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Murine models of accelerated aging and musculoskeletal disease

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ABSTRACT

The primary risk factor for most musculoskeletal diseases, including osteoarthritis, osteoporosis and sarcopenia, is aging. To treat the diverse types of musculoskeletal diseases and pathologies, targeting their root cause, the aging process itself, has the potential to slow or prevent multiple age-related musculoskeletal conditions simultaneously. However, the development of approaches to delay onset of age related diseases, including musculoskeletal pathologies, has been slowed by the relatively long lifespan of rodent models of aging. Thus, to expedite the development of therapeutic approaches for age-related musculoskeletal disease, the implementation of mouse models of accelerated musculoskeletal aging are of great utility. Currently there are multiple genetically diverse mouse models that mirror certain aspects of normal human and mouse aging. Here, we provide a review of some of the most relevant murine models of accelerated aging that mimic many aspects of natural musculoskeletal aging, highlighting their relative strengths and weaknesses. Importantly, these murine models of accelerated aging recapitulate phenotypes of musculoskeletal age-related decline observed in humans.

1. Introduction

1.1. Mechanisms underlying aging

Aging, including musculoskeletal aging, is a complex process involving a number of different pathways with both genetic and environmental components [1–5]. These include chronic, low-grade, "sterile" inflammation; macromolecular damage and organelle dysfunction; stem and progenitor cell dysfunction; and increased senescent cell burden. These four processes are linked, with each process affecting the other three. For example, senescent cells accumulate with aging and at sites of pathogenesis in chronic diseases [6,7] due to increased macromolecular damage (e.g. DNA damage) and organelle dysfunction, so reducing senescent cell burden can lead to reduced inflammation, enhanced function of stem/progenitor cells and reduced cellular damage [8–10,11].

Although the complexity of aging, including musculoskeletal aging, might reflect the complexity of the organism, there is compelling evidence to support the hypothesis that the underlying cause of aging is the cell autonomous, time-dependent accumulation of stochastic damage to cells, organelles and macromolecules. However, it is also clear from heterochronic parabiosis [12–17] and serum transfer [17,18] studies that non-cell autonomous mechanisms play important roles in suppressing or driving degenerative changes in a variety of tissues including skeletal muscle and bone that arise as the consequence of spontaneous, stochastic damage. For example, using heterochronic parabiosis, it was demonstrated that still poorly characterized factors in young blood rejuvenate certain cell types and tissues, including skeletal muscle and heart, in old mice [12–17]. Conversely, factors in older serum can drive skeletal muscle aging [19].

Cellular senescence is also a fundamental property of aging. Senescence is a cell fate that involves loss of proliferative potential of normally replication-competent cells with associated resistance to cell death through apoptosis and generally increased metabolic activity. Frequently, senescent cells develop a senescence-associated secretory phenotype (SASP) that entails increased release of pro-inflammatory cytokines and chemokines, tissue-damaging proteases, hemostatic factors, and growth factors, and other factors that can impact stem and progenitor cell function [8]. These SASP factors contribute to driving aging through non-cell autonomous mechanisms. In support of an

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important role for senescence in aging, selective killing of $p16^{INK4a}$-positive senescent cells extended healthspan in the transgenic INK-ATTAC and p16-3MR mouse models of accelerated aging expressing an inducible apoptotic gene from the $p16^{INK4a}$ promoter [20–24]. Subsequently, it was demonstrated that chronic clearance of $p16^{INK4a}$-positive cells in adult mice extends the median lifespan of naturally aged mice [25]. Clearance of senescent cells in versions of this genetic model or treating mice with novel senolytic compounds, able to induce apoptosis specifically in senescent cells, was able to induce extend healthspan and in some cases lifespan [26–29]. Thus, the increase in cellular senescence that occurs with aging plays a major role in driving age-related diseases including skeletal muscle and bone pathology [8,23,24,30–33].

