2011; Lavasani and others 2012; Tilstra and others 2012). Finally, they are useful for identifying which tissues are most vulnerable to a particular type of stress (Gregg and others 2012). Several segmental progeroid syndromes have been reproduced in mice though there are no models that exhibit all possible aging lesions in an accelerated timeframe. Three such mouse models, the DNA repair deficient *Ercc1*-depleted mice, *BubR1* hypomorphic mouse and the mitochondrial mutator mice are compared in this review (Table 2).

Ercc1

ERCC1-XPF (excision repair cross-complementation group 1- xeroderma pigmentosum group F) is a highly conserved heterodimeric nuclease involved in the repair of damaged DNA. *XPF* encodes the catalytic subunit and ERCC1 is essential for DNA binding and stabilization of XPF. ERCC1-XPF is required for the repair of helix distorting chemical lesions via nucleotide excision repair, the Fanconi anemia pathway of interstrand crosslink repair, and the repair of some double-strand breaks via microhomology-mediated end-joining (Gregg and others 2011).

Deficiency of ERCC1-XPF in humans results in a variety of conditions and clinical outcomes depending on the mutation (Kashiyama and others 2013). These include xeroderma pigmentosum, a skin cancer predisposition syndrome with accelerated aging of the skin and nervous system, cerebro-oculo-facioskeletal syndrome, a disease of severe congenital anomalies and developmental delay, Cockayne syndrome, a developmental and degenerative disease affecting particularly the central nervous system, XFE progeroid syndrome, characterized by rapidly accelerated systemic aging, and Fanconi anemia, characterized by one marrow failure and dramatically elevated risk of leukemia and some solid tumors (Gregg and others 2011).

Nucleotide excision repair (NER) is a highly conserved, multi-step DNA repair pathway involving over 30 proteins that protects DNA from a wide variety of lesions induced by

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diverse agents (Scharer 2013). There are two sub-pathways of NER that differ in damage recognition but share the same repair machinery: transcription-coupled NER (TC-NER) and global genome NER (GG-NER). TC-NER removes lesions that block RNA polymerases, allowing transcription and preventing cell death, while GG-NER removes distorting lesions genome wide, primarily preventing mutations. NER is responsible for removing UV-induced DNA damage, bulky chemical adducts, several types of oxidative damage produced by endogenous metabolism, and lesions induced by crosslinking agents commonly used in chemotherapy. Damaged bases are removed with adjacent residues and the resulting gap is then filled by the replication machinery. ERCC1-XPF is required for incising the damaged strand 5′ of the lesion, which triggers new DNA synthesis and gap filling. Deficiencies in NER are known to induce heritable segmental progeroid syndromes, including xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome (Bootsma D. and others 1998), all of which have been recapitulated in mice (Friedberg and Meira 2006).

Xeroderma pigmentosum (XP) is classified into eight complementation groups (XPA through XPG and XPV). Groups XPA-G are caused by defects in NER. XP is primarily a cancer-predisposition syndrome. Patients exhibit hypersensitivity to sunlight and have a >10,000 fold increase in UVB induced skin and ocular cancer (Tamura and others 2014). But XP also includes segmental progeroid features including accelerated photoaging of the skin, primary peripheral neuropathy, hearing loss, and cerebral atrophy (Gregg and others 2011). Mutations in *XPF* that cause XP are point mutations, sometimes in combination with a frameshift mutation that leads to a truncated protein, which is unstable. But in all XP patients, XPF is expressed to some extent and there is residual catalytic activity. Thus XP-F is typically mild with late onset skin cancer and neurodegeneration

Cockayne syndrome (CS) is classically caused by mutations in *CSA*, *CSB*, *XPB*, *XPD* or *XPG* leading to a defect specifically in TC-NER (Nance and Berry 1992). CS is characterized by numerous developmental abnormalities of varying severity, including growth retardation, microcephaly, delayed psychomotor development, mental retardation and hypogonadism. The patients are photosensitive but without increased risk of skin cancer. CS patients also have several progeroid symptoms, including muscle atrophy, cataracts, osteopenia, cachexia and a prematurely aged appearance. A combination of missense and nonsense mutations in *XPF*, causing impaired assembly of DNA repair complexes and incision of damaged DNA, was recently shown to cause to CS (Kashiyama and others 2013).

To date, only two patients with mutations in *ERCC1* have been reported. The first was homozygous for a missense mutation in exon 7 and diagnosed with a severe form of CS (Kashiyama and others 2013). The second patient had the same missense mutation in combination with a nonsense mutation and was diagnosed with cerebro-oculo-facio-skeletal syndrome (COFS), characterized by devastating pre- and post-natal developmental defects (Jaspers and others 2007). COFS has also been reported in patients with mutations in *CSB*, *XPD* and *XPG*. Thus, COFS is likely a very severe manifestation of CS.

Fanconi anemia (FA) is a disease caused by failure to repair DNA interstrand crosslinks. FA is clinically very heterogeneous, due in part to the fact that there are at least 16

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complementation groups (Clauson and others 2013). Manifestations of FA include congenital anomalies, bone marrow failure and high risk of acute myeloid leukemia (Auerbach 2009). XPF was recently identified as the 16th complementation group of FA (Bogliolo and others 2013; Schuster and others 2013). Again, a complex combination of missense and nonsense mutations in *XPF* causes FA. However, interestingly these mutations affect interstrand crosslink repair specifically with little impact on the other DNA repair functions of ERCC1-XPF (Bogliolo and others 2013).

There is one published case of XFE progeroid syndrome, caused by a homozygous missense mutation in *XPF* that results in substantially reduced expression of the ERCC1-XPF nuclease (Niedernhofer and others 2006). The affected individual had normal early post-natal development, but beginning in early pre-pubescence, there was onset of progressive progeroid symptoms. Multiple organ systems were affected and clinical manifestations included weight loss, old wizened appearance, liver dysfunction, renal insufficiency, visual and hearing loss, epidermal atrophy, sarcopenia, kyphosis, osteopenia, anemia, hypertension, ataxia and cerebral atrophy (Gregg and others 2011; Niedernhofer and others 2006).

Numerous mouse models of NER-deficiency have been made by knocking out genes required for NER or knocking disease causing human mutations into the mouse genome. In virtually all of these models, the mice exhibit a milder phenotype than the human diseases that they model (Friedberg and Meira 2006). The *Xpa*$^{-/-}$ mouse model of XP, have undetectable levels of NER and are hypersensitive to UV and carcinogens, but lack the characteristic neurodegeneration of XP. Murine models of CS express attenuated progeroid symptoms associated with CS including loss of subcutaneous fat, retinal degeneration and neuropathology.

There are two models of XFE progeroid syndrome, a complete knock-out of *Ercc1* and a hypomorphic mutant (Gregg and others 2011). A knock-out strain was first generated by disrupting exon 5 (of 10 exons in *Ercc1*) leading to undetectable levels of the normal length *Ercc1* transcript (McWhir and others 1993). A second knockout mouse was made by inserting a neomycin resistance cassette into exon 7 of *Ercc1*, also leading to undetectable *Ercc1* mRNA (Weeda and others 1997). The phenotype of the two knock-out mice appears to be identical although a direct comparison has not been done. XPF is undetectable in the tissues of the *Ercc1* knockout mouse, indicating destabilization of the endonuclease when ERCC1 is not expressed (Niedernhofer and others 2006). Not surprisingly then, *Xpf*$^{-/-}$ mice appear to phenocopy the *Ercc1*$^{-/-}$ mice (Tian and others 2004).

