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Skeletal phenotypes and molecular mechanisms in aging mice

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ABSTRACT

Aging is an inevitable physiological process, often accompanied by age-related bone loss and subsequent bone-related diseases that pose serious health risks. Research on skeletal diseases caused by aging in humans is challenging due to lengthy study durations, difficulties in sampling, regional variability, and substantial investment. Consequently, mice are preferred for such studies due to their similar motor system structure and function to humans, ease of handling and care, low cost, and short generation time. In this review, we present a comprehensive overview of the characteristics, limitations, applicability, bone phenotypes, and treatment methods in naturally aging mice and prematurely aging mouse models (including *SAMP6*, *POLG* mutant, *LMNA*, *SIRT6*, *ZMPSTE24*, *TFAM*, *ERCC1*, *WERNER*, and *KL/KL*-deficient mice). We also summarize the molecular mechanisms of these aging mouse models, including cellular DNA damage response, senescence-related secretory phenotype, telomere shortening, oxidative stress, bone marrow mesenchymal stem cell (BMSC) abnormalities, and mitochondrial dysfunction. Overall, this review aims to enhance our understanding of the pathogenesis of aging-related bone diseases.

Keywords: Aging; Premature aging; Mice; Bone; Gene knockout

INTRODUCTION

The global population is aging. According to the World Health Organization (WHO), individuals are categorized as young if they are under 44 years old, middle-aged if they are 45–59 years old, young elderly if they are 60–74 years old, elderly if they are 75–89 years old, and longevity elderly if they are over 90 years old. At present, approximately 1 in 11 people worldwide are 65 years of age or older, a number predicted to increase to one in six people by 2050 (United Nations, 2019). Diseases of the skeletal system, such as osteoporosis (OP), are commonly associated with aging. Bone provides leverage and structural support to muscles, promotes movement, stores minerals and growth factors, regulates mineral and acid-base balance, and serves as a site for hematopoiesis. Peak bone mass typically occurs before the age of 40 in both sexes. Women experience significant bone loss around menopause, accounting for approximately one-third of the total calcium mass in bone. This rapid bone loss occurs during the perimenopausal period, which lasts approximately 8 to 10 years. In men, bone mass decreases progressively from age 60, with age-related bone loss occurring at the same rate from age 70 in both men and women (Pignolo, 2023). Therefore, studying the effects of aging on bone is critical.

A suitable animal model of aging is essential for in-depth studies of the etiology, pathology, development, and mechanisms of age-related diseases, as well as for screening and developing antiaging drugs. At present, commonly used models for exploring aging include *Drosophila*, nematodes, mice, rabbits, and nonhuman primates. Mice, in particular, share many aspects of bone biology with humans, including patterns of aging-related bone loss, bone turnover, and bone healing (Foessl et al., 2021). Moreover, the mouse genome is highly similar to the human genome, and advanced gene manipulation technologies allow for detailed studies of disease pathogenesis via gene knockout. As such, mice are considered a more suitable animal model for exploring human-related diseases and the effects of aging on bone compared to other animal models. Herein, we summarize the characteristics, limitations, applicability, bone phenotypes, and treatment approaches for both naturally aging mice and prematurely aging mouse models (including *SAMP6*, POLG mutant, *LMNA*, *SIRT6*, *ZMPSTE24*, *TFAM*, *ERCC1*, *WERNER*, and *KL/KL* -deficient mice).

ANIMAL MODELS OF AGING

The selection of appropriate animal models is crucial for aging

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research. While current animal models for exploring aging include *Drosophila*, nematodes, rabbits, and nonhuman primates, mice are more suitable for studying the effects of aging on bone due to their comparable skeletal structure, similar physiological and pathophysiological bone processes, lower time and economic costs, and fewer ethical concerns.

Given its simple body structure, lack of many mammalian anatomical and physiological features, including a skeletal system, and evolutionary distance from humans, *Caenorhabditis elegans* cannot adequately reflect the effects of aging on the skeleton (Tissenbaum, 2015). Although *Drosophila* can be used to investigate the regulatory mechanisms of bone morphogenetic proteins (Matsuda et al., 2016), its significantly different body structure from humans makes it unsuitable for bone aging research. Therefore, mammals are generally preferred for such studies, with rodents considered conducive to aging-related research due to their availability, environmental adaptability, low cost, extensive research background, and genetic manipulability. Their short lifespan compared to humans also facilitates easier study compared to long-lived animals (Mitchell et al., 2015).

In addition to rodents, other animals have been used in studies of bone aging. For example, rhesus monkeys are commonly used in biomedical research due to their genetic, endocrine, physiological, neuroanatomical, and cognitive similarities to humans (Mitchell et al., 2015). Research has shown that forearm bone mineral density (BMD) and whole-body bone mineral content in both male and female rhesus monkeys decrease with age (Black et al., 2001), similar to the changes observed in the human skeleton. However, female rhesus monkeys reach peak bone mass at 11 years of age (Champ et al., 1996), which is later than occurs in humans. Furthermore, in addition to their expense, the strict social hierarchy and potentially aggressive behavior of monkeys necessitate special care and unique environments, with ethical issues further limiting their use in research (Mitchell et al., 2015). Research has shown that *LMNA* knockout (KO) rabbits exhibit reduced cortical bone width, significantly reduced osteoblasts and osteoclasts, irregularly arranged growth plates, and increased porous areas (Sui et al., 2019), consistent with observations in progeria patients and mice harboring *LMNA* gene mutations (Mounkes et al., 2003; Schmidt et al., 2012). However, rabbits have a lifespan of 9–10 years (Lennox, 2010), which makes their use in experiments relatively long and costly compared to rodents. Additionally, there are fewer studies on aging-associated OP using rabbits than mice. Although rats are also used to study aging-related OP, with both sexes showing declines in bone density and bone mass, as well as increased bone marrow fat and decreased bone turnover with age, as observed in humans (Al Saedi et al., 2020; Duque et al., 2009), mice offer significant advantages. Mice are physiologically similar to rats and are suitable for molecular genetic studies on aging and age-related human diseases (Duque et al., 2009). They are also more cost effective to maintain, require less space, and have a much shorter lifecycle of 1–3 years (Dutta & Sengupta, 2016). Furthermore, while genetic manipulation technology for rats has advanced, mouse genome experimental technology remains superior. The first generation of knockout rats were created using zinc finger nuclease technology in 2009 (Geurts et al., 2009), followed shortly thereafter by the first knockout rats generated using modified embryonic stem cells (Tong et al., 2010). With the advent of CRISPR/Cas9, rats are expected to be more widely used for genome engineering research (Homberg et al., 2017). However, targeted gene mutagenesis in mouse embryonic stem cells began as early as 1987 (Thomas & Capecchi, 1987), with knockout techniques in use from 1989 (Capecchi, 1989). Advancements in genome manipulation technologies have enabled researchers to mimic human genetic defects and mutations in mice through knockouts, mutations, and transgenesis. This has established mice as the preferred model for mammalian biology and genetic disease research, particularly for studying genetic deletions and their impact on bone loss. Consequently, mice are superior to other models, including rats, for in-depth studies on bone aging through gene knockout.

BONE PHENOTYPES IN NATURALLY AGED MICE

Definition and bone phenotype of naturally aged mice

Natural aging mouse models involve maintaining mice under laboratory conditions until they reach the desired age. The classification of age and aging in such mice can vary. Wang et al. (2020) categorized mice as adults at 6–10 months, late adults at 13–14 months, and old mice at 18–24 months. Supporting this, several studies have shown that C57Bl/6J, DBA/2J, A/J, and 129/SvJ strain mice older than 18 months have markedly lower motor activity compared to mice under six months of age (Bordner et al., 2011; Fahlström et al., 2012; Forster et al., 1996; Goodrick, 1975; Hengemihle et al., 1999; Ingram et al., 1981; Lhotellier & Cohen-Salmon, 1989; Meliska et al., 1997; Sprott & Eleftheriou, 1974). Radulescu et al. (2021) defined age categories for inbred laboratory mice (*Mus musculus*) as juveniles (birth to one month), young adults (1–4 months), adults (4–10 months), late adults (10–14 months), aging adults (14–24 months), and aged adults (>24 months), while other studies have classified mice as young (one month) (Hoerder-Suabedissen & Molnár, 2015), young adults (3–6 months) (Flurkey et al., 2007), middle-aged adults (6–14 months) (Lesné et al., 2006), and old adults (14–24 months) (Flurkey et al., 2007). Naturally aging mice are characterized by decreased immune function (Segre & Segre, 1977), decreased cognitive function, including impaired learning and memory formation (Murphy et al., 2006), and poor performance in hippocampal-dependent memory paradigms such as the Morris water maze, environmental fear conditioning, and object location recognition tasks (Neff et al., 2013). Most notably, naturally aging mice exhibit signs of senile OP (SOP) (Perkins et al., 1994).

In theory, natural aging mouse models closely mirror human aging and avoid the need for drug administration or surgery, reducing the risk of unexpected complications. However, these models have several disadvantages. For example, obtaining old mice is challenging due to inconsistent sources, the lengthy time required for young mice to age, high costs, poor health conditions, high mortality rates, and significant variability in drug absorption, metabolism, and distribution. Therefore, artificial aging mouse models are often used in experimental studies.

C57BL/6 laboratory mice, which typically live for 2–3 years, reach peak bone mass at 4–8 months and experience declines in bone mass and quality with age, leading to SOP (Bikle et al., 2002; Cao et al., 2003; Ferguson et al., 2003; Perkins et al., 1994). Both trabecular (Tb) and cortical bones undergo dynamic changes with age. The trabecular bone

volume fraction (BV/TV) significantly decreases from six weeks to 24 months of age, while cortical thickness increases until peak bone mass, then declines (Bikle et al., 2002). The receptor activator of nuclear factor-kappa B ligand (RANKL), a membrane-associated cytokine expressed by osteoblasts essential for osteoclastogenesis (Yasuda et al., 1998), increases with age and is correlated with cancellous bone volume (Cao et al., 2003). Research has shown that 24–month-old BALB/c mice, a common mouse strain, exhibit reduced osteogenic stem cell proliferative potential, contributing to age-related bone loss (Bergman et al., 1996).

Mechanisms underlying effects of natural aging on bone

At present, there are several viewpoints on the mechanisms of bone aging. Firstly, cellular DNA damage responses (DDRs) are considered significant triggers of aging. DNA damage disrupts skeletal homeostasis, and increased DNA damage causes reduced bone formation and bone loss (Hoeijmakers, 2009). Furthermore, the function and efficiency of various DNA repair pathways are thought to decline with age (Stead & Bjedov, 2021). When DNA damage outpaces repair, osteoblasts undergo senescence, resulting in imbalanced bone remodeling. This is evident in models with defective DNA repair, where ataxia-telangiectasia mutated (ATM), a core component of the DNA repair system, is activated upon DNA double-strand breaks to enhance the homologous recombination repair pathway (Jin & Oh, 2019). ATM is a kinase and an important effector of the DDR signaling pathway (Maréchal & Zou, 2013). ATM-deficient mouse models exhibit reduced bone mass, particularly in Tb, accompanied by reduced bone formation, defective osteoblast differentiation, and increased osteoclast formation (Hishiya et al., 2005; Rasheed et al., 2006). Osteoclasts lacking ATM are more resistant to apoptosis and have longer lifespans (Hirozane et al., 2016), leading to dysregulation of bone remodeling. Secondly, the generation of the senescence-associated secretory phenotype (SASP) accelerates cellular senescence in response to DDRs (Rodier et al., 2009). SASP contains several proinflammatory cytokines (e.g., interleukins), proteases (e.g., matrix metalloproteinases), and growth factors that can affect surrounding cells (Coppé et al., 2010). The production of SASP, in turn, triggers DDR and SASP activation in neighboring cells, generating a proinflammatory environment that extends locally and eventually becomes systemic (Olivieri et al., 2015). Increased proinflammatory SASP in the bone microenvironment acts on osteoblasts to impair bone formation, osteoclasts to increase bone resorption, and mesenchymal stem cells to bias differentiation into adipocytes (Khosla et al., 2022). This leads to fat accumulation in the bone marrow cavity, threatening the survival of osteoblasts (Mirsaidi et al., 2014). In addition, age-related telomere shortening contributes to skeletal aging, with telomere dysfunction inducing defects in osteogenic differentiation by increasing P53/P21 expression and down-regulating Runt-related transcription factor (RUNX2) expression (Wang et al., 2012a). Mouse models exhibiting telomere dysfunction show substantial osteoblast dysfunction, with significantly reduced rates of bone mineral deposition and bone formation (Brennan et al., 2014), as well as enhanced osteoclast function due to a proinflammatory microenvironment (Saeed et al., 2011). Furthermore, oxidative stress during aging negatively impacts bone remodeling. This process involves increased levels of reactive oxygen species (ROS), crucial regulators of bone cell function. The effects of ROS on bone metabolism are twofold. Under physiological conditions, ROS produced by osteoclasts contribute to the accelerated destruction of calcified tissues, thus contributing to bone remodeling (Wauquier et al., 2009). Conversely, during aging, ROS production exceeds the average defense capacity due to the accumulation of dysfunctional mitochondria and progressive inefficiency of antioxidant defense mechanisms (Farr et al., 2016). The increase in ROS levels markedly affects the production and survival of osteoclasts, osteoblasts, and osteocytes (Manolagas, 2010). Previous research has shown that aged B6 mice subjected to oxidative stress exhibit peroxisome proliferator-activated receptor γ (PPARγ) signaling in osteoblasts, which reduces Wnt signaling and decreases osteoblast numbers, thereby inhibiting bone formation and increasing bone adipocyte formation (Almeida et al., 2009). Notably, oxidative stress-induced telomere damage may also accelerate telomere shortening, exacerbating its effects on bone remodeling (Muller, 2009) (Figure 1).