2. Musculoskeletal aging

Musculoskeletal aging involves the progressive loss of function in muscle, bone, articular cartilage, tendon, ligament, and intervertebral disc. The most common clinical manifestations of musculoskeletal aging include osteoporosis, osteoarthritis (OA), and sarcopenia with symptoms that are often overlapping that increase their severity, leading to a condition of frailty [34].

2.1. Osteoporosis

Osteoporosis is a common age-related complication characterized by reduced bone mass and strength, leading to increased bone fracture and frailty. The bone is a dynamic organ that maintains its micro and macro-architecture through the delicate balance between bone resorption and bone formation. In humans, the bone mass reaches its peak in the third decade of life and gradually declines with age in both men and women [3]. Upon reaching 80 years of age, the majority of individuals experience a 2 in. reduction in height [35]. Several factors contribute to this loss, such as vertebral compression, postural changes and an exaggerated curvature of the hips and knees [35]. Bone loss is especially rapid in the first few years after menopause [35,36]. After the age of 35, women will experience on average a 1% loss of bone mass per year with an increased 2–3% loss postmenopausal [35,36]. With age, the change in hormonal and circulating factors, increased bone marrow adipogenesis and decreased physical activity drifts the balance toward a higher net bone resorption [36]. The increased bone resorption with age weaken bone structure that increases porosity in cortical bone and erosions in trabeculae, and ultimately increases osteoporosis and fractures [37,38]. Recently it was shown using naturally-aged mice that senescent cells drive osteoporosis through increasing resorption of trabecular and cortical bone, demonstrating that reducing the senescent cell burden improved bone formation [33].

2.2. Osteoarthritis (OA)

With age, joints may become inflamed and less flexible as fluid in joints decreases and cartilage erodes leading to OA. During OA joints become stiff with increased mineral deposits, articular cartilage becomes thinner, and cartilage water content decreases which further potentiates the disease [39]. Connective tissue within ligaments and tendons becomes more rigid and brittle which limits the range of motion of joint and causes functional deficits for OA patients. OA is also one of the most common causes of pain and immobility in the older adult [40]. In fact, the arthritic pain associated with OA is progressive and is the primary complaint leading the patient to the clinic [3]. OA pathogenesis is also strongly associated with the development of SASP in the joint that disrupts the balance of catabolic and anabolic factors, leading to inflammation, decreased joint fluid, and thinning of cartilage [38]. Recent studies have implicated senescent chondrocytes as well as other cells within the synovial capsule in driving the local SASP [41–44]. Thus, senescence and its associated pro-inflammatory phenotype, is a significant contributor to OA pathogenesis.

2.3. Sarcopenia

Sarcopenia is defined as age-related loss of skeletal muscle mass and strength, leading to functional and structural decline in skeletal muscle [45]. Low physical activity has been suggested as the main attributing factor to developing sarcopenia in the older adult [46]. Sarcopenia is specifically a condition of reduced muscle fiber size, myofiber number, or a combination, although the reduction in number appears to be most important [47,48]. Skeletal muscles of older people contain less contractile tissue and more non-contractile tissue, such as fibrosis, compared with the skeletal muscles of younger people [47,48]. A greater percentage of non-contractile tissue (fat and fibrosis) results in a decreased force production capability [1]. The decline in skeletal muscle strength predisposes individuals to development of frailty, arthritis, and increased risk for metabolic disorders [47,48]. This loss of skeletal muscle strength also places increased stress on certain joints (especially the knees), and increases risk of falling and bone fracture. Importantly, the age-associated changes in skeletal muscle involve muscle fiber type switches and metabolic shifts beginning as early as the third decade of life [47,48]. These debilitating effects of sarcopenia are increasingly evident in the seventh, eighth, and ninth decades of life when frailty is often present [47–49]. Indeed, the muscular system undergoes a 40% loss of skeletal muscle mass and 30% decrease in strength by the age of 70 [47,48]. However, it is still unclear to what degree strength loss is a function of disuse versus natural aging.