Deletion of *Ercc1* is lethal in an inbred C57Bl/6 or FVB/n background, but knock-out mice are born with Mendelian frequency in an F1 hybrid background (C57Bl/6:FVB/n) (Niedernhofer and others 2006), indicating that there are modifier genes that influence the severity of the phenotype. *Ercc1* null mutants develop normally in utero but are runted at birth. Their growth curve parallels wild-type littermates postnatally for several weeks than plateaus (McWhir and others 1993; Niedernhofer and others 2006; Weeda and others 1997). Median lifespan is 4 weeks and maximum lifespan is 9 weeks. Mutant mice exhibit a variety of progressive progeroid features, including epidermal atrophy, sarcopenia and kyphosis,

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dystonia, tremors, ataxia and decreased neuronal function (Niedernhofer and others 2006). There is rapid turnover of bone marrow cells, leading to premature exhaustion of hematopoietic stem cells resulting in leukopenia, thrombocytopenia and adipose replacement of the bone marrow (Prasher and others 2005).

Ercc1$^{-/-}$ mice die of liver failure, with increased hepatic serum enzymes and abnormalities that are reminiscent of aged liver including hepatocellular aneuploidy and G2 arrest (McWhir and others 1993; Weeda and others 1997). Re-expression of *Ercc1* in the liver of *Ercc1*$^{-/-}$ mice extends their lifespan to twelve weeks, at which point the animals die of renal insufficiency (Selfridge and others 2001). *Ercc1*$^{-/-}$ mice have profound endocrine changes including reduced growth hormone/insulin-like growth factor-1 signaling, which appears to be an adaptive response to DNA damage demonstrated to extend lifespan (Bartke 2005; Niedernhofer and others 2006). Additionally, tissues of *Ercc1*$^{-/-}$ mice exhibit signs of increased DNA damage response and premature cellular senescence (McWhir and others 1993; Weeda and others 1997).

The hypomorphic mouse, or *Ercc1*$^{-/}$, expresses about 5% of the normal level of ERCC1-XPF. These mice have one null allele and one truncated allele that lacks the last seven amino acids of the protein due to a premature stop codon engineered at position 292. The phenylalanine residue at position 293 is essential for ERCC1 binding to XPF (Tsodikov and others 2005), explaining the severely attenuated expression of the endonuclease heteroduplex. In an inbred genetic F1 hybrid background (C57BL6/J:FVB), the hypomorphic mice are born with Mendelian frequency (de Waard and others 2010). The median lifespan is 19 weeks and the maximum lifespan is 29 weeks (Dolle and others 2011)

Ercc1$^{-/}$ mice are runted postnatally compared to wild-type littermates but develop normally until sexual maturity, at which point they begin to exhibit signs of accelerated aging (Dolle and others 2011; Gregg and others 2011). As with *Ercc1*$^{-/-}$ mice, they exhibit lesions in multiple organ systems, including epidermal, musculoskeletal, central and peripheral nervous systems, cardiovascular, sensorineural, hepatobiliary, renal, hematopoietic and endocrine organs, reflecting a truly systemic accelerated aging (Gregg and others 2011). The *Ercc1*$^{-/}$ mice spontaneously develop loss of vision and hearing (Spoor and others 2012), kyphosis due to osteoporosis (Chen and others 2013) and intervertebral disc degeneration (Vo and others 2010), sarcopenia (Lavasani and others 2012), dystonia and tremors (de Waard and others 2010), progressive primary peripheral neuropathy (Goss and others 2011), ataxia, cerebral atrophy, thymic involution, splenic atrophy, natural killer cell reduction, adipose replacement of the bone marrow (Chen and others 2013; Dolle and others 2011), testicular degeneration, hepatic and renal anisokaryosis, glomerular and renal tubular degeneration, hepatic lipofuscin accumulation, fibrosis, steatosis and pseudocapillarization (Gregg and others 2012) and myocardial degeneration (Dolle and others 2011; Niedernhofer and others 2006). *Ercc1*$^{-/}$ mice have profound spinal cord astrocytosis and microgliosis by four months of age, with significant reduction in the number of motor neurons in the ventral horn of the spinal cord and denervation of the skeletal muscle (de Waard and others 2010). The development of age-dependent motor abnormalities, disruption of neuromuscular connectivity at the neuromuscular junction, degeneration of motor neurons and spontaneous peripheral neurodegeneration (de Waard and others 2010; Goss and others 2011) supports

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the idea that neurons are particularly vulnerable to endogenous DNA damage when not repaired. *Ercc1$^{-/}$* mice also have altered energy metabolism, with a shift to ketosis (Nevedomskaya and others 2010). They have a relative change of lipoprotein levels compared to wild-type mice, with a decrease in LDL and VLDL and increase in HDL in mutant animals (Nevedomskaya and others 2010; Smith and others 2012). Metabolic profiling of *Ercc1$^{-/}$* mice revealed that at younger ages (<10 weeks) there is no significant difference between wild-type and mutant mice. However, as *Ercc1$^{-/}$* mice age (>10 weeks) they display major changes in metabolism. This suggests that the mutant mice develop somewhat normally until they reach sexual maturity and then ‘accelerate aging’. Several metabolic changes are also consistent with organ insufficiency and/or failure, including increased glucose, citrate and succinate in the urine, and decreased hippuric acid secretion indicative of kidney dysfunction and metabolic alkalosis, decreased taurine and allantoin (urine) and increased glutamine and alanine (serum) indicative of liver dysfunction (Nevedomskaya and others 2010). Interestingly these serum and urine changes preceded the pronounced physical changes observed in the *Ercc1$^{-/}$* mice. Additionally, several tissues of *Ercc1$^{-/}$* mice exhibit an increase in DNA damage response and cellular senescence (Gregg and others 2012; Schermer and others 2013; Tilstra and others 2012; Weeda and others 1997).

Ercc1$^{-/}$ mice accumulate genomic mutations at increased frequencies compared to wild-type siblings, but the mutations are largely complex genome rearrangements, which also accumulate, albeit or slowly with age in wild-type mice (Dolle and others 2006). Genome-wide expression profiling of *Ercc1$^{-/}$* mouse liver revealed a highly significant correlation with the transcriptome of old wild-type mice, indicating that the hypomorphic mice appear biologically old (Schumacher and others 2008). Based on transcription profiles, it was also determined that *Ercc1$^{-/}$* mice can be used as model of glomerular aging, as molecular aging processes were comparable to those in wild-type glomeruli (Schermer and others 2013). Thus collectively, there is functional, histopathological, transcriptional, proteomic, metabolomic and ultrastructural data supporting the conclusion that *Ercc1$^{-/}$* mice phenocopy normal murine aging, albeit occurring approximately 6-fold faster.

BubR1

The *BUB1B* gene encodes BUBR1, a core component of the mitotic spindle assembly checkpoint that is also implicated in ciliogenesis and DNA repair (Miyamoto and others 2011). The mitotic spindle assembly checkpoint is critical for accurate sister chromatid segregation during cell division and the maintenance of proper chromosome number. All chromosomes must attach to both spindle poles of a cell, which is mediated by the kinetochore (a protein complex at the centromere of each chromosome) and the spindle microtubules. Until all of the chromosomes are attached and aligned, BUBR1 and other mitotic spindle assembly checkpoint proteins bind CDC20 and anaphase-promoting complex (APC). This inhibits the ubiquitin E3 ligase activity of APC thereby preventing transition from metaphase to anaphase (Zhou and others 2002). Inhibition of the checkpoint or depletion of BUBR1 leads to mitosis under circumstances where the chromosomes cannot be equally distributed, and thereby aneuploidy.