BONE PHENOTYPE OF PREMATURELY AGING MICE

In addition to natural aging, there is an abnormal pattern known as premature aging. Understanding premature aging is crucial for understanding aging. As such, prematurely aging mice should also be considered in studies related to bone aging.

SAMP6 premature aging mouse model

Senescence-accelerated mice (SAM) are a series of rapidly aging mouse models developed by Professors Toshio Takeda and Masanori Hosokawa from Kyoto University, Japan. These mice can be divided into the rapid aging P (SAMP) strain and normal aging R (SAMR) strain (Takeda et al., 1997). After a normal growth period, SAMP mice exhibit rapid and irreversible aging from 4 to 6 months of age, with a significantly shortened lifespan (Mori & Higuchi, 2019). In contrast, SAMR mice age similarly to normal aging mice (Aoyama et al., 2013), with SAMR1 mice often used as a control for SAMP strains (Liu et al., 2022). SAMP mice show increased ROS production by mitochondria and other cellular sites, leading to mitochondrial damage, degradation, and senescence (Manczak et al., 2005). Due to their short lifespan, strain-specific pathological features (Chen et al., 2016), and low bone mass in the vertebrae, femur, and tibia (Chen et al., 2009), SAMP mice have been widely used as experimental models for studying age-related diseases.

The *SAMP6* mouse, a spontaneous OP model, is characterized by low BMD, low peak bone mass, and bone microstructure degradation, uniquely demonstrating bone fragility fractures with aging and significantly lower peak bone mass in 4–5-month-old mice compared to SAMR strains (Matsushita et al., 1986). *SAMP6* mice also exhibit thinner cortical bones, larger periosteal and intraosseous diameters (Chen et al., 2009; Jilka et al., 1996; Matsushita et al., 1986; Silva et al., 2005), lower BV/TV and BMD (Chen et al., 2004, 2005, 2009; Jilka et al., 1996; Matsushita et al., 1986), increased bone marrow cavity and trabecular bone separation (Tb.Sp), decreased maximum elastic stress and load, and reduced osteoblasts (Ji et al., 2023). At four months, *SAMP6* mice display comprehensive SOP with low global BMD, diminished bone marrow osteogenesis, defects in cortical mineralized surfaces, and reduced calcium and phosphorus

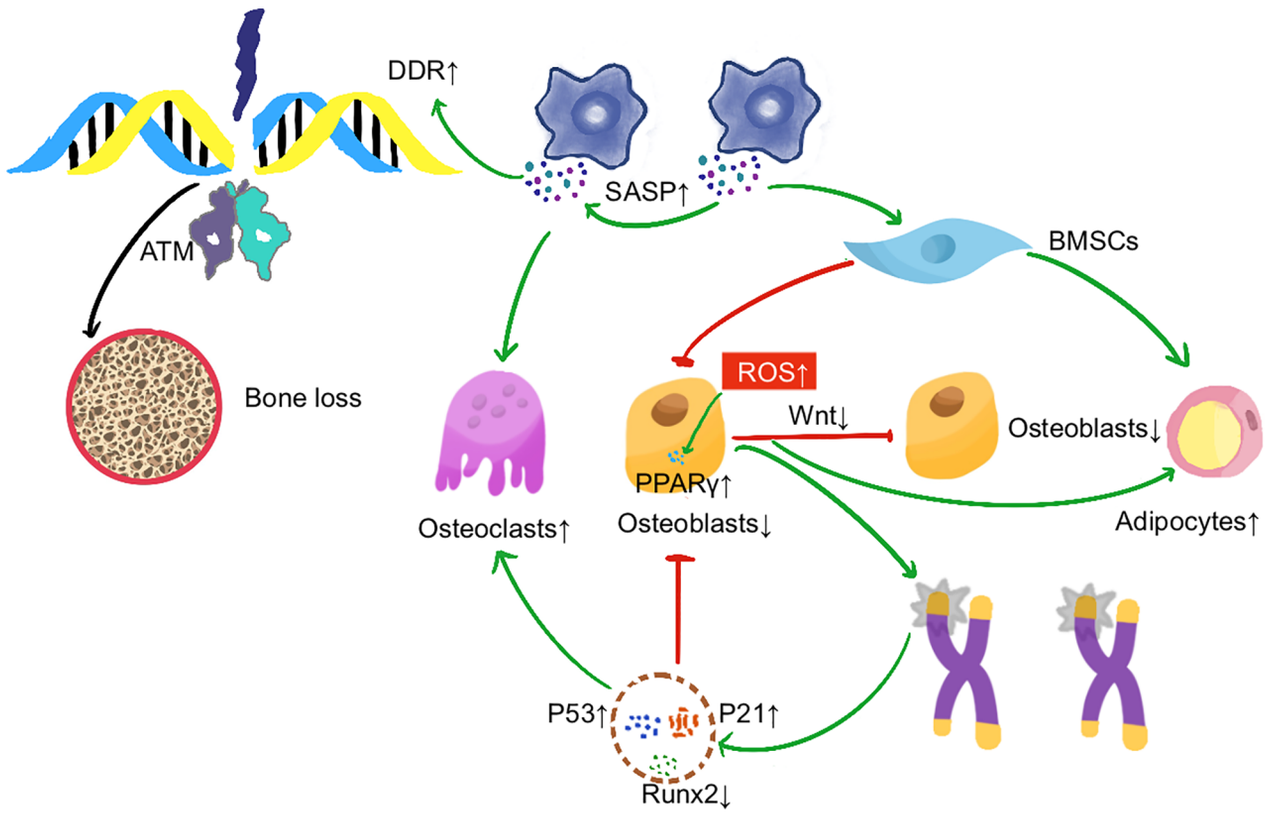

Figure 1 Naturally aging mouse phenotypes

The primary viewpoints on the mechanisms of bone aging are as follows. Firstly, increased DNA damage response (DDR) activates ataxia-telangiectasia mutated (ATM), leading to bone loss. Senescence-associated secretory phenotype (SASP) triggers DDR and SASP activation in neighboring cells. Increased proinflammatory SASP in the bone microenvironment promotes mesenchymal stem cell differentiation into adipocytes, inhibits osteoblast formation, and promote osteoclast formation. Telomere dysfunction leads to defective osteogenic differentiation and enhanced osteoclast function by up-regulating P53/P21 levels and down-regulating Runx2 levels. Oxidative stress activates PPARγ signaling in osteoblasts. As a result, Wnt signaling and osteoblast number are reduced, inhibiting bone formation and increasing bone adipocyte formation. In addition, oxidative stress accelerates telomere shortening.

levels. Furthermore, *SAMP6* mice are characterized by age-dependent inhibition of osteoblast and osteoclast formation but enhanced adipogenesis, leading to an early disturbance of bone homeostasis (Chen et al., 2009; Ichioka et al., 2002; Niimi & Takahashi, 2014). Osteoblasts and osteocytes in the Tb of *SAMP6* mice at two and five months of age show degenerative changes, including mitochondrial swelling and fragmentation, and myelin-like structures (Chen et al., 2004). Additionally, these mice contain fewer osteoblasts on the Tb and inner surface of the bone (Chen et al., 2004; Jilka et al., 1996) and increased bone marrow adiposity, with a high frequency of spontaneous leg fractures due to OP (Al-Azab et al., 2020; Matsushita et al., 1986; Stein et al., 1999).

Bone marrow transplantation experiments have indicated that the cause of OP in *SAMP6* mice is abnormal BMSCs (Takada et al., 2006). Senescence of bone marrow progenitors disrupts their differentiation, favoring adipogenesis over osteogenesis. This mechanism is thought to be responsible for the low activity and OP of osteoblasts in *SAMP6* mice and older humans (Matsushita et al., 1986). Notably, compared to healthy BALB/c mice, BMSCs from *SAMP6* mice display lower survival, increased apoptosis, increased mitochondrial membrane depolarization, impaired mitochondrial network dynamics, enhanced adipogenic differentiation, and higher accumulation of lipid droplets (Sikora et al., 2021). Aged *SAMP6* mice also demonstrate decreased osteoblasts and accelerated fat production (Takahashi et al., 1994; Kajkenova et al., 1997), along with high levels of secreted frizzled-related protein (Sfrp4) in the bone, which inhibits the Wnt signaling pathway, leading to diminished Wnt signaling in osteoblasts, inhibition of osteoblast proliferation, and decreased BMD (Haraguchi et al., 2016; Nakanishi et al., 2006). In addition, the expression of miR-494-3p in exosomes derived from aged osteocytes in *SAMP6* mice is decreased, inhibiting osteogenic differentiation and accelerating age-related bone mass loss via the PTEN/PI3K/AKT pathway (Yao et al., 2024). Increased adipogenesis in the bone marrow of *SAMP6* mice is also associated with up-regulated PPARγ, the master regulator of adipogenesis (Cao et al., 2015), leading to a significant increase in PPARγ-positive cells (Azuma et al., 2018) and enhanced lipogenesis in the bone. Overall, the bone phenotype of SAMP6 mice is characterized by decreased osteogenesis and increased adipogenesis.

Unlike *LMNA*-deficient mice (Mounkes et al., 2003), *Zmpste24-deficient* mice (Pendás et al., 2002), polg$^{mut/mut}$ mice (Trifunovic et al., 2004), Klotho-deficient mice (Kuro-O et al., 1997), and *ERCC1*-deficient mice (Niedernhofer et al., 2006), the pathogenesis of aging and aging-related diseases in SAM mice is caused by single gene variants, making them similar to humans in this respect (Mori & Higuchi, 2019). In addition, fractures in aged *SAMP6* mice result from low maximal bone mass, consistent with the cause of SOP in humans (Azuma et al., 2018). Single nucleotide polymorphisms on the SFRP4

gene are known to determine BMD in postmenopausal women (Lee et al., 2010), while *SFRP4* is reported to be overexpressed in the bone tissue of SAMP6 mice, suggesting shared molecular genetic pathways in bone mass regulation between humans and mice (Mori & Higuchi, 2019). Although SAMP6 mice exhibit various properties relevant to human SOP, they also possess certain limitations. Notably, they exhibit lower bone mass in the mid-axis and coccygeal regions compared to age-matched SAMR1 mice, with little further reduction in bone mass from 5 to 12 months of age (Chen et al., 2009). In addition, aging, lifespan, and pathological changes can vary markedly in SAMP mice under different feeding environments and dietary conditions, with proper microbial control and environmental management in laboratories shown to delay aging and prolong lifespan (Mori & Higuchi, 2019). SAMP6 mice have been extensively used to explore the pathogenesis, prevention, and treatment of SOP. Notably, studies have shown that compound 125 can up-regulate BMP2, accelerate bone turnover, and increase osteoblast proportion (Zhou et al., 2023), *Dolichos lablab* Linne can up-regulate BMP-2/Smad and Wnt/β-catenin to promote osteoblast and calcified nodule formation (Kim et al., 2023), and orcinol glucoside can alleviate bone mass loss, inhibit osteoclast formation and bone resorption activity, and reduces oxidative stress in osteoclasts (Gong et al., 2022).