3. Mouse models of accelerated aging with distinct musculoskeletal phenotypes

For development of treatments for age-related musculoskeletal diseases and conditions, including intervertebral disc degeneration (IDD), osteoarthritis (OA), osteoporosis and poor healing of bone fractures, it is important to perform pre-clinical studies in relevant aging model systems. However, due to the time and cost needed for natural aging studies in mice, the majority of studies on musculoskeletal disease have been done on younger mice carrying disease-specific transgenes (see Table 1). To facilitate the development of approaches to slow aging and age-related pathologies of skeletal muscle and bone, numerous mouse models of accelerated aging, including some that model human diseases, have been developed. Importantly, these experimental murine models of aging recapitulate musculoskeletal decline observed in human aging, but in an accelerated manner. A list of some of the more widely used and characterized models are shown in Table 1 and discussed below.

3.1. Mouse models of human progeria diseases

Human progeria and progeroid syndromes are heritable disorders characterized by the earlier onset of multiple age-related phenotypes. Since most of these progeroid syndromes recapitulate some, but not all features of normal aging, they are sometimes referred to as “segmental progeroid syndromes” [72]. Interestingly, these rare progeria and progeroid syndromes can be modeled in worm, flies and, in particular, mice to create rapid preclinical models for aging studies. In general, the human progeroid syndromes are caused by defects in some form of genome maintenance either directly or indirectly [73]. This suggests that DNA damage is a key type of cellular damage that drives aging-related degenerative changes. One example is Werner syndrome, an accelerated aging syndrome caused by inherited defects in the Werner syndrome RecQ like helicase (WRN) required for telomere maintenance and replicating damage genomes [74]. Mouse models of Werner syndrome have osteoporosis and pathological fractures by 8 months of age [60]. Another example is the mouse model of ataxia telangiectasia (AT) caused by a mutation in the telangiectasia mutated (ATM) gene. ATM

Table 1
Common progeria models with pronounced musculoskeletal phenotypes.

Model	Progeria axis	Condition(s)	Onset of symptoms	Median lifespan	Mitigating therapies
BubR1$^{H/H}$	DDR	Kyphosis, cachexia [50]	~3 months	~6 months	*BubR1*$^{H/H}$*;INK-ATTAC* [20], *SIRT2tg/BubR1*$^{H/H}$ [51]
Ercc1$^{-/\Delta}$	DDR	IDD [52], muscle wasting [11], Osteoporosis [53,54]	~8 weeks	~16 weeks	Young stem cells [11], Senolytics [26,27], DR [55]
Ercc1$^{-/-}$	DDR	Osteopaenia, sarcopaenia, kyphosis [56]	~2 weeks	~4 weeks	Young stem cells [11]
TTD (*Xpd*)	DDR	Osteoporosis, osteosclerosis, cachexia [57]	~3 months	~12 months	N/A
Atm$^{-/-}$	DDR	osteoporosis [49], osteopaenia [58]	~6 weeks	~3 months	N/A
[a]Wrn$^{-/-}$;Terc$^{-/-}$	DNA replication, telomere maintenance	Osteoporosis [59,60]	12–16 weeks	24 weeks	N/A
PolgA$^{mut/mut}$	mtDNA replication	Weight loss, kyphosis, osteoporosis [61]	~24 weeks	48 weeks	N/A
Lmna$^{-/-}$	Lamin A processing	Muscle dystrophy [62]	~4 weeks	~6 weeks	*Lmna*$^{-/-}$*;Sun1*$^{-/-}$ [63]
Zmpste24$^{-/-}$	Lamin A processing	Sarcopaenia, osteopaenia, micrognathia, muscular dystrophy, SBF [64–66], [b]cartilage degeneration	~8 weeks	~16 weeks	Young Stem Cells [64], [b]Senolytics
Klotho (*kl/kl*$^{-/-}$)	Hormonal	osteoporosis [67]	4 weeks	~8 weeks	N/A
Nfkb1$^{-/-}$	NF-KB signaling	Cachexia, muscle weakness, kyphosis [68]	4 weeks	~16 months	N/A
Cis2d$^{-/-}$	Mitochondrial degeneration	Muscle atrophy, bone density loss [69]	8 weeks	~20 months	N/A
SAMP6	Mitochondrial dysfunction, oxidative stress	Osteoporosis [70]	~3 months	~9 months	N/A
SAMP3	Mitochondrial dysfunction, oxidative stress	Degenerative joint disease [71]	~3 months	~9 months	N/A