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Aneuploidy increases with age in tissues of mice (Faggioli and others 2012). Interestingly BUBR1 expression declines in multiple tissues of mice as they age (Baker and others 2004). Overexpression of BUBR1 in the mouse, attenuates aneuploidy, reduces chromosomal instability and tumorigenesis, and extends median and maximum lifespan (Baker and others 2013a), suggesting that the decline in BUBR1 expression might contribute to aging. Indeed, many age-related phenotypes are attenuated when BUBR1 is forcibly overexpressed, including the accumulation of senescent cells, loss of muscle stem cells, myofiber diameter and exercise capacity, renal inflammation and glomerulosclerosis, and cardiac performance (Baker and others 2013a).

In humans, *BUB1B* mutations cause Mosaic variegated aneuploidy (MVA), as autosomal recessive disease characterized by a high frequency of mosaic aneuploidies and an increased risk of cancer (Garcia-Castillo and others 2008). Interestingly, MVA patients often exhibit progeroid traits including shortened lifespan, growth retardation and short stature, cataracts, corneal opacities, and glaucoma.

To study the role of *BubR1* in disease and aging, Baker *et al* developed transgenic mice expressing various levels of BUBR1 (Baker and others 2004). Complete deletion of BUBR1 expression causes early embryonic lethality due to massive apoptosis. Mice created with one null and one hypomorphic allele express approximately 4% of normal level of BUBR1 died within hours birth, likely due to respiratory insufficiency (Baker and others 2004). *BubR1*$^{+/-}$ mice express ~30% of the normal levels of BUBR1 and display no obvious phenotype. However, there is extensive aneuploidy in primary mouse embryonic fibroblasts, derived from the mice and the mice are susceptible to chemically-induced tumorigenesis, particularly of the lung and colon.

Mutant mice carrying two *BubR1* hypomorphic alleles (*BubR1*$^{H/H}$ mice) mice express ~10% of the normal levels of BUBR1 protein and have profound accelerated aging (Baker and others 2004). *BubR1*$^{H/H}$ mice are normal in appearance and size at birth but have slow post-natal growth. Lesions shown by *BubR1*$^{H/H}$ mice include dwarfism, lordokyphosis, facial dysmorphisms, cachexia, infertility of males and females (due to defects in meiotic chromosome segregation). Progeroid features include vascular fibrosis, impaired aortic and carotid elasticity, cardiac arrhythmias, arterial wall stiffening, cataracts, sarcopenia, gliosis in the brain, loss of subcutaneous fat, thinning of the dermis, impaired wound healing, skin abnormalities (subdermal fat loss, reduced dermal thickness and impaired wound healing) and reduced stress tolerance (Baker and others 2013a; Baker and others 2004; Baker and others 2013b; Hartman and others 2007; Matsumoto and others 2007).

Beginning at approximately two months of age, *BubR1*$^{H/H}$ mouse cells display a high frequency of chromosome missegregation, as well as increasing aneuploidy, and the emergence of progeroid phenotypes. This suggests a role for chromosomal instability in the development of progeroid features, though it is likely that other factors are also involved, as other models with higher aneuoploidy rates do not undergo premature senescence and aging (Wijshake and others 2012). Interestingly, *BubR1*$^{H/H}$ mice do not show an increased incidence of cancer, though they are susceptible to DMBA-induced tumorigenesis (Baker and others 2004). The median lifespan of the *BubR1*$^{H/H}$ mice is six months, approximately

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four- to fivefold shorter than wild-type mice in the same genetic background (Baker and others 2011; Hartman and others 2007).

BubR1$^{H/H}$ mice have been used to investigate of the role of cellular senescence in aging (Baker and others 2008; Baker and others 2011). p16^{Ink4a} and p19^{Arf}, which increase with age in rodent and human tissues, are selectively induced in skeletal muscle, fat, and eyes of *BubR1*$^{H/H}$ mice. Primary mouse embryonic fibroblasts derived from *BubR1*$^{H/H}$ mice senesce prematurely *ex vivo* (Hartman and others 2007). Inactivation of p16^{Ink4a} in *BubR1*$^{H/H}$ mice reduces cellular senescence and accelerated aging of the skeletal muscle and fat, while p19^{Arf} inactivation increased senescence and aging in these mice (Baker and others 2008). Selective removal of p16^{Ink4a}- positive, senescent cells in *BubR1*$^{H/H}$ mice delays the onset of lordokyphosis and cataracts, and attenuates the loss of myofiber size, subcutaneous fat and exercise capacity (Baker and others 2011). This study provided the first direct experimental evidence that senescent cells drive aging *in vivo*. Interestingly, the in *BubR1*$^{H/H}$ mouse, p53 has been shown to be protective against the development of age-related lesions (Baker and others 2013b), as opposed to other progeroid mouse models (*Zmpste24*$^{-/-}$ and *Ercc1*$^{-/}$) in which p53 drives the early aging phenotype.

Polγ

Mitochondria are an essential organelle with critical functions in cellular metabolism, calcium signaling, ROS generation, pyrimidine biosynthesis and apoptosis. However, its most crucial function is ATP generation via the electron transport chain (ETC) and oxidative phosphorylation (OXPHOS). Intracellular ROS are produced as a byproduct of oxidative phosphorylation. The mitochondrial theory of aging suggests that ROS produced by the mitochondria, damage key mitochondrial components, such as mitochondrial DNA (mtDNA), membranes and respiratory chain proteins (Jang and Van Remmen 2009; Kujoth and others 2007). Damage accumulates over time, ultimately leading to mitochondrial dysfunction and impaired respiration, further increasing ROS production and oxidative damage, eventually triggering activation of cell death pathways. This “vicious cycle” of ROS and damage is hypothesized to be a major determinant of mammalian lifespan (reviewed in (Cui and others 2012)). However, transgenic mice with modifications in mitochondrial antioxidant capacity yielded conflicting results, and in total do not fully support the mitochondrial theory of aging (Jang and Van Remmen 2009).

Mitochondria have a 16.5kb circular genome, which comprises approximately 1-3% of total cellular DNA in animals, encoding for tRNAs, rRNAs and polypeptides essential for ETC and OXPHOS. Mitochondrial DNA (mtDNA) replicates within the organelle, independently of the nuclear genome and the cell cycle. mtDNA replication is controlled by DNA polymerase gamma (POLG or Polγ), an enzyme encoded by the nuclear genome, and the only DNA polymerase known to function in the mitochondria. POLG has a C-terminal polymerase domain that catalyzes DNA synthesis, an N-terminal $3' \rightarrow 5'$exonuclease that proofreads newly replicated DNA and 5′ dRP lyase activity for the excision repair of abasic sites in the mitochondrial genome.