POLG$^{mut/mut}$ premature aging mouse model

DNA polymerase gamma (polg) is the only DNA polymerase in mitochondria, thought to be responsible for all DNA synthesis reactions, including mitochondrial DNA (mtDNA) replication and repair (Kaguni, 2004). Its exonuclease activity is crucial for preventing errors in mtDNA synthesis *in vivo* (Vanderstraeten et al., 1998). Polg$^{mut/mut}$ mice, generated from mitochondrial mutations in *POLG* (nucleus-encoded catalytic subunit of mtDNA polymerase) (Kujoth et al., 2005; Trifunovic et al., 2004), were the first model to demonstrate the pathogenic role of mtDNA variants in the premature aging phenotype (Trifunovic et al., 2004). *POLG* mutations significantly reduce the 3'–5' exonuclease activity required for proofreading (Kujoth et al., 2005; Trifunovic et al., 2004), leading to the accumulation of mtDNA mutations, accelerated aging, and premature death. Aging in these mice is characterized by alopecia, gray hair, hunchback, decreased physical activity, decreased body weight and BMD, cardiac enlargement, and hypoglycemia (Trifunovic et al., 2004; Yu et al., 2022). The accumulation of mtDNA mutations and deletions results in highly localized mitochondrial dysfunction and increased oxidative stress, which may contribute to the multitarget aging process (Fayet et al., 2002; Larsson, 2010; Lei et al., 2021; Liang et al., 2020). In addition, markers of mitochondrial oxidative damage, such as protein carbonyls, and markers of lipid oxidation, such as 4-hydroxy-2-nonenal, nitrotyrosine, and 8-OHDG, are significantly increased in polg mutant mice (Kolesar et al., 2014). While the levels of mitochondrial complexes I and IV in osteoblasts decrease with age in wild-type (WT) mice, their levels are even lower in polg mutant mice (Dobson et al., 2016).

Whole-body BMD is significantly reduced in polg$^{mut/mut}$ mice at 40 weeks of age, consistent with the clinical features of OP. These mice also exhibit significant kyphosis and a decreasing trend in whole-body bone mineral content to length ratios (Trifunovic et al., 2004), as well as accelerated bone turnover, leading to the sudden occurrence of OP (Dobson et al., 2020). Several studies have shown that mitochondrial dysfunction contributes to the pathogenesis of OP (Miyazaki, 2013; Trifunovic et al., 2004). The mitochondrial dysfunction caused by the *POLG A* mutation results in decreased osteoblast cell density and increased osteoclast cell density, leading to respiratory chain dysfunction in both cell types. This dysfunction enhances osteoclast activity and reduces the ability of osteoblasts to form new bone, leading to a premature osteoporotic phenotype in mutant mice (Dobson et al., 2020). Polg$^{mut/mut}$ mice display increased respiratory chain defects in osteoblasts, providing insight into the pathology and causes of SOP at the protein and cellular levels (Haas, 2019). Given the higher ROS levels associated with the accumulation of mtDNA mutations, polg$^{mut/mut}$ mice also demonstrate telomere attrition, chromosome fusion and breakage, and elevated 8-oxoguanine (8-oxoGua) levels (Liu et al., 2002). Increased 8-oxoGua leads to telomere shortening and impairs mtDNA integrity and mitochondrial function, which, in turn, leads to increased ROS and 8-oxoGua production, further accelerating aging (Yu et al., 2022).

Polg$^{mut/mut}$ model mice are generated by mtDNA mutations. Unlike other aging mouse models, polg$^{mut/mut}$ mice exhibit premature OP due to impaired cellular respiratory chains (Dobson et al., 2020) and increased ROS production resulting from mitochondrial dysfunction (Liu et al., 2002). While they do not fully replicate the complete pathological process of OP, they are valuable for exploring the role of mitochondria in OP. Additionally, polg$^{mut/mut}$ mice can be used to study age-related kyphosis. Highly kyphotic homozygous polg (D257A) mice show extensive osteopenia, more pronounced in the posterior than anterior thoracolumbar spine (Roessinger et al., 2022).

LMNA premature aging mouse model

The *LMNA* gene, consisting of 12 exons on chromosome one, encodes lamin A and C, which are integral components of the nuclear envelope (Sui et al., 2019). Mutations in the *LMNA* gene are associated with various human genetic diseases, including Hutchinson-gilford progeria syndrome (HGPS) and mandibuloacral dysplasia (MAD) (Eriksson et al., 2003). HGPS is a sporadic, rare, fatal, autosomal dominant pediatric segmental disease (Ahmed et al., 2018), most commonly caused by mutations in the *LMNA* gene (Scaffidi & Misteli, 2006). Although patients appear normal at birth, symptoms begin to appear in the first few years of life, including severe growth retardation, loss of subcutaneous adipose tissue, alopecia, skin atrophy and wrinkles, micrognathia, delayed tooth eruption, irregular secondary dentin formation, pulp occlusion, and joint stiffness (Gardner & Majka, 1969; Gordon et al., 2007; Merideth et al., 2008; Ullrich & Gordon, 2015), as well as skeletal abnormalities in bone morphology and structure (Gordon et al., 2011). Mutations in lamin A disrupt the nuclear membrane, leading to impaired cellular functions such as DNA repair, gene transcription, and signal transduction (Villa-Bellosta et al., 2013). Moreover, studies have shown that loss of inner lamin A may lead to defects in nuclear function (Gordon et al., 2012).

Various mouse models of progressive HGPS have been established to study the underlying disease mechanisms (Vidak & Foisner, 2016). One model involves the knockout of the mutant *LMNA* allele *LMNA HG*, which produces only the precursor protein and no WT lamin A or lamin C. This knockout mouse exhibits a phenotype similar to that of HGPS children, including alopecia, partial lipodystrophy, OP, and

premature death, but lacks cardiovascular defects (Yang et al., 2005). Homozygous *LMNA HG/HG* mice, which express only progerin but not lamin A or C, show severe skeletal abnormalities, including spontaneous limb fractures, poor bone mineralization, and premature death (Yang et al., 2006). Progerin is a truncated form of prolamin A produced by a point mutation in the *LMNA* gene that activates a hidden splice donor site (De Sandre-Giovannoli et al., 2003). This mutation leads to permanent farnesylation and the accumulation of progerin around the nucleus, resulting in the loss of progerin in the inner nuclear region (Dechat et al., 2008). Another established model involves human *LMNA* carrying the *G608G* mutation on a 164 kb bacterial artificial chromosome, which shows progressive loss of vascular smooth muscle cells, a feature of HGPS patients, but does not display most other pathological features (Varga et al., 2006). The *LMNAL530P/L530P* model, involving exon 9 skipping and resulting in the in-frame deletion of 40 amino acids in the C-terminal globular domain of lamin A and C proteins, exhibits a phenotype that overlaps with HGPS (Hernandez et al., 2010; Mounkes et al., 2003). Another model involves a mouse knockout strain carrying the HGPS mutant gene in the mouse *LMNA* gene, producing a precursor protein due to the aberrant splicing of endogenous lmna Mrna (Osorio et al., 2011). The genetically engineered LMNA-deficient mouse model also exhibits several defects, including growth retardation, muscular dystrophy, and weakened myocardium (Sullivan et al., 1999).

HGPS patients show irregular cortical bones with poor biomechanical properties, extensive osteocyte and osteoblast loss, bone mineralization defects, decreased red bone marrow cells, and significant reductions in long bone type I collagen and osteoblast markers such as alkaline phosphatase (ALP) and osteocalcin (OCN). Bone mineralization defects occur because HGPS mutant osteoblast-specific expression increases DNA damage and affects Wnt signaling, leading to possible inflammation (Schmidt et al., 2012). Similarly, the cortical bones of five-week-old HGPS mice (long bones, spine, thorax, skull, and mandible) show a marked loss of lamellae, an increase in the embedded non-remodeling and nonmineralized matrix, an increase in the number of osteocytes, a decrease in cells in the bone marrow cavity, and an increase in adipocytes in the bone marrow space. These mutant mice exhibit growth retardation, gait imbalance, and spontaneous fractures (Schmidt et al., 2012). The increase in adipocytes may be associated with PPARγ, a positive regulator of adipocyte differentiation (Moerman et al., 2004). PPARγ ligands are normally restricted to the nuclear periphery via lamin A/C, so the absence of lamin promotes their release, activating PPARγ and inducing MSCs to differentiate into adipocytes (Boguslavsky et al., 2006). At 13 weeks, HGPS mice show increased cortical bone area and thickness. In addition, HGPS mutant osteoblast-specific expression disrupts cell-cell interactions among osteoblasts, osteoclasts, and osteocytes, leading to significant reductions in osteoblast-specific markers (ALP and OCN) and in Wnt-mediated lymphoid enhancer-binding factor one, a regulator of osteoblast maturation. The expression of osteocyte and osteoclast-related genes (Phex, Mepe, and Mmp9) is also inhibited (Schmidt et al., 2012). Consistent with this, osteoblasts, osteocytes, and osteoclasts are significantly reduced in $lmna^{-/-}$ mice compared to WT mice, with abnormal changes in the shape and size of osteoclasts (Li et al., 2011). This reduction in related to the nuclear envelope protein MAN-1. Loss of lamin A/C can disrupts nuclear membrane proteins, such as MAN-1, against osteogenic proteins, thereby affecting the migration and activation of RUNX2. MAN-1, a protein on the nuclear envelope, is closely regulated by lamin A through direct physical interactions (Östlund et al., 2006).

$Lmna^{-/-}$ mice are a widely used and established model for studying premature aging. Their pathological features are similar to those of zmpste24-deficient mice, but distinct from other premature aging mouse models. These mice are established by *LMNA* gene deletion, which disrupts lamin A/C synthesis and triggers nuclear dysfunction, leading to HGPS (Gordon et al., 2012). As a classic HGPS model, $lmna^{-/-}$ mice accumulate presenile proteins, exhibit histological and transcriptomic features of premature aging, and present key clinical manifestations of human HGPS, including shortened lifespan and bone senescence. Thus, $lmna^{-/-}$ mice are instrumental in studying the pathological mechanisms of premature aging syndrome (Cenni et al., 2018). However, the use of gene knockout techniques in $lmna^{-/-}$ mice presents limitations, as different knockout methods can result in varying pathologies, making it challenging to accurately mimic human HGPS. In addition, $lmna^{-/-}$ mice can also serve as a model to investigate the role of lamin A/C in bone metabolism, given their essential functions in osteoblast differentiation and normal bone biogenesis (Li et al., 2011; Vidal et al., 2012).

Sirtuin 6 (SIRT6) premature senescence mouse model

Sirt6 is a highly specific histone deacetylase that targets H3K9 and H3K56, playing a vital role in DNA repair, telomerase function, genome stability, and cellular senescence (Michishita et al., 2008). It regulates telomere chromatin stability (Kawahara et al., 2009) and the nuclear factor kappa-B (NF-κB)-mediated inflammatory microenvironment, thereby providing bone protection in OP patients (Wu et al., 2015).

Sirt6-deficient mice exhibit a short lifespan, multiorgan aging, decreased blood glucose and insulin-like growth factor concentrations, increased DNA instability, and early bone loss (Lombard et al., 2008). These mice show approximately 30% bone loss and die at approximately four weeks of age (Mostoslavsky et al., 2006). *SIRT6* knockout mice exhibit reduced cartilage, lower long bone calcification, significantly impaired TB formation, reduced trabecular number (Tb.N) and trabecular volume, significantly reduced serum OCN concentration, and significantly increased TRAP5b concentration, indicating enhanced bone resorption, decreased bone formation, smaller bone size, lower BMD (Zhang et al., 2016), and impaired osteoblast differentiation (Zhang et al., 2017). *SIRT6* knockout directly promotes osteoclast differentiation, leading to excess osteoclasts and hyperactive bone resorption (Zhang et al., 2016), which is related to the up-regulation of NF-κB signaling-related genes, including NEMO, ICAM-1N, C/EBPa, and INOS, caused by *SIRT6* deficiency (Zhang et al., 2018). Additionally, *SIRT6* deficiency inhibits osteogenesis by promoting H3K9 hyperacetylation of the Dickkopf-related protein 1 (Dkk1) promoter, a potent negative regulator of osteoblast formation (Sugatani et al., 2015). Of note, mice with specific knockout of *SIRT6* in osteoblasts/osteocytes exhibit severe bone loss and deformities (Zhang et al., 2021b).