Abbreviations: DNA damage response (DDR), Intervertebral Disk Degeneration (IDD), Dietary Restriction (DR), Spontaneous Bone Fractures (SBF), Mitochondrial DNA (mtDNA).

[a] G4-G6 Generations.

[b] Unpublished data from our group.

plays a key role in initiating the response to different types of DNA damage and thus AT patients have increased DNA damage with signs of accelerated aging [75]. Mice deficient in ATM have accelerated aging, in particular neurodegeneration, but also have a severe osteopenic phenotype with decreased bone formation [49,58].

Several of the progeroid mouse models of accelerated aging due to loss DNA repair activity that mimic natural aging are the *Ercc1*$^{-/-}$ and *Ercc1*$^{-/\Delta}$ models which carry mutations in the ERCC1 subunit of the XPF-ERCC1 endonuclease important for multiple types of DNA repair [56,76–78]. The XPF-ERCC1 nuclease is involved in nucleotide excision repair, inter-strand cross link repair and repair of double strand breaks [56]. Mutations in XPF/ERCC1 actually can lead to four different disease, depending upon the severity, including Fanconia Anemia (FA), Cockayne Syndrome (CS), Cerebro-oculo-facio-skeletal syndrome (COFS) and XPF-ERCC1 (XFE) progeroid syndrome [57]. In general, patients with mutations in XPF show dramatic signs of accelerated aging [76].

Complete deletion of *Ercc1* or *Xpf* in mice results in mice with a lifespan of only 1 month with evidence of highly accelerated aging [56,76]. However, expression of only 5–10% the normal level of XPF/Ercc1 in *Ercc1*$^{-/\Delta}$ mice resulted in accelerated aging [56,76,77]. *Ercc1*$^{-/\Delta}$ mice are born with normal mendelian frequency and are healthy until adulthood (8–9 wks) when they then begin to show spontaneous, progressive symptoms associated with old age [11,76]. Careful comparison of 5 month-old *Ercc1*$^{-/\Delta}$ mice to 24–36 month-old WT mice revealed significant correlations between the old and progeroid mice. This included loss of organ function, progressive histopathology, ultra-structural changes and gene expression changes relative to young WT mice in the hematopoietic, hepatobiliary, musculoskeletal, auditory, ophthalmologic and peripheral nervous systems [11,76]. In addition, the changes in the kidney, cornea and central nervous system are near identical between progeroid and old WT mice, further demonstrating the relevance of this model to natural aging [52–54,76,79–81].