Point mutations and deletions in mtDNA accumulate in multiple tissues with aging and correlates with mitochondrial morphological changes that also appear in aged animals, thus

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suggesting a central role of mtDNA mutations in aging and age-related pathologies (reviewed in (Cui and others 2012)). Increased frequency of mtDNA mutations with aging is more pronounced in long-lived post-mitotic cells with high levels of oxidative phosphorylation, such as cardiomyocytes, skeletal muscle fibers and neurons, but increases are seen in nearly all tissues. Additionally, mitochondrial number decrease in aged livers of several mammals, including mice and humans, leading to decreased mtDNA copy number and mitochondrial proteins. Pathogenic mutations in mtDNA lead to ATP depletion, cellular dysfunction and ultimately cell death due to activation of apoptosis. However, whether mitochondrial mutations cause mammalian aging or are merely correlated with it, remains an area of debate.

mtDNA is more susceptible to oxidative damage than nuclear DNA and has a higher mutation rate due to several factors including the close proximity of mtDNA to the electron transport chain where there is greater likelihood of exposure to ROS, absence of protective histones, and lack of buffering by introns (Cui and others 2012). In addition, mtDNA has limited capacity for DNA repair, as mitochondria lack some DNA repair mechanisms present in the nucleus. For example, nucleotide excision repair does not occur in the mitochondria. Thus the repair of oxidative damage depends upon base excision repair, which is reported to wane with age in the mouse brain (Alexeyev and others 2013). In contrast, recent evidence suggests a role for replication errors occurring early on life that undergo polyclonal expansion with age and finally lead to mitochondrial dysfunction, as the main cause of accelerated aging (Ameur and others 2011).

In humans, numerous, diverse inherited disorders are caused by mutations in mtDNA, including diabetes, neurodegeneration and cancer (NIH 2015). In 2001, the first disease mutations were identified in *POLG*, that caused progressive external ophthalmoplegia (PEO) and since then ~150 mutations in *POLG* have been implicated in a variety of diseases including Alpers syndrome and other infantile hepatocerebral syndromes, ataxia-neuropathy syndromes, Charcot-Marie-Tooth disease, idiopathic parkinsonism, nucleoside reverse-transcriptase inhibitor toxicity, deafness, peripheral neuropathy, male infertility and a decreased age of menopause (below 35 years of age)(Taylor and Turnbull 2005).

The absence of a human progeroid syndrome caused by mtDNA instability suggests that mtDNA mutations do not contribute to fundamental mechanisms of human aging. Similarly, there are no segmental progeroid syndromes that can be explicitly attributed to genes that regulate oxidative stress. However, the fact that *POLG* mutations are associated with a variety of age-related pathologies and diseases including cataracts, Parkinson's disease, early menopause, diabetes, deafness and decreased cardiac and skeletal muscle function, implicates mtDNA instability in impacting frailty.

To directly test this, mitochondrial mutator mice were generated by two independent groups using a knock-in strategy (Trifunovic and others 2004). These mice were made by introducing an AC→CT substitution that corresponded to positions 1054 and 1055 of *Polg to* create $Pol\gamma^{D257A/D257A}$ This missense mutation (D257A) resulted in a critical substitution in the conserved second exonuclease domain of $Pol\gamma$, impairing its proof-reading ability, but not affecting polymerase activity. Thus, mice homozygous for this mutation have

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accelerated accumulation of mutations in their mtDNA, including random point mutations, linear molecules with large deletions, circular mtDNA molecules with large deletions and molecules containing multimers in regions containing non-coding mtDNA (Bailey and others 2009; Someya and others 2008).

Polγ$^{D257A/D257A}$ mice are born in Mendelian fashion without an obvious phenotype and young mutants are indistinguishable from wild-type littermates (Trifunovic and others 2004). The premature aging phenotype that develops in each strain of mutant mouse is very similar, differing only in the time of onset of phenotypes (6-7 months vs. 9 months of age) (Kujoth and others 2005; Trifunovic and others 2004). Aging-associated lesions include weight loss, hearing loss, hair graying and alopecia, loss of subcutaneous fat, decreased spontaneous activity, kyphosis, osteoporosis and loss of bone mass, sarcopenia, loss of intestinal crypts and intestinal dysplasia, thymic involution, infertility, testicular atrophy associated with depletion of spermatogonia, and cardiac hypertrophy and dysfunction (Trifunovic and others 2004; Vermulst and others 2007; Vermulst and others 2008). polγ$^{D257A/D257A}$ mice have normal blood counts until four months of age, but then develop an age-dependent macrocytic anemia with abnormal erythroid maturation and megaloblastic changes, as well as defects in lymphopoiesis. In one strain, the median lifespan is ~48 weeks, with a maximal lifespan of 61 weeks, while the other mutant strain has a median lifespan of 59 weeks and maximum lifespan of 66 weeks, which is 50% less than wild-type mice in the same genetic background.

Compared to wild-type littermates, mtDNA mutations are increased 3-11 fold in multiple tissues, and because mutation load is already substantial by two months of age and somewhat uniform between tissues, it was suggested that much of the mutation accumulation occurred during embryonic and/or fetal development (Kujoth and others 2007; Trifunovic and others 2004). While both point mutations and deletions in mtDNA accumulate with age in these mice, mtDNA deletions were identified as a driving force behind the premature aging phenotype of these mice, though the rate at which mtDNA mutations reach phenotypic expression is greatly variable among tissues (Vermulst and others 2008). Interestingly, a mouse model that expresses a mutant-dominant version of mtDNA helicase, Twinkle, also accumulates low-levels of large scale mtDNA deletions. Although these mice display mitochondrial dysfunction, they have a normal lifespan, suggesting mtDNA mutations and abnormal mitochondrial function may not be sufficient to promote progeroid like symptoms (Tyynismaa and others 2005).

Importantly, in the *Polγ*$^{D257A/D257A}$ mice, there is no change in mitochondrial ROS production, no increase in DNA, RNA, protein or lipid markers of oxidative stress and antioxidant defense systems are not up-regulated (Edgar and Trifunovic 2009; Kujoth and others 2007). Increased mtDNA mutations in *Polγ*$^{D257A/D257A}$ mice, are also not associated with impaired cellular proliferation or accelerated cellular senescence (Kujoth and others 2005). However, by 12 weeks of age, *Polγ*$^{D257A/D257A}$ mice exhibit decreased electron transport chain activity with decreased oxygen consumption and ATP production by mitochondria (Jang and Van Remmen 2009; Kujoth and others 2007). The mtDNA mutations in mutant mice also correlate with the induction of apoptotic markers, particularly in tissues with rapid cellular turnover (Kujoth and others 2007; Kujoth and others 2005). It

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was proposed that the accumulation of mtDNA mutations led to mitochondrial dysfunction and associated impairment of energy metabolism, inducing apoptosis (Someya and others 2008). Because levels of apoptotic markers also increase during normal aging in mice, accumulation of mtDNA mutations that promote apoptosis and result in loss of critical and irreplaceable cells may be a central mechanism driving tissue dysfunction in mammalian aging (Kujoth and others 2005).

Mice heterozygous for the mutant allele ($Pol\gamma^{D257A/+}$) have normal lifespans and no premature aging phenotype (Jang and Van Remmen 2009; Vermulst and others 2008). They have been found to have approximately a 500-fold increase in mtDNA point mutations compared to wild-type mice, disputing the role of mtDNA point mutations as a lifespan limiting factor (Jang and Van Remmen 2009). Additional mutator mice have also been made using tissue-specific $Pol\gamma^{181A}$ exonuclease deficient transgenes expressed primarily in the heart or brain (Kujoth and others 2007).