SIRT6 can interact directly with NF-κB to antagonize NF-κB-induced gene expression, inhibit NF-κB signaling, partially restore lifespan, and improve short-lived sirt6-deficient mice

(Kawahara et al., 2009). Deletion of SIRT6 impairs the proliferation, migration, and oxidative stress tolerance of BMSCs (Zhai et al., 2016). Sirt6-deficient mice also develop rapid bone loss in parallel with accelerated aging, making them a classic model for the study of aging-related OP (Mostoslavsky et al., 2006).

Sirt6 attenuates NF-κB signaling through H3K9 deacetylation, while hyperactive NF-κB signaling may trigger premature aging (Liao & Kennedy, 2014). Excessive ROS generation *in vivo* decreases sirt6 levels (Carreira et al., 2018), which activates the NF-κB signaling pathway, leading to decreased bone quality. However, sirt6 levels in human BMSCs (hBMSCs) increase with age, indicating compensatory overexpression (Zhai et al., 2016). Sirt6 also regulates osteoblast proliferation and differentiation, weakens bone mineralization, and directly regulates osteoclast differentiation (Zhang et al., 2016). Additionally, sirt6 enhances the regulation of OP by BMSCs via the regulation of mitophagy. Inhibition of sirt6 decreases autophagy levels and the osteogenic ability of BMSCs (Shen et al., 2020).

Compared to other premature aging mouse models, sirt6$^{-/-}$ mice have a notably shorter lifespan, with most dying within four weeks and displaying severe bone loss characteristic of human low turnover osteopenia (Xu et al., 2023). Sirt6 plays a complex regulatory role in the human body, with its impact on the same signaling pathway potentially differing across diseases (Liu et al., 2021). Therefore, the therapeutic effects observed in sirt6 knockout mice must be extensively verified for their clinical applicability to humans. Sirt6$^{-/-}$ mice, which exhibit rapid bone loss synchronously with accelerated aging, can serve as a classic model for studying aging-related OP (Mostoslavsky et al., 2006). In addition, their premature aging and early death before four weeks make them valuable for premature aging research (Xu et al., 2023).

ZMPSTE24 premature senescence mouse model

Zmpste24, the mouse homolog of human FACE-1, is a multi-transmembrane protein widely distributed in mammalian tissues (Freije et al., 1999; Tam et al., 1998), consisting of 10 exons along a 38 kb genomic segment (Pendás et al., 2002). Structurally, Zmpste24 is related to the yeast metalloprotease Afc1p/ste24p, involved in the maturation of fungal pheromones (Boyartchuk et al., 1997). Functionally, Zmpste24 is an intact membrane metalloproteinase in the endoplasmic reticulum, and mice lacking this gene exhibit abnormal growth, early death, fur loss, kyphosis, abnormal gait, muscle weakness, average or low blood glucose levels, and abnormal anterior layer protein A processing (Bergo et al., 2002; Varela et al., 2005).

ZMPSTE24 knockout mice are generated by replacing the exon encoding the zinc-binding domain with a neomycin resistance cassette (Leung et al., 2001). These mice show markedly reduced RUNX2 levels, significantly decreased numbers of osteoblasts and osteocytes, and increased expression of adipogenic genes PPARγ and C/EBPα (Rivas et al., 2009).

Both *ZMPSTE24* and *LMNA* are involved in lamin A synthesis, and mutations in *ZMPSTE24* can also induce HGPS. However, the two genes have different roles, with *LMNA* encoding the precursor of lamin A, prelamin A, and *ZMPSTE24* encoding the zinc metalloproteinase Zmpste24, which processes prelamin A (Worman & Michaelis, 2023). When Zmpste24 cleavage is blocked, farnesylated and carboxy-methylated prelamin A accumulates, leading to HGPS (Worman & Michaelis, 2018; Young et al., 2005).

In addition, mutations in the *ZMPSTE24* gene can result in atypical precursor syndrome, which includes restrictive dermatosis and MAD (Navarro et al., 2005). Patients with MAD exhibit aging symptoms similar to those with HGPS, which appear 1–2 years after birth. However, MAD symptoms typically manifest at approximately 4–5 years and include skeletal abnormalities, partial alopecia, insulin resistance, lipodystrophy, and abnormal skin pigmentation. MAD is classified into type A and type B. Type A includes *LMNA* mutations that affect Zmpste24 protease processing, while type B involves mutations that impair the hydrolytic activity of Zmpste24 protease (Cenni et al., 2018). Patients with type B disease show marked skeletal abnormalities, including fractured vertebrae, amorphous subcutaneous calcium deposits, progressive submental changes at the proximal end of long bones, and severe OP with fractures and delayed union (Cunningham et al., 2010).

Zmpste24-deficient mice develop spontaneous fractures. By 24 to 30 weeks of age, rib fractures are visible near the junction of almost every rib, surrounded by dense fibrous tissue. These fracture sites are cell-free, with minimal inflammatory infiltration and little evidence of healing. Multiple fractures also occur in the scapula, clavicle, sternum, zygomatic arch, mandible, and humerus (Bergo et al., 2002).

Homozygous deletion of *LMNA* in mice or haploid *LMNA* in humans results in mature lamin A deficiency, leading to cardiomyopathy and muscular dystrophy. Unlike *LMNA* mutant or null mice, Zmpste24$^{-/-}$ mice do not show a reduction in mature lamin A, but rather exhibit permanent acylation of these proteins, leading to premature germ-like cell defects and disease (Bonne et al., 1999). In addition, Zmpste24$^{-/-}$ mice show overall hypoacetylation of histones H2B and H4, which may contribute to progeroid cell defects and disease (Osorio et al., 2010). Zmpste24$^{-/-}$ mice can serve as research models for HGPS, restrictive dermatosis, MAD, and other diseases. Mating Zmpste24$^{-/-}$ mice with transgenic mice with reduced NF-κB signaling prolongs lifespan and prevents the progression of premature aging traits (Osorio et al., 2012). Furthermore, resveratrol alleviates aging-like characteristics in Zmpste24$^{-/-}$ mice by promoting the interactions between Sirt1 and lamin A, restoring the decline of adult stem cells, improving Tb structure and BMD, and significantly prolonging lifespan (Liu et al., 2012).

Mitochondrial transcription factor A (TFAM) premature senescence mouse model

Tfam is a nuclear DNA-encoded protein essential for maintaining and promoting mtDNA transcription and replication (Dairaghi et al., 1995; Ekstrand et al., 2004; Lu et al., 2023; Parisi & Clayton, 1991). Tfam is a 25 kDa protein composed of an amino-terminal high mobility group (HMG) domain, an essential linker region, a secondary HMG structure, and a bare carboxy-terminal tail (Rantanen et al., 2001), which directly regulates mtDNA copy number *in vivo* (Ekstrand et al., 2004). Tfam levels are age-related, showing a reduced binding ability of all protein regions in extremely aged mice compared with aged mice (Lenaers et al., 2020). Tissue-specific knockdown of *TFAM* disrupts mitochondrial genome integrity, inducing the production of inflammatory cytokines and tumor necrosis factor-α (TNF-α), leading to accelerated aging, neuromuscular and vascular dysfunction, and

molecular features of premature aging (Desdín-Micó et al., 2020).

Tfam-deficient mice can be generated using several approaches. Notably, tfam double-floxed mice can be combined with Cre recombinase-containing actin promoter-driven mice to generate tfam-deficient mice, which are then backcrossed 10 times to WTC57BL/6J (B6) mice to remove the Cre transgene and purify the genetic background (Woo et al., 2012). Another approach involves disrupting the *TFAM* gene and generating *TFAM* knockout mice via the introduction of the loxP site by homologous recombination in embryonic stem cells (Gu et al., 1994), followed by excision of *TFAM* exons 6 and 7 by Cre-mediated *in vivo* recombination. The resulting knockout mice are embryonically lethal, surviving only to E8–E10.5, while heterozygous mice are born at standard frequencies but with reduced *TFAM* expression, mtDNA levels, and mitochondria-encoded protein levels (Larsson et al., 1998). Tissue-specific deletion of the tfam protein results in mtDNA defects, mtDNA deletion, and severe respiratory chain defects (Wang et al., 1999).

Limb mesenchyme-specific *TFAM* knockout (Prx1-Cre: TFAM-cKO) mice exhibit significantly shortened limbs after birth, spontaneous fractures, severe limb deformities, bone hypoplasia, and significantly reduced bone matrix mineralization. Tfam plays a crucial role in Ca^{2+} storage and bone matrix mineralization in osteoblasts (Yoshioka et al., 2022). The bone fragility observed in tfam-cKO mice is associated with inhibition of type I collagen deposition, impaired bone matrix mineralization, and poor apatite localization (Yoshioka et al., 2022). Additionally, tfam deficiency leads to adenosine triphosphate (ATP) depletion and increased bone resorption activity, with endogenous ATP release negatively regulating osteoclast function through an autocrine/paracrine feedback loop (Miyazaki, 2013).

$Tfam^{-/-}$ mice, similar to polg $A^{-/-}$ mice (Dobson et al., 2020), show impaired osteoblast differentiation and proliferation due to mitochondrial dysfunction, resulting in reduced expression of Col1a1, which encodes collagen I. However, tfam-cKO mice have a higher incidence of postnatal fractures and severe limb deformities, suggesting that tfam and polg A may have additional functions beyond maintaining mtDNA during bone formation (Yoshioka et al., 2022). $Tfam^{-/-}$ mice also display aging characteristics such as decreased BMD and muscle atrophy, making them an effective model for studying aging. However, the molecular and cellular changes in $tfam^{-/-}$ mice are complex and involve multiple tissues and organs, complicating the interpretation of specific aging mechanisms and bone disease occurrence. In practical applications, $tfam^{-/-}$ mice are primarily used to study diseases caused by tfam-mediated mitochondrial dysfunction, such as mitochondrial myopathy (Chatel et al., 2021) and OP.

ERCC1 premature senescence mouse model

The *ERCC1* gene encodes a protein essential for DNA binding (Tsodikov et al., 2005) and repair (Chen et al., 2013). *ERCC1* deficiency leads to persistent DNA damage and cellular senescence in primary osteoblasts and BMSCs (Chen et al., 2013), further leading to premature cellular replicative senescence (Coppé et al., 2010; Rodier et al., 2009) and bone tissue senescence in $ercc1^{-/\Delta}$ mice. The aging process is associated with increased levels of p16INK4A, a cysteinyl kinase inhibitor linked to cellular senescence (Sharpless & Depinho, 2004).

The $ercc1^{-/\Delta}$ mouse model was initially constructed by disrupting exon 5 of *ERCC1*, resulting in the deletion of the last four exons of the transcript, which contain the xeroderma pigmentosum group F (XPF) interaction domain (Enzlin & Schärer, 2002; Sijbers et al., 1996). The second established knockout model was generated by inserting a neomycin resistance cassette into exon 7 of *ERCC1* (Weeda et al., 1997).