Another important feature of the *Ercc1*$^{-/\Delta}$ mice is that as adults they spontaneously develop most, if not all, of the major degenerative disease associated with human aging including musculoskeletal degeneration [76,81]. As expected, older *Ercc1*$^{-/\Delta}$ mice have more oxidative DNA damage than do age-matched WT mice in multiple organs [79,82]. Notably, *Ercc1*$^{-/\Delta}$ mice have the same types and comparable numbers of oxidative DNA lesions in kidney as 2.5 year-old WT mice [82]. In addition, *Ercc1*$^{-/\Delta}$ mice accumulate senescent cells in the same tissues as WT mice and to the same level. In fact, total body luminescence is similar in 4–5 month-old *p16*$^{+/Luc}$*;Ercc1*$^{-/\Delta}$ mice and 1 year-old *p16*$^{+/Luc}$ mice, suggesting a similar burden of senescent cells rather than excessive damage in the progeroid mice [83]. Furthermore, muscle-derived stem/progenitor cells (MDSPCs) isolated from *Ercc1*$^{-/\Delta}$ mice were found to have reduced proliferation, myogenic differentiation, and impaired skeletal muscle regeneration capacities [11,84]. However, exposing progeroid *Ercc1*$^{-/\Delta}$ MDSPCs to conditioned media from WT MDSPCs rescued the myogenic differentiation defect *in vitro* [84], suggesting non-cell autonomous factors promote adult stem cell dysfunction with accelerated aging and likely the progeroid phenotype. Collectively, these data demonstrate that *Ercc1*$^{-/\Delta}$ mice are an excellent model of the normal aging process, albeit occurring more rapidly, and arising due to physiologically relevant, endogenous, stochastic damage that drives cellular senescence and stem cell dysfunction.

Ercc1$^{-/\Delta}$ mice also develop early onset of osteoporosis [76,81]. Similarly, they develop age-related intervertebral disc degeneration (IDD), including loss of disc height and degenerative structural changes, similar to naturally aged mice [85]. In particular, the *Ercc1*$^{-/\Delta}$ mice show signs of accelerated loss of disc (proteoglycan) PG, reduced matrix PG synthesis, and enhanced apoptosis and cell senescence [85]. Furthermore, the mice show accelerated loss of grip strength and evidence of skeletal muscle wasting. Importantly, certain treatments have been

shown to improve the pathology of *Ercc1*$^{-/\Delta}$ mice, extending healthspan and even lifespan [11]. These treatments include caloric restriction, injection of young stem cells, NF-κB inhibitors and a mitochondrial targeted free radical scavenger [11,26,86]. Importantly, treatment of *Ercc1*$^{-/\Delta}$ with several different senolytics also resulted in extended healthspan including improving intervertebral disc pathology, documenting the role of senescent cells in driving accelerated aging [27,28]. Since some of these approaches also extend healthspan in naturally aged mice, these results suggest that the *Ercc1*$^{-/\Delta}$ mouse model represents a rapid and accurate model of spontaneous age-related musculoskeletal aging.

Other examples of relevant models of accelerated musculoskeletal aging are the mouse models of Hutchinson-Gilford Progeria Syndrome (HGPS). HGPS is a systemic disease of dramatically accelerated aging, caused by a mutation in lamin A, a nuclear structural protein, or in proteins that affect lamin A structure. Lamin A is synthesized as a prelamin that is farnesylated, methylated and then processed by the protease Zmpste24 [87,88]. Mutations that affect the processing prelamin A or the level of the protein result in HGPS [87,88]. Disruption of the nuclear lamin structure leads to changes in gene expression and genome fidelity resulting in DNA damage and apoptosis. Both HGPS patients and mouse models of the disease, including the lamin A knockout (*Lmna*$^{-/-}$), have significantly reduced bone density, kyphosis and pathologic fractures [89]. Interestingly, crossing *Lmna*$^{-/-}$ mice with *Sun1*$^{-/-}$ mice (a lamin associated structural protein linking nucleoproteins to the cytoskeleton) reduces tissue pathologies and enhances lifespan [63].