There are criticisms about the utility the $Pol\gamma^{\mathrm{D257A/D257A}}$ mouse as a model for mammalian aging. It has been noted that while their pathologies may be similar to those seen in aged humans, they do not necessarily reflect those observed in normal aged mice (Jang and Van Remmen 2009). Several lesions, including anemia and loss of intestinal crypts, are far more severe in mutants than in normally aged mice and other lesions such as weight loss, alopecia and kyphosis, are uncommon in healthy aged mice (Maronpot 1999). The hearing loss in the mtDNA mutator mouse occurs via a different mechanism than that in normal aged mice, and sarcopenic muscle from the mutant mouse has high mitochondrial fission and autophagy levels, not seen in normally aged muscle (Joseph and others 2013).

Conclusions and Future Directions

Because genome maintenance mechanisms are generally highly conserved between species, mice defective in such pathways are especially important models, as they can exhibit premature appearance of aging symptoms (Hasty and others 2003). Mutant mice deficient in DNA repair exhibiting premature senescence and progeroid lesions support the involvement of DNA damage-induced senescence in the process of aging. The study of such mice can provide valuable information regarding basic mechanisms of aging, as well as natural defense systems that promote longevity (Hasty and others 2003). They also can be exploited as rapid models in pre-clinical studies to address certain aspects of aging (Baker and others 2011; Lavasani and others 2012; Tilstra and others 2012).

Mouse models of accelerated aging are not perfect models of natural aging in mice or humans. Often, this is because they were not intended to be. Instead, they were generated to ask specific questions about the physiological function of a protein (Baker and others 2004; Niedernhofer and others 2006) or to test a specific hypothesis about the contribution of particular type of damage to aging (Kujoth and others 2005; Trifunovic and others 2004). There is often incomplete overlap between the histopathologic lesions seen in rapidly aging mice and those commonly associated with normal aging indicating that the models are segmental or tissue-specific. However the mice that were generated specifically to model a human progeroid syndrome have translational potential (Chen and others 2013;

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Niedernhofer and others 2006) for discovering therapeutics for rare diseases and potentially aging in the general populaiton.

Aging results from a complex interplay between genetics of an organism (human or mouse) and the stresses placed on it by its particular environment. The genetic background of mice not surprisingly therefore has an important role in modifying the penetrance and expression of clinical manifestations of DNA repair deficiencies. Environmental factors including housing conditions, infectious agents, and diet likely play a role in the expression of aging phenotypes in mouse models, and perhaps in humans as well (Collins and Tabak 2014).

Another important consideration is the sex of the animals. With the exception of lesions associated with the reproductive tract, the sex of the animal is often not reported with the phenotypic descriptions of aging in mouse models and preclinical studies Many of the traits examined in mouse models used in aging research are influenced by sex-linked biological factors, such as bone density and neurodegeneration. Indeed, several therapeutics discovered to impact lifespan of wild-type mice display efficacy only in males or to (Harrison and others 2014) a greater extent in females (Miller and others 2014).

In lifespan studies, the most vulnerable organ or body system fails first, causing death of the animal and preventing acquisition of information about the long-term effects on other, potentially more relevant, organ systems. This can be overcome with the use of floxed (conditional) alleles of relevant genes. Tissue-specific deletion of a gene enables one to determine if for example DNA damage accumulation or mtDNA mutations affect only that tissue (cell-autonomous mechanism of aging) or other tissues as well (non-cell autonomous). In addition, using a conditional allele, it is possible to knockout gene expression in adult animals to discover if phenotypes are purely degenerative or if they have a developmental component. Future studies incorporating currently available and newly developed animal models will undoubtedly facilitate the rapid development and refinement of genetic or pharmacologic therapeutic interventions that reduce DNA damage, promote DNA repair, or optimize the cellular response to DNA damage to prolong healthy lifespan and aging (Baker and others 2011; Hasty and others 2003; Lavasani and others 2012; Tilstra and others 2012).

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References

Alexeyev M, Shokolenko I, Wilson G, LeDoux S. The maintenance of mitochondrial DNA integrity--critical analysis and update. Cold Spring Harbor perspectives in biology. 2013; 5:a012641. [PubMed: 23637283]

Ameur A, Stewart JB, Freyer C, Hagstrom E, Ingman M, Larsson NG, Gyllensten U. Ultra-deep sequencing of mouse mitochondrial DNA: mutational patterns and their origins. PLoS genetics. 2011; 7:e1002028. [PubMed: 21455489]

Auerbach AD. Fanconi anemia and its diagnosis. Mutation research. 2009; 668:4–10. [PubMed: 19622403]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bailey LJ, Cluett TJ, Reyes A, Prolla TA, Poulton J, Leeuwenburgh C, Holt IJ. Mice expressing an error-prone DNA polymerase in mitochondria display elevated replication pausing and chromosomal breakage at fragile sites of mitochondrial DNA. Nucleic acids research. 2009; 37:2327–2335. [PubMed: 19244310]

Baker DJ, Dawlaty MM, Wijshake T, Jeganathan KB, Malureanu L, van Ree JH, Crespo-Diaz R, Reyes S, Seaburg L, Shapiro V, Behfar A, Terzic A, van de Sluis B, van Deursen JM. Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. Nat Cell Biol. 2013a; 15:96–102. [PubMed: 23242215]

Baker DJ, Jeganathan KB, Cameron JD, Thompson M, Juneja S, Kopecka A, Kumar R, Jenkins RB, de Groen PC, Roche P, van Deursen JM. BubR1 insufficiency causes early onset of aging-associated phenotypes and infertility in mice. Nature genetics. 2004; 36:744–749. [PubMed: 15208629]

Baker DJ, Perez-Terzic C, Jin F, Pitel KS, Niederlander NJ, Jeganathan K, Yamada S, Reyes S, Rowe L, Hiddinga HJ, Eberhardt NL, Terzic A, van Deursen JM. Opposing roles for p16Ink4a and p19Arf in senescence and ageing caused by BubR1 insufficiency. Nat Cell Biol. 2008; 10:825–836. [PubMed: 18516091]

Baker DJ, Weaver RL, van Deursen JM. p21 both attenuates and drives senescence and aging in BubR1 progeroid mice. Cell Rep. 2013b; 3:1164–1174. [PubMed: 23602569]

Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, Kirkland JL, van Deursen JM. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature. 2011; 479:232–236. [PubMed: 22048312]

Bartke A. Minireview: role of the growth hormone/insulin-like growth factor system in mammalian aging. Endocrinology. 2005; 146:3718–3723. [PubMed: 15919742]

Bogliolo M, Schuster B, Stoepker C, Derkunt B, Su Y, Raams A, Trujillo JP, Minguillon J, Ramirez MJ, Pujol R, Casado JA, Banos R, Rio P, Knies K, Zuniga S, Benitez J, Bueren JA, Jaspers NG, Scharer OD, de Winter JP, Schindler D, Surralles J. Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia. American journal of human genetics. 2013; 92:800–806. [PubMed: 23623386]

Bootsma, D.; Kraemer, KH.; Cleaver, JE.; H, JHJ. Nucleotide excision repair syndromes: Xeroderma pigmentosum, Cockayne Syndrome, and trichothiodystrophy. In: Kinzler, BV.; a, KW., editors. The genetic basis of human cancer. New York: McGraw-Hill; 1998.

Chen Q, Liu K, Robinson AR, Clauson CL, Blair HC, Robbins PD, Niedernhofer LJ, Ouyang H. DNA damage drives accelerated bone aging via an NF-kappaB-dependent mechanism. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2013; 28:1214–1228.

Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. DNA Repair (Amst). 2004; 3:1187–1196. [PubMed: 15279807]

Clauson C, Scharer OD, Niedernhofer L. Advances in understanding the complex mechanisms of DNA interstrand cross-link repair. Cold Spring Harbor perspectives in medicine. 2013; 3:a012732. [PubMed: 24224206]

Collins FS, Tabak LA. Policy: NIH plans to enhance reproducibility. Nature. 2014; 505:612–613. [PubMed: 24482835]

Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annual review of pathology. 2010; 5:99–118.

Cui H, Kong Y, Zhang H. Oxidative stress, mitochondrial dysfunction, and aging. Journal of signal transduction. 2012; 2012:646354. [PubMed: 21977319]

de Waard MC, van der Pluijm I, Zuiderveen Borgesius N, Comley LH, Haasdijk ED, Rijksen Y, Ridwan Y, Zondag G, Hoeijmakers JH, Elgersma Y, Gillingwater TH, Jaarsma D. Age-related motor neuron degeneration in DNA repair-deficient Ercc1 mice. Acta Neuropathol. 2010; 120:461–475. [PubMed: 20602234]

Dizdaroglu M, Jaruga P, Birincioglu M, Rodriguez H. Free radical-induced damage to DNA: mechanisms and measurement. Free radical biology & medicine. 2002; 32:1102–1115. [PubMed: 12031895]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Dolle ME, Busuttil RA, Garcia AM, Wijnhoven S, van Drunen E, Niedernhofer LJ, van der Horst G, Hoeijmakers JH, van Steeg H, Vijg J. Increased genomic instability is not a prerequisite for shortened lifespan in DNA repair deficient mice. Mutation research. 2006; 596:22–35. [PubMed: 16472827]

Dolle ME, Kuiper RV, Roodbergen M, Robinson J, de Vlugt S, Wijnhoven SW, Beems RB, de la Fonteyne L, de With P, van der Pluijm I, Niedernhofer LJ, Hasty P, Vijg J, Hoeijmakers JH, van Steeg H. Broad segmental progeroid changes in short-lived Ercc1(-/Delta7) mice. Pathobiol Aging Age Relat Dis. 2011; 1

Edgar D, Trifunovic A. The mtDNA mutator mouse: Dissecting mitochondrial involvement in aging. Aging (Albany NY). 2009; 1:1028–1032. [PubMed: 20157586]

Faggioli F, Wang T, Vijg J, Montagna C. Chromosome-specific accumulation of aneuploidy in the aging mouse brain. Human molecular genetics. 2012; 21:5246–5253. [PubMed: 22962300]

Friedberg EC, Meira LB. Database of mouse strains carrying targeted mutations in genes affecting biological responses to DNA damage Version 7. DNA Repair (Amst). 2006; 5:189–209. [PubMed: 16290067]

Garcia-Castillo H, Vasquez-Velasquez AI, Rivera H, Barros-Nunez P. Clinical and genetic heterogeneity in patients with mosaic variegated aneuploidy: delineation of clinical subtypes. American journal of medical genetics Part A. 2008; 146A:1687–1695. [PubMed: 18548531]

Gilchrest BA. Photoaging. The Journal of investigative dermatology. 2013; 133:E2–6. [PubMed: 23820721]

Goldman DP, Olshansky SJ. Delayed aging versus delayed disease: A new paradigm for public health. Public Policy & Aging Report. 2013; 23:16–18.

Goss JR, Stolz DB, Robinson AR, Zhang M, Arbujas N, Robbins PD, Glorioso JC, Niedernhofer LJ. Premature aging-related peripheral neuropathy in a mouse model of progeria. Mechanisms of ageing and development. 2011; 132:437–442. [PubMed: 21596054]

Gregg SQ, Gutierrez V, Robinson AR, Woodell T, Nakao A, Ross MA, Michalopoulos GK, Rigatti L, Rothermel CE, Kamileri I, Garinis GA, Stolz DB, Niedernhofer LJ. A mouse model of accelerated liver aging caused by a defect in DNA repair. Hepatology. 2012; 55:609–621. [PubMed: 21953681]

Gregg SQ, Robinson AR, Niedernhofer LJ. Physiological consequences of defects in ERCC1-XPF DNA repair endonuclease. DNA Repair (Amst). 2011; 10:781–791. [PubMed: 21612988]

Harman D. Aging: a theory based on free radical and radiation chemistry. Journal of gerontology. 1956; 11:298–300. [PubMed: 13332224]

Harrison DE, Strong R, Allison DB, Ames BN, Astle CM, Atamna H, Fernandez E, Flurkey K, Javors MA, Nadon NL, Nelson JF, Pletcher S, Simpkins JW, Smith D, Wilkinson JE, Miller RA. Acarbose, 17-alpha-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. Aging cell. 2014; 13:273–282. [PubMed: 24245565]

Hartman TK, Wengenack TM, Poduslo JF, van Deursen JM. Mutant mice with small amounts of BubR1 display accelerated age-related gliosis. Neurobiol Aging. 2007; 28:921–927. [PubMed: 16781018]

Hasty P, Campisi J, Hoeijmakers J, van Steeg H, Vijg J. Aging and genome maintenance: lessons from the mouse? Science. 2003; 299:1355–1359. [PubMed: 12610296]

Herbig U, Ferreira M, Condel L, Carey D, Sedivy JM. Cellular senescence in aging primates. Science. 2006; 311:1257. [PubMed: 16456035]

Jang YC, Van Remmen H. The mitochondrial theory of aging: insight from transgenic and knockout mouse models. Experimental gerontology. 2009; 44:256–260. [PubMed: 19171187]

Jaspers NG, Raams A, Silengo MC, Wijgers N, Niedernhofer LJ, Robinson AR, Giglia-Mari G, Hoogstraten D, Kleijer WJ, Hoeijmakers JH, Vermeulen W. First reported patient with human ERCC1 deficiency has cerebro-oculo-facio-skeletal syndrome with a mild defect in nucleotide excision repair and severe developmental failure. American journal of human genetics. 2007; 80:457–466. [PubMed: 17273966]

Joseph AM, Adhihetty PJ, Wawrzyniak NR, Wohlgemuth SE, Picca A, Kujoth GC, Prolla TA, Leeuwenburgh C. Dysregulation of mitochondrial quality control processes contribute to

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

sarcopenia in a mouse model of premature aging. PLoS One. 2013; 8:e69327. [PubMed: 23935986]

Kashiyama K, Nakazawa Y, Pilz DT, Guo C, Shimada M, Sasaki K, Fawcett H, Wing JF, Lewin SO, Carr L, Li TS, Yoshiura K, Utani A, Hirano A, Yamashita S, Greenblatt D, Nardo T, Stefanini M, McGibbon D, Sarkany R, Fassihi H, Takahashi Y, Nagayama Y, Mitsutake N, Lehmann AR, Ogi T. Malfunction of nuclease ERCC1-XPF results in diverse clinical manifestations and causes Cockayne syndrome, xeroderma pigmentosum, and Fanconi anemia. American journal of human genetics. 2013; 92:807–819. [PubMed: 23623389]

Kirkwood TB. Understanding the odd science of aging. Cell. 2005; 120:437–447. [PubMed: 15734677]

Kraemer KH, DiGiovanna JJ. Forty Years of Research on Xeroderma Pigmentosum at the US National Institutes of Health. Photochemistry and photobiology. 2014

Kudlow BA, Kennedy BK, Monnat RJ Jr. Werner and Hutchinson-Gilford progeria syndromes: mechanistic basis of human progeroid diseases. Nature reviews Molecular cell biology. 2007; 8:394–404.