ERCC1-XPF is a structurally specific nuclease composed of two subunits, ERCC1 and XPF (Gaillard & Wood, 2001), which are unstable in the absence of each other (Biggerstaff et al., 1993). Human ERCC1-XPF is one of two DNA endonucleases required for the dual incision step of nucleotide excision repair (NER). The ERCC1-XPF enzyme recognizes the junction between single- and double-stranded DNA and cleaves with specific polarity. NER is a DNA repair pathway that removes a wide range of lesions caused by ultraviolet radiation and chemicals from the genome (Lindahl & Wood, 1999). $Ercc1^{-/\Delta}$ mice, which express about 5% of the normal level of ERCC1-XPF, are well-suited models of human diseases such as premature aging (Gurkar & Niedernhofer, 2015; Yousefzadeh et al., 2019). These mice accumulate spontaneously generated endogenous DNA damage at a faster rate than naturally aging mice, resulting in a comparable senescent cell burden (Wong et al., 2020; Yousefzadeh et al., 2019). Thus,$ercc1^{-/\Delta}$ mice can serve as a representative model of early onset of age-related diseases (Harkema et al., 2016), spontaneously developing multiple age-related diseases during their seven-month lifespan, including OP, cardiovascular disease, cataracts, hearing and vision loss, peripheral neuropathy, hepatic fibrosis, brain atrophy with cognitive decline, and intervertebral disc degeneration (Dollé et al., 2011; Gregg et al., 2012; Harkema et al., 2016). In mice deficient in this gene, the skeleton exhibits severe, progressive OP (Chen et al., 2013; Gregg et al., 2011; Vo et al., 2010), including microcephaly, bilateral microphthalmia, micrognathia, brachycephaly, and clubfoot (Chen et al., 2013). Furthermore, ERCC1-deficient mice show substantial reductions in bone volume, trabecular thickness (Tb.Th), and Tb.N, with increased Tb.Sp, accompanied by a significant reduction in osteoblasts, an increase in osteoclast surface area and number, and a reduction in osteogenic progenitor cells in BMSCs, leading to accelerated senescence of BMSCs and osteoblasts. This senescence is characterized by decreased proliferation, accumulation of DNA damage, and a senescence-associated secretory phenotype that promotes the secretion of inflammatory cytokines such as interleukin-6 (IL-6), TNF-α, and RANKL in osteoclasts, creating an inflammatory bone microenvironment that facilitates osteoclast formation (Chen et al., 2013).

$Ercc1^{-/\Delta}$ mice exhibit an aging pattern similar to naturally aging mice across multiple tissues, including the liver, large intestine, kidney, pancreas, and spleen (Yousefzadeh et al., 2020). Due to rapid DNA damage accumulation, ercc1−/Δ mice exhibit accelerated aging and enhanced cellular senescence, showing similarities with WT mouse and human aging. They serve as a precise model of aging, with the process occurring approximately six times faster than normal, and the hierarchical order of aging marker expression closely mirroring that in WT mice (Gurkar & Niedernhofer, 2015; Yousefzadeh et al., 2020). ERCC1 proteins are involved in nucleotide excision repair, interstrand cross-linking repair, and homologous recombination, playing an essential role in

genomic maintenance and body health (Dollé et al., 2011). Thus, ercc1$^{-/\Delta}$ mice exhibit damage to multiple systems, facilitating the study of multiple organs but may present with more severe symptoms when focusing on a single system or organ.

ERCC1-XPF is a nuclease that cleaves the junction between double- and single-stranded DNA (Manandhar et al., 2015). Reduced levels of ERCC1-XPF lead to accelerated aging in humans and mice, manifesting as XPF-ERCC1 (XFE) progeroid syndrome (Niedernhofer et al., 2006). Mice mimicking human XFE age approximately six times faster than WT mice due to the absence of the ERCC1-XPF DNA repair endonuclease complex (Gurkar & Niedernhofer, 2015; Niedernhofer et al., 2006). Ercc1$^{-/\Delta}$ mice also experience increased DNA damage, particularly cyclosporine adducts, in multiple organs with age (Wang et al., 2012b), as well as longer and larger nuclei (Choi et al., 2011). Notably, the symptoms of human progeria syndrome due to ERCC1-XPF deficiency are strikingly similar to those of ercc1-deficient mice, including osteopenia (Niedernhofer et al., 2006).

Ercc1-deficient mice exhibit accelerated epigenetic senescence associated with human-related diseases due to DNA repair defects leading to persistent, irreparable DNA damage (Perez et al., 2024). Ercc1$^{-/\Delta}$ mice have a short and highly uniform lifespan, making them an ideal model for studying the relationship between DNA damage and aging, possessing many features of natural aging across various tissues (Birkisdóttir et al., 2022). Ercc1$^{-/\Delta}$ mice, with lifespans shortened to less than 6 months, exhibit anatomical, physiological, and molecular features of aging in multiple tissues (Weeda et al., 1997; Yousefzadeh et al., 2020). They provide a rapid and cost-effective model for evaluating aging therapeutics (Yousefzadeh et al., 2020) and are an effective tool for accelerating vascular aging to explore the underlying mechanisms (Golshiri et al., 2021).

Cellular senescence in ercc1$^{-/\Delta}$ mice is promoted due to enhanced endogenous DNA damage (Nidadavolu et al., 2013; Niedernhofer et al., 2018; Robinson et al., 2018; Yousefzadeh et al., 2020). The accelerated senescence associated with ERCC1-XPF deficiency is attributed to cellular senescence and death rather than a consequence of telomere-dependent replicative senescence (Gregg et al., 2011). XPF mutations lead to increased cytoplasmic localization of the human XPF-ERCC1 nuclease complex, preventing it from participating in DNA repair (Ahmad et al., 2010).

WERNER premature aging mouse model

Werner (Wrn) is a member of the RecQ family of DNA helicases, characterized by an N-terminal 3'-5' exonuclease domain (Huang et al., 1998; Opresko et al., 2004). Wrn is localized to telomeres exclusively during the S phase of the cell cycle (Crabbe et al., 2004; Opresko et al., 2004), where it plays a crucial role in telomere metabolism. It is required for efficient replication of lagging strand telomeric DNA (Crabbe et al., 2004; Griffith et al., 1999; Opresko et al., 2004), and most of the pleiotropic effects observed in Wrn defects are due to critical telomere shortening (Chang, 2005b). Werner syndrome (WS) in humans is also associated with telomere dysfunction (Chang, 2005b).

Human WS is an autosomal recessive genetic disease characterized by clinical symptoms of premature aging and aging-related diseases, such as cardiovascular disease, OP, and cancer (Kipling & Faragher, 1997). The disorder results from mutations in Wrn, Rec-Q helicase, and exonuclease, which hydrolyze ATP to separate double-stranded DNA into single strands for replication, recombination, transcription, and repair (Monnat, 2010). Mutations in the *Wrn* gene lead to early onset aging phenotypes, including skin atrophy, hair graying and loss, OP, malignancy, and shortened lifespan (Vanhooren & Libert, 2013). The incidence of spinal bone deformities is higher in male WS patients than in females, with both sexes exhibiting decreased cortical bone thickness (Shiraki et al., 1998). One of the primary targets of Wrn helicase is telomeric DNA. Given that laboratory mouse telomeres are approximately five times longer than human telomeres, mice must lack telomerase for 3–6 generations before phenotypic defects become evident (Herrera et al., 1999; Rudolph et al., 1999). However, when the telomerase RNA gene (*Terc*), which encodes the RNA component of telomerase, is deleted alongside *Wrn*, Wrn$^{-/-}$-Terc$^{-/-}$ mice rapidly develop a WRN-like phenotype (Chang et al., 2004). These mice show low bone mass and age-related OP due to a shortened lifespan of BMSCs and impaired osteogenic potential and osteoblast differentiation under normal osteoclast differentiation (Pignolo et al., 2008). In juvenile Wrn$^{-/-}$-Terc$^{-/-}$ mice, bone volume, number, and Tb.Th are reduced, while Tb.Sp is increased; in young mice, cortical bone thickness decreases, porosity and bone marrow fat content increase, with these changes accelerating in aged mice (Brennan et al., 2014).

In the absence of telomerase activity in mice, telomeres become shorter after several generations, leading to telomere replicative senescence (Chang, 2005a). When telomere damage surpasses a certain threshold, osteoblast differentiation is impaired, associated with increased expression of p53 and p21 Waf1/Cip1 (p21) and decreased expression of RUNX2 (Wang et al., 2012a). This results in p53-mediated osteoblast injury and mesenchymal progenitor cell (MPC) senescence. The cyclin-dependent kinase inhibitor p21, downstream of p53, is significantly up-regulated, while RUNX2 is inhibited in the MPCs of Wrn$^{-/-}$-Terc$^{-/-}$ mice (Wang et al., 2012a). The fibroblast growth factor p21 inhibits osteoblast differentiation and protects the stem cell pool by regulating cell proliferation and turnover (Bellosta et al., 2003). Additionally, p16 promotes cell senescence by inhibiting cell proliferation, with p16-deficient WS mice showing a reduction in DNA damage response pathways, leading to decreased apoptosis and cell senescence, and an attenuated aging phenotype (Zhang et al., 2021a).

Werner-defective mouse models differ from other aging mouse models due to a lack of *Wrn*, which leads to telomere dysfunction and induces various diseases (Chang, 2005a). The Wrn$^{-/-}$-Terc$^{-/-}$ mouse model redefines the overall mechanism of bone mass loss during human aging (Pignolo et al., 2008). However, the distribution of OP in WS is abnormal, with greater impact on the limbs than on the axial skeleton (Hofer et al., 2005; Mason et al., 2005). *Wrn*$^{-/-}$-*Terc*$^{-/-}$ mutations cause a bone phenotype similar to age-related bone loss in humans, making it a suitable model for studying SOP. Notably, these mutant mouse model may recapitulate the senescence of osteoblasts and their precursors (Pignolo et al., 2008). In addition, WS is a typical premature aging syndrome that mimics natural aging and can also be used in the study of immune inflammation (Goto, 2008).

KLOTHO premature aging mouse model

Klotho, a transmembrane protein mainly expressed in the renal distal convoluted tubules and choroid plexus (Kuro-O

et al., 1997), primarily functions as a coreceptor for fibroblast growth factor 23 (FGF23) (Kurosu et al., 2006; Urakawa et al., 2006). Klotho is a potent regulator of bone formation and bone mass in osteocytes (Komaba et al., 2017), with the Klotho gene considered a potential candidate for the genetic regulation of common age-related diseases, such as OP and cervical spondylosis (Ogata et al., 2002). *KLOTHO* locus gene-deficient (Kl/Kl) mice can be generated by crossing heterozygous Klotho mice (Kawaguchi et al., 1999).

Kl/Kl mice generally develop symptoms at 3–4 weeks of age, exhibiting syndromes similar to human premature aging, including arteriosclerosis, emphysema, premature thymus degeneration, skin atrophy, reduced spontaneous activity, ectopic calcification, OP, growth retardation, infertility, and shortened lifespan, with death occurring at approximately two months of age (Kuro-O et al., 1997). Interestingly, the marked decrease in osteoclast activity and population in Kl/Kl-deficient mice coincides with high serum calcium, phosphate (Kuro-O et al., 1997), and osteoprotegerin (OPG) levels (Yamashita et al., 2001). Kl/Kl mice also show a reduction in osteoblast progenitors and lower osteoblast ALP activity and matrix nodule formation (Kawaguchi et al., 1999). Overexpression of *KLOTHO* in cultured osteoblasts inhibits mineralization and osteogenic activity during osteocyte differentiation (Komaba et al., 2017), while *KLOTHO* gene deletion accelerates osteocyte senescence and affects the spatial distribution of osteocytes and synthesis of bone matrix proteins (Suzuki et al., 2005). The bone matrix of *Kl/Kl*-deficient mice contains extensive unmineralized areas, while mineralized osteocytes and their lacunae show a large amount of OCN and dentin matrix protein-1 (DMP-1) staining. This may be due to the excessive production of calcium-binding molecules, such as OCN and DMP-1, by osteocytes, leading to concentrated mineralization around these cells and disruption of mineralization integrity in the bone matrix (Sasaki et al., 2013). BMSCs from Kl/Kl mice exhibit hyperactive proliferation *in vivo* and *in vitro* but decreased function (Feng et al., 2023). However, BMSCs overexpressing *KLOTHO* show enhanced proliferation, secretion, and migration (Ni et al., 2021), with *KLOTHO* overexpression also prolonging the lifespan of Kl/Kl-deficient mice (Kurosu et al., 2005). Kl/Kl mice develop osteopenia and OP, characterized by elongated long bones, thin cortical bone in the diaphysis, and increased epiphyseal trabeculae in the vertebral body (Yamashita et al., 2000). They show increased bone volume of the proximal tibial epiphysis, with an 8AA0% increase in Tb.N, a 300% increase in Tb.Th, a 60% decrease in Tb.Sp, and low bone turnover (Yamashita et al., 2000). The cancellous bone volume in the epiphysis of *Kl/Kl* mice is three times that of WT mice, with osteopenia in vertebrae and long bones. The elongation of trabecular bone is due to relatively low levels of bone resorption (Yamashita et al., 1998). T The number and surface area of osteoclasts and osteoblasts are significantly reduced (Kawaguchi et al., 1999; Kuro-O et al., 1997; Yamashita et al., 1998). Additionally, high OPG expression is observed in the femora of *Kl/Kl* mice, with *Klotho* gene deletion inhibiting bone resorption two weeks after bone marrow ablation (Yamashita et al., 2000).