Of the many different murine models of HGPS, mice deficient in the Lamin A processing *Zmpste24* metalloprotease in particular exhibit several musculoskeletal deficits associated with aging [65]. These *Zmpste24*$^{-/-}$ mice have multiple age-related musculoskeletal co-morbidities such as spontaneous bone fracture, kyphosis, dystonia, muscle wasting, growth retardation, and cachexia [65,66]. For example, by 30 weeks of age, several ribs in *Zmpste24*$^{-/-}$ mice become broken near the costovertebral junction associated with exuberant fibrous tissue [65]. The fracture sites in *Zmpste24*$^{-/-}$ mice are acellular, generally lack inflammatory infiltrate with little evidence of repair [65]. In addition to the ribs, *Zmpste24*$^{-/-}$ mice manifest bone fractures in multiple other locations including the scapula, clavicle, sternum, zygomatic arch, mandible, and humerus [65]. Furthermore, by 8 weeks of age the mice exhibit bone fractures at the posterior portion of the zygomatic arch where the masseter originates [65]. These fractures do not heal normally. Instead, the arch region is replaced by fibrous tissue containing bone and necrotic debris, further highlighting the deficits in regeneration/repair potential in the *Zmpste24*$^{-/-}$ model [65]. In addition, the thoracic vertebrae of *Zmpste24*$^{-/-}$ mice also have significantly reduced bone density [65]. Three-dimensional analysis of trabecular bone within the 12th vertebral body indicated that the ratio of bone volume to the total volume is reduced by more than 30% in the *Zmpste24*$^{-/-}$ mice [65]. Interestingly, bone abnormalities in *Zmpste24*$^{-/-}$ mice are not associated with changes in plasma levels of calcium or phosphate [65]. In addition, adult stem cells such as MDSPCs isolated from *Zmpste24*$^{-/-}$ mice were found to have reduced proliferation, myogenic differentiation, and impaired muscle regeneration capacities in dystrophic mice [64]. However, exposing progeroid *Zmpste24*$^{-/-}$ MDSPCs to conditioned media from WT MDSPCs rescued the myogenic differentiation defect *in vitro* [64], suggesting non-cell autonomous factors likely promote the stem cell dysfunction and the HGPS progeroid phenotype.

3.2. The BubR1$^{H/H}$ mouse model of accelerated aging

An example of how murine models of accelerated aging can be used to document the role of specific pathways in musculoskeletal aging is the *BubR1*$^{H/H}$ mouse model [50]. The *BubR1*$^{H/H}$ mouse carries two hypomorphic alleles of the *BUB1B* gene, which encodes BUBR1, a core component of the mitotic spindle assembly checkpoint [50]. *BubR1*$^{H/H}$ mice have accelerated and elevated cellular senescence due to chromosome mis-segregation as well as increasing aneuploidy [20,50]. Further, *BubR1*$^{H/H}$ mice also exhibit severe cachexia and kyphosis, highlighting the utility for the model to potentially examine skeletal muscle wasting in an accelerated aging environment [50]. A reduction in the percent of senescent cells in the *BubR1*$^{H/H}$ mouse carrying the INK-ATTAC cassette, expressing caspase 8 fused to a drug-inducible dimerization motif under the regulation of the p16^{INK4a} promoter, can improve healthspan [20]. These results regarding the therapeutic effect of reducing the senescent cell burden from the *BubR1*$^{H/H}$ INK-ATTAC mouse model were the first to document a role for cellular senescence in driving aging [20]. Also of interest is that fact that human aging is associated with decreased expression of *BubR1* in multiple tissues [50].

3.3. Additional mouse models of accelerated aging due to elevated senescence or mitochondrial dysfunction

One of the earliest accelerated aging models are the inbred strain accelerated senescence-prone (SAMP) mouse strains that exhibit increased senescence and shorter lifespan and healthspan. The different strains of SAMP mice develop many age related pathologies associated with elevated levels of oxidative stress and mitochondrial dysfunction in various tissues that is thought to drive senescence [40]. Certain SAMP strains have been found to harbor musculoskeletal deficiencies, principally SAMP6 and SAMP3 which exhibit senile osteoporosis and degenerative temporomandibular joint disease respectively at around 3 months of age [70,71]. However, the limitation to the SAMP mice is that the specific mutations that contribute to driving senescence and possibly other aging pathways are poorly defined. Also, different inbred SAMP strains carry different aging phenotypes. Similarly, the *PolgA*$^{mut/mut}$ mouse model of accelerated aging have a knock-in missense mutation within an endonuclease-proofreading domain of the catalytic subunit of the mtDNA polymerase Polγ. These mice have elevated mutations in their mitochondrial DNA that leads to increased ROS and mitochondrial dysfunction. These mice also have been reported to show signs of osteoporosis [61].