Kujoth GC, Bradshaw PC, Haroon S, Prolla TA. The role of mitochondrial DNA mutations in mammalian aging. PLoS genetics. 2007; 3:e24. [PubMed: 17319745]

Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, Hofer T, Seo AY, Sullivan R, Jobling WA, Morrow JD, Van Remmen H, Sedivy JM, Yamasoba T, Tanokura M, Weindruch R, Leeuwenburgh C, Prolla TA. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. Science. 2005; 309:481–484. [PubMed: 16020738]

Lavasani M, Robinson AR, Lu A, Song M, Feduska JM, Ahani B, Tilstra JS, Feldman CH, Robbins PD, Niedernhofer LJ, Huard J. Muscle-derived stem/progenitor cell dysfunction limits healthspan and lifespan in a murine progeria model. Nature communications. 2012; 3:608.

Maronpot, R. Pathology of the Mouse: Reference and Atlas. St. Louis, MO: Cache River Press; 1999.

Matsumoto T, Baker DJ, d'Uscio LV, Mozammel G, Katusic ZS, van Deursen JM. Aging-associated vascular phenotype in mutant mice with low levels of BubR1. Stroke. 2007; 38:1050–1056. [PubMed: 17272762]

McWhir J, Selfridge J, Harrison DJ, Squires S, Melton DW. Mice with DNA repair gene (ERCC-1) deficiency have elevated levels of p53, liver nuclear abnormalities and die before weaning. Nature genetics. 1993; 5:217–224. [PubMed: 8275084]

Miller RA, Harrison DE, Astle CM, Fernandez E, Flurkey K, Han M, Javors MA, Li X, Nadon NL, Nelson JF, Pletcher S, Salmon AB, Sharp ZD, Van Roekel S, Winkleman L, Strong R. Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction. Aging cell. 2014; 13:468–477. [PubMed: 24341993]

Miyamoto T, Porazinski S, Wang H, Borovina A, Ciruna B, Shimizu A, Kajii T, Kikuchi A, Furutani-Seiki M, Matsuura S. Insufficiency of BUBR1, a mitotic spindle checkpoint regulator, causes impaired ciliogenesis in vertebrates. Human molecular genetics. 2011; 20:2058–2070. [PubMed: 21389084]

Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. American journal of medical genetics. 1992; 42:68–84. [PubMed: 1308368]

NCoA. Chronic Disease. In: Aging N.C.o.. , editor. Improve Health. Washington, D.C.: Center for Healthy Aging; 2011.

Nevedomskaya E, Meissner A, Goraler S, de Waard M, Ridwan Y, Zondag G, van der Pluijm I, Deelder AM, Mayboroda OA. Metabolic profiling of accelerated aging ERCC1 d/- mice. J Proteome Res. 2010; 9:3680–3687. [PubMed: 20507129]

Niedernhofer LJ, Garinis GA, Raams A, Lalai AS, Robinson AR, Appeldoorn E, Odijk H, Oostendorp R, Ahmad A, van Leeuwen W, Theil AF, Vermeulen W, van der Horst GT, Meinecke P, Kleijer WJ, Vijg J, Jaspers NG, Hoeijmakers JH. A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. Nature. 2006; 444:1038–1043. [PubMed: 17183314]

NIH. Conditions related to mitochondrial genes. In: Communication L.H.N.C.f.B.. , editor. Genetics Home Reference: YOur guide to understanding genetics conditions. USA.gov: Department of Health & Human Services; 2015.

Park A. How To Live 100 years. TIME. 2010

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Prasher JM, Lalai AS, Heijmans-Antonissen C, Ploemacher RE, Hoeijmakers JH, Touw IP, Niedernhofer LJ. Reduced hematopoietic reserves in DNA interstrand crosslink repair-deficient Ercc1-/- mice. The EMBO journal. 2005; 24:861–871. [PubMed: 15692571]

Scharer OD. Nucleotide excision repair in eukaryotes. Cold Spring Harbor perspectives in biology. 2013; 5:a012609. [PubMed: 24086042]

Schermer B, Bartels V, Frommolt P, Habermann B, Braun F, Schultze JL, Roodbergen M, Hoeijmakers JH, Schumacher B, Nurnberg P, Dolle ME, Benzing T, Muller RU, Kurschat CE. Transcriptional profiling reveals progeroid Ercc1(-/Delta) mice as a model system for glomerular aging. BMC Genomics. 2013; 14:559. [PubMed: 23947592]

Schumacher B, van der Pluijm I, Moorhouse MJ, Kosteas T, Robinson AR, Suh Y, Breit TM, van Steeg H, Niedernhofer LJ, van Ijcken W, Bartke A, Spindler SR, Hoeijmakers JH, van der Horst GT, Garinis GA. Delayed and accelerated aging share common longevity assurance mechanisms. PLoS genetics. 2008; 4:e1000161. [PubMed: 18704162]

Schuster B, Knies K, Stoepker C, Velleuer E, Friedl R, Gottwald-Muhlhauser B, de Winter JP, Schindler D. Whole exome sequencing reveals uncommon mutations in the recently identified Fanconi anemia gene SLX4/FANCP. Human mutation. 2013; 34:93–96. [PubMed: 23033263]

Selfridge J, Hsia KT, Redhead NJ, Melton DW. Correction of liver dysfunction in DNA repair-deficient mice with an ERCC1 transgene. Nucleic acids research. 2001; 29:4541–4550. [PubMed: 11713303]

Smith SC, Robinson AR, Niedernhofer LJ, Hetman M. Downregulation of cholesterol biosynthesis genes in the forebrain of ERCC1-deficient mice. Neurobiology of disease. 2012; 45:1136–1144. [PubMed: 22245387]

Someya S, Yamasoba T, Kujoth GC, Pugh TD, Weindruch R, Tanokura M, Prolla TA. The role of mtDNA mutations in the pathogenesis of age-related hearing loss in mice carrying a mutator DNA polymerase gamma. Neurobiol Aging. 2008; 29:1080–1092. [PubMed: 17363114]

Spoor M, Nagtegaal AP, Ridwan Y, Borgesius NZ, van Alphen B, van der Pluijm I, Hoeijmakers JH, Frens MA, Borst JG. Accelerated loss of hearing and vision in the DNA-repair deficient Ercc1(delta/-) mouse. Mechanisms of ageing and development. 2012; 133:59–67. [PubMed: 22257940]

Tamura D, DiGiovanna JJ, Khan SG, Kraemer KH. Living with xeroderma pigmentosum: comprehensive photoprotection for highly photosensitive patients. Photodermatology, photoimmunology & photomedicine. 2014; 30:146–152.

Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. Nature reviews Genetics. 2005; 6:389–402.