FGF23 is a bone-derived circulating hormone, crucial for phosphate and vitamin D metabolism (Kurosu et al., 2006; Urakawa et al., 2006). Membrane-anchored Klotho, an important regulator of mineral homeostasis, functions as a coreceptor for FGF23 (Kurosu et al., 2006; Martin et al., 2012; Urakawa et al., 2006). While FGF23 is primarily a growth factor, in the presence of soluble Klotho, it directly affects osteocyte differentiation and mineralization (Baron & Kneissel, 2013). This effect is partially mediated by the induction of Dkk1 and subsequent inhibition of the Wnt/β-catenin pathway (Baron & Kneissel, 2013; Carrillo-López et al., 2016). The Wnt/β-catenin pathway plays a vital role in osteoblast activity, bone development and bone mass maintenance (Baron & Kneissel, 2013). Dkk1 antagonizes Wnt signaling by inhibiting the binding of Wnt ligands to the receptor complex consisting of frizzled protein and lipoprotein receptor-associated protein 5/6. However, loss of Klotho function in osteocytes impairs FGF23-induced Dkk1 effects, resulting in Wnt pathway activation and increased osteoblast activity (Komaba & Lanske, 2018).

Kl/Kl mice are a well-established model that mimics human aging characteristics, including OP (Suzuki et al., 2005). These mice exhibit osteopenia, predominantly cortical osteopenia, similar to human SOP, and die prematurely at around two months of age (Kawaguchi, 2006). This bone loss indicates that decreased bone formation exceeds bone resorption, resulting in net bone loss and mirroring the pathophysiology of SOP in humans (Kawaguchi et al., 2000). *KLOTHO* gene defects lead to independent impairment of osteoblast and osteoclast differentiation, resulting in reduced low-turnover bone mass, also characteristic of human SOP. Therefore, Kl/Kl mice are an important model for studying the molecular mechanisms underlying age-related bone loss (Kawaguchi et al., 1999), and have also been used to study chronic kidney disease (Kuro-O, 2011). However, although disease manifestations in *KLOTHO* knockout mice are similar to those in humans in many respects, species differences still exist. Multiple factors regulate premature aging in humans, which must be comprehensively considered.

We summarized the mechanisms of bone aging in mice (Table 1) and compared the bone phenotypes of aging mice and humans (Table 2). We also described the phenotypic and pathological characteristics of premature aging mice (Figure 2, 3).

However, mice may not always be the most suitable model for studying skeletal phenotypes. Despite apparent similarities in skeletal biology between mice and humans, significant differences also exist between the two species, including variations in organizational structures, remodeling activity, genetic evolution, and mechanical loading patterns (Elefteriou & Yang, 2011). For instance, bone growth in mice is affected by total bone growth plate height, resting zone height, and cell proliferation activity, but is correlated with the width of the bone growth plate rather than its height in humans (Wilson et al., 2021). Therefore, when selecting mice as a model for bone studies, it is essential to carefully consider the similarities and differences between mouse and human bones to choose the most appropriate model.

TREATMENT

Bone loss naturally occurs with aging in humans, leading to complications such as bone fragility and associated fractures, which can be disabling and fatal. OP is an incurable degenerative disease in both Chinese and Western medicine, directing scientific efforts towards alleviating bone loss and preventing OP. Methods to mitigate bone loss include drug therapy, exercise, and stem cell transplantation. Drug therapy is a primary approach and can help reduce bone loss. For

Table 1 Summary of bone aging mechanisms in mice

Mouse type	Mechanism
Naturally aged mice	① Accumulation of DDR leads to reduced bone formation and bone loss (Hoeijmakers, 2009). ② Generation of SASP activates DDR and SASP of neighboring cells (Rodier et al., 2009). ③ Telomere dysfunction increases expression of P53/P21 and decreases expression of RUNX2, leading to defects in osteogenic differentiation (Wang et al., 2012a). ④ Oxidative stress inhibits bone formation and increases bone adipocyte formation (Almeida et al., 2009), while deepening effects of telomere shortening on bone remodeling (Muller, 2009).
SAMP6 mice	BMSCs are abnormally differentiated and differentiate in favor of adipogenesis rather than osteogenesis (Chen et al., 2009; Ichioka et al., 2002; Niimi & Takahashi, 2014).
POLG$^{mut/mut}$ mice	① Polg A mutations cause mitochondrial dysfunction, leading to respiratory chain dysfunction in both osteoblasts and osteoclasts, resulting in reduced osteoblast number and osteogenic ability, increased osteoclast number and activity, and premature OP phenotype (Dobson et al., 2020). ② Higher levels of ROS cause telomere attrition and loss, chromosome fusion and fragmentation, and premature senescence (Liu et al., 2002).
LMNA mice	Mutations and deletions of lmna, which cause lamin A/C synthesis disorders, leading to nuclear membrane structural changes, such as DNA repair-related proteins, gene transcription and signal transduction abnormalities, cellular function destruction, and skeletal abnormalities (Villa-Bellosta et al., 2013).
SIRT6 mice	Loss of *SIRT6* results in uninhibited NF-kB signaling, with hyperactive NF-κB signaling potentially triggering premature aging, leading to skeletal abnormalities (Liao & Kennedy, 2014).
ZMPSTE24 mice	Mutations or deletions in *ZMPSTE24* gene cause loss of Zmpste24 protease function, leading to skeletal abnormalities.
TFAM mice	Deletion or mutation of *TFAM* gene disrupts mitochondrial genome integrity, leading to impaired mtDNA maintenance, transcription and replication, premature senescence, and skeletal abnormalities (Desdín-Micó et al., 2020).
ERCC1 mice	*ERCC1* deficiency leads to persistent DNA damage and cellular senescence in primary osteoblasts and BMSCs, associated with increased p16INK4A levels (Sharpless & Depinho, 2004).
WERNER mice	*WERNER* deletion causes telomere dysfunction, up-regulates p21, and inhibits osteoblast differentiation and defective telomere-mediated osteoblast differentiation (Bellosta et al., 2003).
KLOTHO mice	Functional loss of Klotho in osteocytes impairs biological effects of FGF23-induced Dkk1, resulting in Wnt pathway activation and increased bone formation in osteoblasts (Komaba & Lanske, 2018).

example, calcium supplementation can prevent bone calcium from entering the bloodstream, reduce bone resorption, and slow bone loss (Zhu & Prince, 2012). Vitamin D can promote calcium absorption, directly acting on osteoblasts and osteoclasts to promote bone mineralization and inhibit bone resorption (Hou et al., 2018). Strontium ranelate (SrR), a clinically used drug containing strontium salt (Pilmane et al., 2017), is more effective than vitamin D3 in treating postmenopausal OP (Kołodziejska et al., 2021). However, SrR can cause a variety of adverse effects, including skin damage, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (Abrahamsen et al., 2014), limiting its use in OP treatment (Reginster et al., 2015). The most widely used anti-resorptive drugs are bisphosphonates and the RANKL inhibitor denosumab.

Bisphosphonates are the primary treatment for OP (Center et al., 2020) and can be taken with calcium supplements. Bisphosphonates bind to hydroxyapatite on the bone surface, preventing the release of cytokines that activate osteoclasts. This inhibition leads to increased osteoclast apoptosis and decreased bone resorption (Camacho et al., 2020). Denosumab, a fully human RANKL monoclonal antibody, prevents RANKL from activating its receptor on osteoclasts and preosteoclasts, leading to increased bone mass. Compared to bisphosphonates, denosumab more rapidly improves BMD in both cortical and cancellous bone, thereby reducing fracture risk (Camacho et al., 2020). Additionally, teriparatide treatment significantly reduces both vertebral and nonvertebral fractures while improving quality of life. Furthermore, intermittent low-dose parathyroid hormone analogues increase osteoclast activity, promote bone formation, and reduce bone resorption (Augustine & Horwitz, 2013). Estrogen replacement therapy and estrogen plus progesterone therapy are also viable options for treating bone loss in postmenopausal women (Levin et al., 2018). Exercise is another strategy used to mitigate bone loss, with aerobic endurance and resistance exercise shown to exert positive effects on bone metabolism (Stunes et al., 2022). Sustained sprinting and strength training can improve tibial characteristics in middle-aged and elderly male sprinters (Suominen et al., 2021). Additionally, tai chi can benefit patients by increasing BMD and bone Gla protein levels while alleviating OP-induced pain (Zhang et al., 2019). Stem cell therapy can also mitigate bone loss (Sanghani-Kerai et al., 2018), with localized transplantation of BMSCs resulting in an increase in Tb and improvement in bone microarchitecture and stiffness (Hu et al., 2018). Similarly, local injection of human umbilical cord mesenchymal stem cells promotes osteoblast differentiation and Tb formation and reduces bone loss (Hendrijantini et al., 2018).

In addition to the commonly used treatments for alleviating bone loss mentioned above, we also summarize the specific therapeutic approaches targeting skeletal injury in the prematurely aging mouse models discussed in this paper. Orcinol glucoside, a phenolic glycoside isolated from *Curculigo orchioides* Gaertn, has shown promise in SAMP6 mice by preventing SOP through the activation of the Nrf2/Keap1 and mTOR signaling pathways, thereby attenuating oxidative stress and osteoclast autophagy (Gong et al., 2022). *Dolichos lablab* Linné treatment in SAMP6 mice promotes osteoblast and calcified nodule formation by up-regulating BMP-2/Smad and Wnt/β-linker protein pathways, enhancing BMD and fracture healing (Kim et al., 2023). Acupuncture on the Shenshu point in SAMP6 mice has been shown to enhance testosterone secretion, decreases bone renewal, and partially alleviate OP by promoting bone formation, restoring bone mass, and improving bone structure (Zhang et al., 2009). Additionally, allogeneic bone marrow cell transplantation directly into the bone marrow cavity of irradiated SAMP6 mice promotes the normalization of cancellous bone and BMD (Takada et al., 2006). Lactoferrin, an iron-binding glycoprotein, promotes the normalization of bone formation and structure in SAMP6 mice by promoting osteogenesis (Chen et al., 2019). Additionally, glucagon-like