3.4. Mouse models of accelerated aging not driven by DNA damage

In contrast to the many mouse models of accelerated aging driven by DNA damage, mice carrying a specific mutation in the secreted protein Klotho have accelerated aging with evidence of early onset osteoporosis and osteopenia as well as signs of skeletal muscle pathology [67]. Klotho is a novel, type-I membrane β-glucuronidase that can be released from different cells types [67]. Thus, the klotho-deficient mice are relatively unique since the defect is in a secreted protein that has ranging non-cell autonomous effects in contrast to the many progeria models with cell autonomous defects in genome maintenance.

The transcription factor NF-κB is upregulated with aging [90]. In fact, bioinformatics studies have determined that NF-κB is the transcription factor most associated with mammalian aging [90–92]. Overexpression of several subunits of NF-κB, including p65/RelA, in certain cell types, induces hallmark features of cellular senescence including decreased proliferation and morphologic changes, such as enlarged, multinucleated cells that are granular in appearance [93]. Consistently, heterozygosity in p65/RelA reduces senescence and inflammation with aging in mouse models of accelerated aging [86] as well as improves stem cell function [94]. Importantly, deletion of the p50 subunit of the transcription factor NF-κB (*Nfkb1*$^{-/-}$ mice) results in a mouse model of accelerated aging with evidence of cachexia, skeletal muscle weakness and kyphosis [68]. The p50 subunit can form a heterodimer with the p65/RelA subunit to stimulate expression of genes with NF-κB binding sites whereas homodimers of p50 appear to repress expression from specific promoters.

4. Summary

The analysis of different models of accelerated aging, including murine models of human progeria, have shown that many have evidence of bone and skeletal muscle pathology similar to natural aging. In addition, treatment with certain compounds shown to extend healthspan and/or lifespan in naturally aged mice was able to improve pathologies in several of the models of accelerated aging. These results suggest that similar pathways such as DNA damage, oxidative stress and stem cell dysfunction, are driving musculoskeletal aging in both accelerated and natural aging. Taken together these results clearly document the utility of using certain murine models of accelerated aging to accelerate testing for therapeutic approaches able to slow musculoskeletal aging. It is important to mention that it is now feasible to target a specific genetic defect driving accelerated aging, such as loss of DNA repair, nuclear structure or reduced chromosome segregation, to specific cell types using conditional transgenic models. In this manner, a specific tissue (e.g. bone or skeletal muscle) can be aged to assess the non-cell autonomous effect of that tissue on aging of other tissues. For example, we have generated mouse models where *Ercc1* is deleted specifically in skeletal muscle, fat, lung, ß cells, forebrain neurons, immune cells, hepatocytes as well as other cell types. These mice currently are being analyzed for both cell autonomous and non-cell autonomous effects on aging.

Studying age-associated musculoskeletal decline in an accelerated aging model is tempting due to the practical benefits of a shortened lifespan. However, results should always be interpreted with care given that these animals may show certain traits associated with normal mouse aging, but lack others. For example, murine models of HGPS (ex. *Zmpste24*$^{-/-}$) display several characteristics of normal chronological aging such as frailty and cachexia, but lack others like dementia. Indeed, this is the case for human HGPS patients as well. As a result, there does not exist a single mouse model that fully represents all aspects of biological aging [97,98]. However, detailed transcriptomic, proteomic and metabolomic analysis suggests that of the many models of accelerated aging, the *Ercc1*$^{-/\Delta}$ mouse model best mirrors natural aging including aging of the musculoskeletal system. The use of these systemic accelerated aging models, in combination with mouse models of tissue targeted aging, will certainly expedite not only understanding the mechanisms that drive musculoskeletal aging, but the development of drugs that can extend musculoskeletal health.

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