Tian M, Shinkura R, Shinkura N, Alt FW. Growth retardation, early death, and DNA repair defects in mice deficient for the nucleotide excision repair enzyme XPF. Molecular and cellular biology. 2004; 24:1200–1205. [PubMed: 14729965]

Tilstra JS, Robinson AR, Wang J, Gregg SQ, Clauson CL, Reay DP, Nasto LA, St Croix CM, Usas A, Vo N, Huard J, Clemens PR, Stolz DB, Guttridge DC, Watkins SC, Garinis GA, Wang Y, Niedernhofer LJ, Robbins PD. NF-kappaB inhibition delays DNA damage-induced senescence and aging in mice. J Clin Invest. 2012; 122:2601–2612. [PubMed: 22706308]

Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, Bohlooly YM, Gidlof S, Oldfors A, Wibom R, Tornell J, Jacobs HT, Larsson NG. Premature ageing in mice expressing defective mitochondrial DNA polymerase. Nature. 2004; 429:417–423. [PubMed: 15164064]

Tsodikov OV, Enzlin JH, Scharer OD, Ellenberger T. Crystal structure and DNA binding functions of ERCC1, a subunit of the DNA structure-specific endonuclease XPF-ERCC1. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102:11236–11241. [PubMed: 16076955]

Tyynismaa H, Mjosund KP, Wanrooij S, Lappalainen I, Ylikallio E, Jalanko A, Spelbrink JN, Paetau A, Suomalainen A. Mutant mitochondrial helicase Twinkle causes multiple mtDNA deletions and a late-onset mitochondrial disease in mice. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102:17687–17692. [PubMed: 16301523]

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

United Nations D.o.E.a.S.A.. , editor. UN. World Population Ageing 2013. New York: United Nations; 2013.

Vermulst M, Bielas JH, Kujoth GC, Ladiges WC, Rabinovitch PS, Prolla TA, Loeb LA. Mitochondrial point mutations do not limit the natural lifespan of mice. Nature genetics. 2007; 39:540–543. [PubMed: 17334366]

Vermulst M, Wanagat J, Kujoth GC, Bielas JH, Rabinovitch PS, Prolla TA, Loeb LA. DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice. Nature genetics. 2008; 40:392–394. [PubMed: 18311139]

Vo N, Seo HY, Robinson A, Sowa G, Bentley D, Taylor L, Studer R, Usas A, Huard J, Alber S, Watkins SC, Lee J, Coehlo P, Wang D, Loppini M, Robbins PD, Niedernhofer LJ, Kang J. Accelerated aging of intervertebral discs in a mouse model of progeria. Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2010; 28:1600–1607. [PubMed: 20973062]

Wang J, Clauson CL, Robbins PD, Niedernhofer LJ, Wang Y. The oxidative DNA lesions 8,5′-cyclopurines accumulate with aging in a tissue-specific manner. Aging cell. 2012; 11:714–716. [PubMed: 22530741]

Weeda G, Donker I, de Wit J, Morreau H, Janssens R, Vissers CJ, Nigg A, van Steeg H, Bootsma D, Hoeijmakers JH. Disruption of mouse ERCC1 results in a novel repair syndrome with growth failure, nuclear abnormalities and senescence. Curr Biol. 1997; 7:427–439. [PubMed: 9197240]

Wijshake T, Malureanu LA, Baker DJ, Jeganathan KB, van de Sluis B, van Deursen JM. Reduced life- and healthspan in mice carrying a mono-allelic BubR1 MVA mutation. PLoS genetics. 2012; 8:e1003138. [PubMed: 23300461]

Zhou J, Yao J, Joshi HC. Attachment and tension in the spindle assembly checkpoint. Journal of cell science. 2002; 115:3547–3555. [PubMed: 12186941]

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Highlights

- Mouse models of progeroid syndromes can be exploited to accelerate aging research.
- The majority of diseases with accelerated aging are linked to genomic instability.
- Mice with very diverse causes of genomic instability have similar aging features.
- No one progeria model mimics all aspects of mammalian aging.

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Table 1

Inherited human diseases of accelerated aging.

Progeroid syndrome	Tissues affected	Genome maintenance system altered	References
Xeroderma pigmentosum	skin cancer premature aging of the epidermal,central nervous system	nucleotide excision repair	(Kraemer and DiGiovanna 2014)
Cockayne syndrome	premature aging of the central nervous, adipose and musculoskeletal systems	transition-coupled nucleotide excision repair	(Nance and Berry 1992)
Trichothiodystrophy	aged appearance	transition-coupled repair nucleotide excision	(Bootsma D. and others 1998)
Ataxia telangiectasia	Cancer premature aging of the central nervous and endocrine systems	double-strand break repair	(Chun and Gatti 2004)
AT-like disorder	premature aging of the central nervous and endocrine systems	double-strand break repair	(Chun and Gatti 2004)
Werner's syndrome	Cancer premature aging of the cardiovascular, musculoskeletal, epidermal, endocrine and ocular systems	telomere maintenance	(Kudlow and others 2007)
Fanconi anemia	Cancer premature aging of the bone marrow	interstrand crosslink repair	(Auerbach 2009)
Hutchinson-Gilford	premature aging of the cardiovascular, musculoskeletal and reproductive systems	chromatin organization; timely repair of double-strand breaks	(Kudlow and others 2007)
XFE progeroid syndrome	systemic premature aging	nucleotide excision repair, interstrand crosslink repair, repair of some strand breaks with 3′ flaps	(Niedernhofer and others 2006)

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Table 2

Comparison of diverse mouse strains with accelerated aging due to genomic instability.

	Ercc1$^{-/-}$	***Ercc1$^{-/}$***	***Bubr1*$^{H/H}$**	**pol$\gamma^{D257A/D257A}$**
Human disease modeled	XFE progeria syndrome	XFE progeria syndrome	Mosaic Variegated Aneuploidy	None
Mutated gene	*Ercc1*	*Ercc1*	*Bubr1*	*Polg*
Consequence of mutation	Compromised in multiple DNA repair pathways	Compromised in multiple DNA repair pathways	Defective mitotic spindle assembly checkpoint	Inability to proofread newly synthesized mtDNA
% Normal protein expression	0%	10%	10%	0%
Pathologies				
Growth retardation*	+	+	+	-
Kyphosis	+	+	+	+
Sarcopenia	+	+	+	+
Skin changes&	+	-	+	+
Hematologic abnormalities#	+	-	-	+
SQ fat loss	-	-	+	+
Neurologic abnormalities ^	+	+	+	-
Osteoporosis	-	+	-	+
Hearing loss	-	+	-	+
Hematopoietic organ atrophy and/or involution%	-	+	-	+
Impaired vision$	-	+	+	-
Cardiovascular abnormalities	-	+	+	+
Other	Liver failure	Disc degeneration, renal dysfunction; infertility	Impaired wound healing, facial dysmorphisms, cachexia, infertility	Loss of intestinal crypts and intestinal dysplasia, infertility
Lifespan	3-4 weeks (McWhir and others 1993; Niedernhofer and others 2006; Weeda and others 1997)	Median: 16 weeks; maximum: 29 weeks (Dolle and others 2011)	Median: 6 months (Baker and others 2004)	Median: 48 weeks; maximum: 61 weeks (Trifunovic and others 2004) Median: 416 days; maximum: 460 days (Kujoth and others 2005)
Premature cell senescence?	+	+	+	-

*Growth retardation includes runting and dwarfism

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[&] Skin changes include atrophy, reduced dermal thickness, hair graying, and alopecia

[#] Hematologic abnormalities include leukopenia and thrombocytopenia

Neurologic abnormalities include dystonia, tremors, ataxia, neurodegeneration, brain and/or spinal cord astrocytosis and microgliosis

[%] Hematopoietic organs include spleen and thymus

[$] Impaired vision includes cataracts