Table 2 Summary of bone phenotypes in mice and humans

Type	Bone phenotypes in mice	Bone phenotypes in humans
Naturally aged	Bone mass, cancellous bone volume fraction, and cortical bone thickness, after reaching peak values, decrease with age and exhibit SOP (Bikle et al., 2002).	Bone remodeling homeostasis is disrupted, and bone resorption exceeds bone formation in SOP, leading to thinning of cortical bone, reduction in Tb.Th and Tb.N, increase in Tb.Sp in patients, bone mass and strength reduction, bone fragility and increased risk of fracture (Khandelwal & Lane, 2023).
SAMP6	Compared with aging R-strain mice, SAMP6 mice exhibit thinner cortex, larger periosteal and intraosseous diameters (Chen et al., 2009; Jilka et al., 1996; Matsushita et al., 1986; Silva et al., 2005), and lower BV/TV and BMD (Chen et al., 2004, 2005, 2009; Jilka et al., 1996; Matsushita et al., 1986).	Skeletal phenotype of SAMP6 mice corresponds to SOP.
POLG $^{mut/mut}$	OP appears prematurely. Polg$^{mut/mut}$ mice at 40 weeks show significantly reduced whole-body BMD, significant kyphosis, and decreasing tendency in whole-body bone mineral content to length ratio (Trifunovic et al., 2004).	No relevant skeletal studies have been conducted on patients with POLG deletion. However, the discovery of mitochondrial complex defects in osteoblasts from older adults compared to younger adults is consistent with this mouse model (Hipps et al., 2022), suggesting that respiratory chain defects, resulting from accumulation of age-related pathogenic mtDNA mutations, are associated with an increased risk of death. These findings may be significant in the pathogenesis of age-related OP in humans.
LMNA	Irregular cortical bone with poor biomechanical properties, extensive loss of osteocytes and osteoblasts, defects in bone mineralization, decreased red marrow cells, and significant reductions in type I collagen, ALP, and OCN in long bones (Schmidt et al., 2012).	Patients with HGPS exhibit slender, long bones, thin but abnormally dense cortical bone, sparse and narrow Haversia canals, unclear bone trabeculae, and insufficient mineralization (Lee et al., 2012). Ossific defects show an extensive patent anterior fontanelle, which may remain open during childhood and adolescence (Debusk, 1972). In HGPS patients, osteolysis commonly occurs in distal phalanges, clavicle, mandible, neurocranial and visceral skull (Lamis et al., 2022), and first rib (Sivaraman et al., 1999).
SIRT6	Bone resorption is enhanced, bone formation is decreased, bones show smaller body size and lower BMD, long bones show lower calcification, trabecular bone formation is significantly impaired, and number and volume are reduced (Zhang et al., 2016).	There are no relevant skeletal studies with *sirt6*-deficient patients, but sirt6-KO mice exhibit similar SOP symptoms to humans. Sirt6 plays an essential role in DNA repair, telomerase function, genome stability and cellular senescence, especially in preventing premature senescence of human cells (Michishita et al., 2008).
ZMPSTE24	Spontaneous fractures and severe OP. RUNX2 expression is markedly reduced, osteoblasts and osteocytes are significantly reduced, and expression of adipogenic genes PPARγ and C/EBPα is increased (Rivas et al., 2009).	Patients harbor two heterozygous compound mutations in *ZMPSTE24* gene and present with different skeletal features, including coracoid process of vertebrae, development of amorphous subcutaneous calcified deposits, progressive epiphyseal changes in proximal long bones, and severe OP with fractures and delayed healing. Skull exhibits typical features of MAD-A, including mandibular hypoplasia, premature teething and crowding of dentition (Cunningham et al., 2010). Patients may present with skeletal disorders, including decreased bone density in spine and limbs, multiple spontaneous fractures, osteolysis of femoral head, and cranial sutures that remain unhealed. These symptoms typically appear at around 15 years old (Ben Yaou et al., 2011). Patients with MAD-B caused by *ZMPSTE24* mutation exhibit growth retardation, partial lipodystrophy, skin pigmentation, and prominent bone defects, including mandibular hypoplasia and progressive bone resorption in distal phalanges and clavicles (Worman & Michaelis, 2023).
TFAM	Significant shortening of limbs with spontaneous fractures, severe limb deformities, bone hypoplasia, and significantly reduced mineralization of bone matrix, impaired osteoblast proliferation, differentiation, and function (Yoshioka et al., 2022).	There are no relevant skeletal studies on patients with *TFAM* deficiency. However, tfam is a core component of the human mitochondrial transcription machinery and is vital in maintaining mitochondrial function (Shi et al., 2012).
ERCC1	Skeletal manifestations are severe, with progressive OP (Chen et al., 2013; Gregg et al., 2011; Vo et al., 2010), microcephaly, bilateral microphthalmia, micrognathia, brachycephaly, and clubfoot. Bone tissue volume, Tb.Th, and Tb.N are significantly decreased, and Tb.Sp is increased (Chen et al., 2013).	Patients with Ercc1 show microcephaly, premature closure of fontanelles, bilateral microphthalmia (Jaspers et al., 2007), and osteopenia (Niedernhofer et al., 2006). Due to severe symptoms in Ercc1 patients and few related cases, few studies have been conducted on Ercc1 patient bone, and in-depth research is lacking.
WERNER	① Lifespan of BMSCs is shortened, and osteogenic potential and osteoblast differentiation are impaired (Pignolo et al., 2008). ② Juvenile Wrn$^{-/-}$-Terc$^{-/-}$ mice show reduced trabecular volume, Tb.Th, and Tb.N, and increased trabecular spacing (Brennan et al., 2014). ③ Young Wrn$^{-/-}$-Terc$^{-/-}$ mice show thinner cortical bone, increased porosity, and increased bone marrow fat content (Brennan et al., 2014). ④ In aged Wrn$^{-/-}$-Terc$^{-/-}$ mice, changes in trabecular bone, cortical bone and bone marrow fat content are accelerated (Brennan et al., 2014).	Patients lacking werner exhibit OP (Neveling et al., 2007), low serum levels of insulin-like growth factor 1, which can promote bone formation, and reduced osteoblast activity (Rubin et al., 1994).

Continued

Type	Bone phenotypes in mice	Bone phenotypes in humans
KLOTHO	Kl/Kl-deficient mice develop osteopenia and OP, including thinning of epiphyseal trabeculae of vertebral body and cortical bone of diaphysis, but lengthening of bone, increased bone volume (Yamashita et al., 2000), and extensive unmineralized areas in bone matrix (Sasaki et al., 2013). At the cellular level, the number and surface area of osteoclasts (Kuro-O et al., 1997) and osteoblasts (Kawaguchi et al., 1999) are significantly reduced in Kl/Kl-deficient mice, and BMSCs show excess proliferation and functional impairment (Sasaki et al., 2013).	Klotho gene deficiency in humans increases bone resorption and causes chronic renal failure (Koh et al., 2001). In addition, bone loss in SOP in humans is characterized by a decrease in bone formation over bone resorption, similar to the mechanism in Kl/Kl-deficient mice (Kawaguchi et al., 2000).

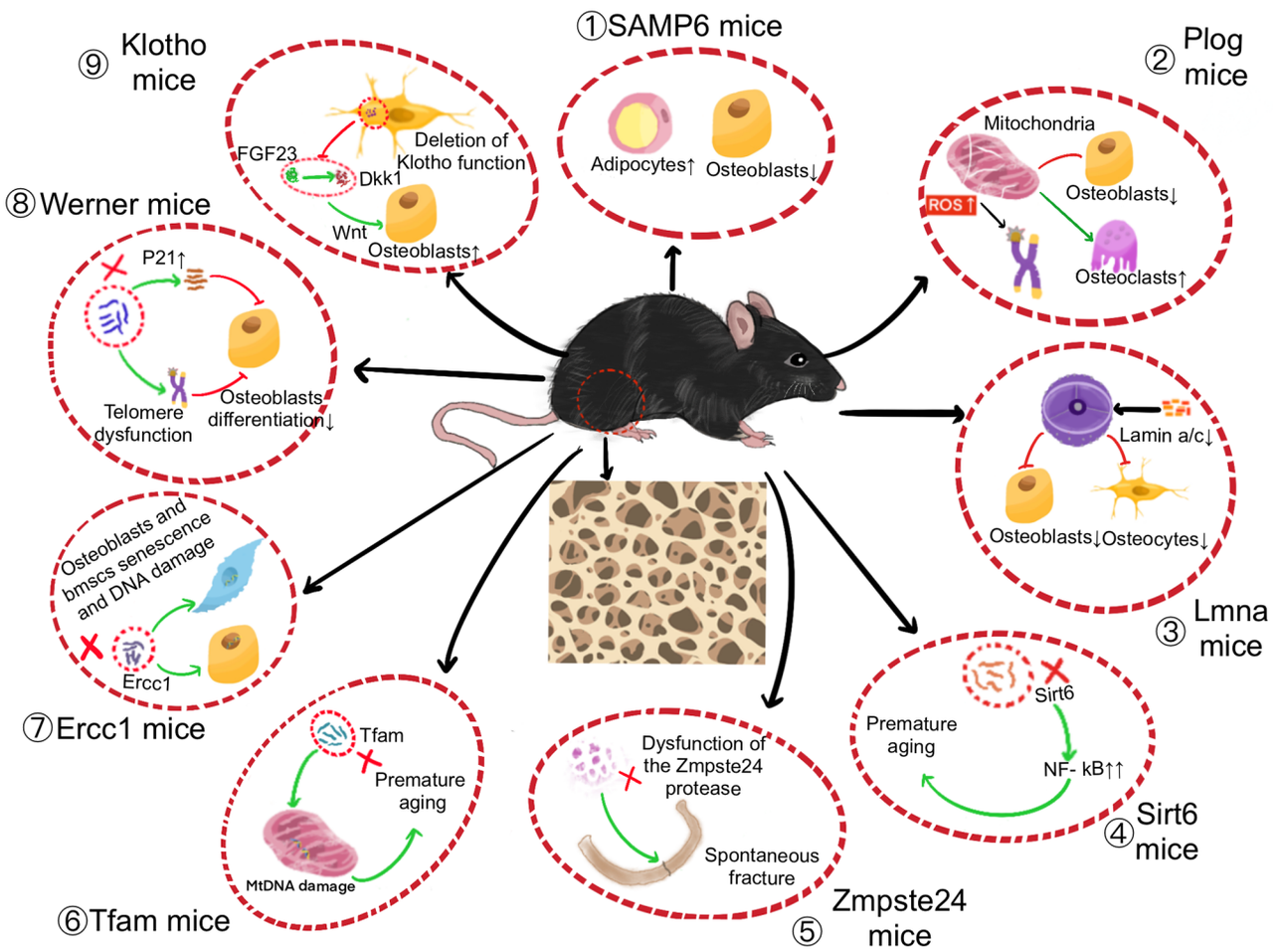

Figure 2 Phenotypes of prematurely aging mice

SAMP6 mutant prematurely aging mice: Abnormal differentiation of bone marrow stem cells, increased adipogenesis, and decreased osteoblasts. Polg$^{mut/mut}$ premature aging mice: Mitochondrial dysfunction reduces number and osteogenic ability of osteoblasts, increases number and activity of osteoclasts, and increases ROS, leading to telomere dysfunction, chromosome fusion, and breakage. Lmna premature aging mice: *LMNA* mutation and deletion cause lamin A/C synthesis disorder, resulting in nuclear membrane structural changes, destruction of cellular functions, and extensive loss of osteocytes and osteoblasts. Sirt6 premature aging mice: Loss of sirt6 leads to uninhibited NF-κB signaling, with hyperactive NF-κB signaling potentially triggering premature aging. Zmpste24 premature senescence mice: Loss of Zmpste24 protease function, resulting in spontaneous fracture. Tfam premature senescence mice: Deletion or mutation of *TFAM* gene results in impaired mtDNA maintenance, transcription, and replication, inducing premature senescence in mice. Ercc1 premature senescence mice: *ERCC1* deficiency leads to persistent DNA damage and cellular senescence in primary osteoblasts and BMSCs. Werner premature aging mice: *WERNER* deletion causes telomere dysfunction, significantly up-regulated p21, and inhibited osteoblast differentiation. Klotho premature aging mice: Functional loss of Klotho in osteocytes impairs the biological effects of FGF23–induced Dkk1, resulting in Wnt pathway activation and increased osteoblast activity.

peptide-2 treatment attenuates bone loss in SAMP6 mice, as evidenced by increased BMD, improved femoral microarchitecture, and enhanced osteogenic activity (Huang et al., 2023). Human parathyroid hormone 1–34 (PTH 1–34), administered subcutaneously at 20 μg/kg three times per week for 12 weeks in SAMP6 mice, significantly reduces BMD loss and improves trabeculae microstructure and femoral epiphysis bone strength (Washimi et al., 2010). Similarly, low-dose PTH (10 μg/kg per day) administration in SAMP6 mice effectively promotes senescent bone loss, increases bone mass, and enhances bone formation by increasing osteoblast activity and modulating specific Wnt effectors, suggesting the therapeutic potential of intermittent low doses of PTH to increase bone formation activity in skeletal senescence

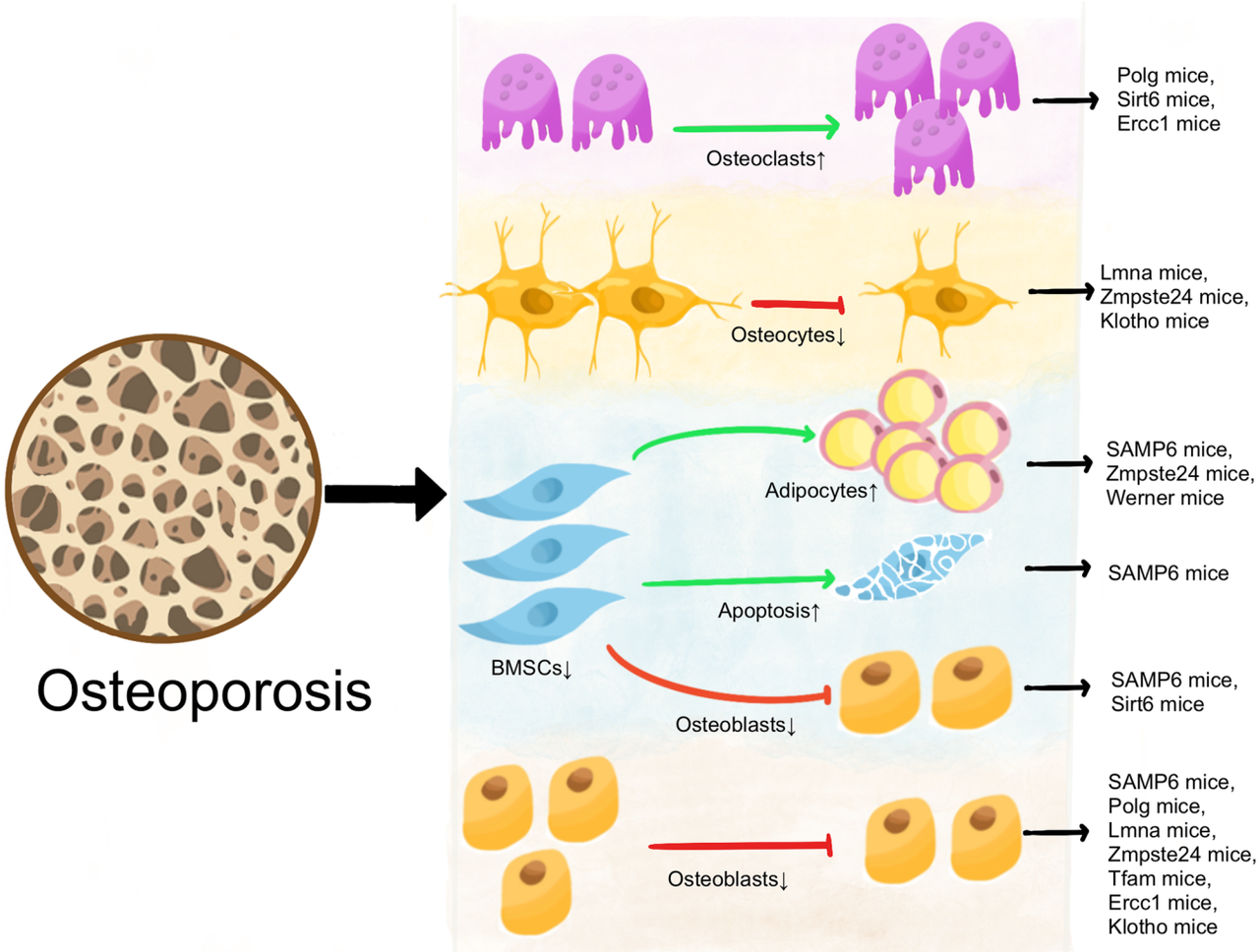

Figure 3 Pathological features of each premature aging mouse models

Polg, Sirt6, and Ercc1 mice show increased number of osteoclasts. Lmna, Zmpste24, and Klotho mice show reduced number of osteocytes. BMSCs in mice are also affected, with increased apoptosis, as in SAMP6 mice, increased adipogenic differentiation, as in SAMP6, Zmpste24, and Werner mice, and decreased osteogenic differentiation, as in SAMP6 and Sirt6 mice. Osteoblasts are also reduced in SAMP6, Polg, Lmna, Zmpste24, Tfam, Ercc1, and Klotho mice.

(Saidak et al., 2014).

In 100-day-old polg$^{mut/mut}$ mice, treatment with the mitochondrially targeted antioxidant 10-(6'-plastoquinonyl) decyltriphenylphosphonium cation (SkQ1) ameliorates most syndromes associated with polg dysfunction and significantly delays aging characteristics, resulting in increased bone mineral content from the scapula to lumbar spinal cord, reduced spinal kyphosis, and increased lifespan (Shabalina et al., 2017).

In the lmna mouse model, three main treatments are used. The first involves inhibiting IL-6 activity using tocilizumab, a neutralizing antibody against the IL-6 receptor, which counteracts the premature aging features in *LMNA G609G/G609G* mice. Notably, *in vivo* administration of tocilizumab improves osteoblast differentiation, Tb organization, and femoral biomechanical length in *LMNA G609G/G609G* mutant mice, while also preventing locomotor deficits and maintaining a good quality of life (Squarzoni et al., 2021). Additionally, bone defects associated with HGPS can be reversed by silencing the *LMNA* mutant gene at postnatal week 3, resulting in restored bone marrow and osteoclast activity and improved bone mineralization at 12 and 48 weeks. HGPS mice silenced at postnatal week 3 show faster improvement than those silenced at postnatal week 5, indicating that earlier suppression induces a greater chance of recovery (Strandgren et al., 2015). *In vivo* treatment of *LMNA* mutant mice with morpholino antisense-based oligonucleotides blocks pathogenic *LMNA* splicing and significantly reduces progerin accumulation and its associated nuclear defects (Osorio et al., 2011). Morpholinos are small modifying oligonucleotides that can block splicing events by preventing the splicing machinery from accessing the splice site (Parra et al., 2011).

Among the main treatments targeting sirt6 premature aging mice, metformin significantly promotes *SIRT6* expression and inhibits NF-kB phosphorylation during the proliferation and differentiation of mouse preosteoblasts (Mu et al., 2018). Additionally, pyrrolo[1,2-a]quinoxaline derivatives, synthesized as sirt6 activators, bind directly to the sirt6 catalytic core and activate sirt6-dependent deacetylation of peptide substrates and intact nucleosomes (You et al., 2017). Long-chain fatty acids have also been shown to effectively enhance SIRT6 enzyme activity (Feldman et al., 2013). Similarly, quercetin binds to SIRT6-selective acyl-binding channels at high concentrations, increasing SIRT6 activity (Rahnasto-Rilla et al., 2017; You et al., 2019).

Targeted treatments have been shown to improve skeletal symptoms in zmpste24-deficient mice. Notably, combining

pravastatin and zoledronate significantly improves HGPS phenotypes in Zmpste24–deficient mice, including growth retardation, weight loss, lipodystrophy, alopecia, bone defects, bone mineralization, and cortical thickness (Varela et al., 2008). Senolytic drugs, such as dasatinib, quercetin, and fisetin, effectively target and eliminate senescent cells, improving skeletal age-related degeneration in HGPS in Zmpste24 prematurely aging mice. Although dasatinib plus quercetin do not significantly attenuate Tb loss, fisetin reduces BMD loss in Zmpste24-deficient mice (Hambright et al., 2023). Inhibition of isoprenylcysteine carboxyl methyltransferase (ICMT) expression in Zmpste24$^{-/-}$ mice improves the disease phenotype, resulting in higher Tb.N, Tb.Th, BMD, bone volume, and bone content at 13–15 weeks of age (Ibrahim et al., 2013). Furthermore, Zmpste24-deficient mice treated with farnesyltransferase inhibitors (FTIs) (ABT-100) exhibit enhanced body weight, grip strength, bone integrity, and survival at 20 weeks of age (Fong et al., 2006).

Various methods can enhance the bone phenotype of ercc1$^{-/\Delta}$ mice. Notably, ercc1$^{-/\Delta}$ mice heterozygous for Atm exhibit significantly reduced NF-κB activity, decreased cellular senescence, improved myogenic stem/progenitor cell function, and attenuated age-related skeletal and intervertebral disc pathology, resulting in an extension of a healthy lifespan and improved bone quality, including reduced vertebral OP and Tb.Sp and increased TH.N (Zhao et al., 2020). Transplantation of BMSCs derived from young mice prolongs lifespan and health in ercc1$^{-/-}$ mice, as extracellular vesicles released by young BMSCs rescue cellular senescence and stem cell dysfunction in culture and reduce the senescent cell burden in vivo, effects not observed with BMSCs derived from old mice (Dorronsoro et al., 2021). Additionally, treatment with the HSP90 inhibitor 17-DMAG prolongs healthy lifespan, delays the onset of several age-associated symptoms, and reduces p16INK4a expression in ercc1$^{-/\Delta}$ mice (Fuhrmann-Stroissnigg et al., 2017).

Therapeutic approaches targeting werner premature aging mice primarily involve inhibiting the expression of specific genes. For instance, the absence of p16 significantly rescues the senescent phenotype of WS mice, as evidenced by reduced cellular senescence and apoptosis, along with increased telomere length and cell proliferation (Zhang et al., 2021a).

Regarding treatment of the Kl/Kl mouse bone phenotype, two approaches are used. Rapamycin, a general inhibitor of mTORC1 signaling, coordinates mTORC1 activity and autophagy in Kl/Kl mice, promoting BMSC rejuvenation, restoring the bone phenotype, and prolonging lifespan (Feng et al., 2023). Additionally, treatment with growth hormone increases trabecular volume and BMD in the tibial epiphyseal region of Klotho mice, although it does not improve osteoporotic alterations of cortical bone present in the mutant mice (Kashimada et al., 2002).

DISCUSSION

Skeletal system diseases are prevalent in aging populations. Many genes and signaling pathways are conserved between mice and humans, making mice excellent research models that can overcome many complex ethical issues involved in human aging research. As such, various prematurely aging mouse models have been established. Bone mass in naturally aging mice peaks between 4 and 8 months of age, then declines with age. However, SAMP6 mice develop spontaneous OP markedly earlier than naturally aging mice. Furthermore, polg$^{mut/mut}$ knockout mice exhibit a significant decrease in BMD at 40 weeks of age. Lmna knockout mice exhibit damaged cortical bone structure, defective bone mineralization, and disordered production of osteoblasts, osteoclasts, and osteocytes. Sirt6 knockout mice are characterized by substantial bone loss and impaired bone trabeculation. Zmpste24 knockout mice display frequent spontaneous fractures at 24–39 weeks. Tfam knockout mice are noted for short bones in the extremities, often accompanied by spontaneous fractures, bone hypoplasia, and significantly reduced bone matrix mineralization. *ERCC1* knockout mice exhibit severe and progressive OP, with significantly reduced bone volume, Tb.Th, and Tb.N and increased Tb.Sp. Aged werner knockout mice display a bone phenotype very similar to that of human age-related bone loss. Kl/Kl mice demonstrate osteopenia, OP, and disturbed production of bone-related cells, including osteocytes, osteoclasts, and osteoblasts.

While SAMP6 and Klotho mice both regulate osteogenesis via the Wnt signaling pathway, they also exhibit some differences. Notably, SAMP6 mice inhibit the Wnt signaling pathway by increasing the level of Sfrp4 to suppress the formation of osteoblasts (Haraguchi et al., 2016; Nakanishi et al., 2006). In contrast, defective *Klotho* in osteocytes impairs the biological effects of FGF23-induced Dkk1, resulting in Wnt pathway activation and increased bone formation in osteoblasts (Komaba & Lanske, 2018).

The bone phenotypes of naturally and prematurely aging mice show a declining trend in bone mass and quality from birth to a particular stage after reaching peak bone mass. In naturally aging mice, the decrease in bone mass post-peak is mainly due to aging-related factors, such as reduced bone turnover and bone mass loss due to defective osteoblast progenitor cells and impaired osteoblast differentiation or function. Prematurely aging mice have shorter lifespans than naturally aging mice, with bone aging caused by the loss of specific gene functions, leading to disrupted bone balance, bone formation disorder, and reduced bone mass. Although prematurely aging mouse models exhibit bone phenotypes similar to naturally aging mice, such accelerated aging models cannot fully recapitulate the pathogenesis of bone aging-related diseases. Therefore, appropriate mice must be selected for bone aging studies. For example, the *SAMP6* knockout mouse model is suitable for studying the mechanisms of OP, while *LMNA* knockout mice are ideal for researching the disease mechanisms of OP in patients with premature aging syndrome.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

L.L.Z. provided a brief introduction to this article. Q.G., Y.Z., Z.K.W., and X.H.L. were responsible for manuscript writing. Q.G. drew the figures. L.L.Z. and J.Z. revised the manuscript. All authors read and approved the final version of the manuscript.

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