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Mini Review

Aging of Osteochondral Tissue: Molecular Mechanisms Involved

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Abstract

Bone and cartilage, while exhibiting distinct structural and functional properties, originate from a common mesenchymal lineage and function as integrated components of the joint unit. Throughout aging, both tissues undergo parallel cellular and molecular alterations, including increased oxidative stress, persistent low-grade inflammation, and disrupted mechanotransductive signaling. These age-related changes progressively compromise tissue homeostasis, structural organization, and regenerative potential, thereby promoting the development of osteoarthritis and other degenerative joint disorders. Elucidating the convergent mechanisms underlying skeletal tissue aging may provide a foundation for novel, integrated therapeutic strategies targeting joint degeneration.

Keywords: *Bone; Cartilage; Inflammation; Osteoarthritis*

Introduction

The skeletal system is composed of mineralized tissues, such as bone, and non-mineralized connective tissues, including articular cartilage, which together ensure joint stability, mobility, and effective load distribution. Although bone is highly vascularized and cartilage is avascular, both tissues arise from mesenchymal progenitor cells and rely on a tightly regulated balance between anabolic and catabolic activities to preserve tissue integrity. During aging, this balance becomes increasingly disrupted, resulting in alterations in extracellular matrix composition, reduced cellular responsiveness, and impaired cross-talk between skeletal tissues. These changes collectively contribute to decreased mechanical resilience, compromised repair capacity, and progressive joint degeneration [1,2].

Bone and cartilage: Structure, function and aging

Bone tissue is a dynamic connective tissue that provides mechanical support, protects vital organs, and plays a crucial role in mineral homeostasis. Its structure is based on an organic matrix rich in type I collagen and an inorganic mineral component composed mainly of hydroxyapatite crystals. Bone cells include osteoblasts, osteoclasts, and osteocytes, which coordinate the continuous process of bone

remodeling. This tightly regulated balance between bone formation and resorption is essential for maintaining skeletal strength. With aging, bone remodeling becomes progressively unbalanced, primarily due to reduced osteoblast activity and increased or prolonged osteoclast-mediated resorption. Age-related hormonal changes, oxidative stress, and altered mechanical loading further impair bone formation and mineralization. In addition, aging is associated with changes in bone microarchitecture, particularly in trabecular bone, leading to decreased bone mass, reduced structural connectivity, and increased porosity. These alterations compromise the mechanical properties of bone, resulting in increased fragility and a higher risk of fractures in elderly individuals [3].

Articular cartilage is a specialized form of hyaline cartilage that covers the articular surfaces of synovial joints, ensuring low-friction movement and efficient load distribution. It consists of chondrocytes embedded in an extracellular matrix rich in type II collagen and proteoglycans, which provide tensile strength and resistance to compression [4]. The tissue is organized into distinct zones that reflect differences in cell morphology, collagen orientation, and biochemical composition. Articular cartilage has a limited regenerative capacity due to its avascular nature. Aging profoundly affects cartilage homeostasis by reducing chondrocyte density and metabolic activity, as well as their ability to maintain and repair the extracellular matrix. Age-related changes include decreased proteoglycan content, increased collagen cross-linking, accumulation of matrix damage, and reduced water retention. Furthermore, senescent chondrocytes exhibit altered responses to mechanical and inflammatory stimuli, promoting a catabolic environment within the joint. These degenerative processes reduce cartilage elasticity and resilience, contributing to progressive cartilage thinning and increasing susceptibility to degenerative joint diseases such as osteoarthritis [5]. Moreover, senescent chondrocytes also support the formation of an intra-articular inflammatory microenvironment through the secretion of SASP (senescence-associated secretory phenotype), which mediates crosstalk between senescent chondrocytes and neighboring cells and ultimately promotes neighboring cell senescence [6].

Methods

This mini-review is based on a critical synthesis of recent literature concerning cellular senescence, extracellular matrix alterations, and molecular signaling in bone and cartilage aging. Particular attention was given to studies exploring shared molecular pathways (Wnt/β-catenin, SIRT1, NF-κB, AMPK-(AMP-activated protein kinase)), the role of oxidative stress and inflammaging, and the mechanical and metabolic coupling between subchondral bone and articular cartilage (Table 1).

Aspects	Bone Aging	Cartilage Aging	Shared Mechanism
Cellular	↓ Osteoblast function, ↑ osteoclast activity	↓ Chondrocyte proliferation, ↑ senescence	SASP, oxidative stress
Matrix	Loss of collagen quality, ↑ AGEs	Loss of proteoglycans, ↑ AGEs	ECM stiffening
Mechanical	↓Mechanosensitivity (osteocytes)	↓ Mechanotransduction (chondrocytes)	Reduced adaptability
Vascular	Microvascular rarefaction	Nutrient diffusion decline	Bone-cartilage crosstalk
Molecular	↓ Wnt, SIRT1, AMPK	↓ SIRT1, AMPK	Shared signaling impairment
Outcome	Osteoporosis / sclerosis	Osteoarthritis	Joint frailty and degeneration

Table 1: *The role of oxidative stress and inflammaging and the mechanical and metabolic coupling between subchondral bone and articular cartilage.*

Cellular senescence and reduced regenerative capacity

With aging, osteoblasts, osteocytes, and chondrocytes exhibit a progressive decline in proliferative capacity, accompanied by the accumulation of senescent cells. Senescent skeletal cells acquire a senescence-associated secretory phenotype (SASP), characterized

by increased secretion of pro-inflammatory mediators such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α). This chronic inflammatory microenvironment promotes osteoclast-mediated bone resorption and cartilage matrix degradation, thereby establishing a self-perpetuating cycle of skeletal degeneration.

Skeletal stem and progenitor cells (SSPCs) comprise a heterogeneous population of cells that includes skeletal stem cells (SSCs), lineage-committed progenitors, differentiated chondrocytes, osteoblasts, osteocytes, and bone marrow adipocytes. SSCs represent tissue-specific stem cells located at the apex of the skeletogenic hierarchy and possess the capacity to differentiate into multiple skeletal lineages, including chondrocytes, osteoblasts, osteocytes, and marrow adipocytes. Within the bone marrow niche, distinct subsets of bone marrow stromal cells (BMSCs) exhibit SSPC-like potential and are distributed in a spatiotemporally regulated manner. Aging is associated with a shift in the differentiation potential of these progenitor populations, favoring adipogenic over osteogenic and chondrogenic lineages. This alteration in skeletal cell composition contributes significantly to impaired bone regeneration and overall tissue aging [7].

During endochondral ossification, tightly regulated chondrocyte proliferation, differentiation, and apoptosis are essential processes. In pathological contexts, such as post-traumatic osteoarthritis, mechanical injury and chondrocyte death lead to the release of danger-associated molecular patterns (DAMPs), which trigger inflammatory cascades that exacerbate cartilage degeneration. In bone tissue, inhibition of osteoblast apoptosis through overexpression of the anti-apoptotic protein BCL-XL has been shown to preserve bone mass and architecture during aging [8].

During normal skeletal development, pre-osteoblasts invade the zone of terminally hypertrophic chondrocytes in association with vascular ingrowth. Terminal hypertrophic chondrocytes subsequently undergo apoptosis or transdifferentiate into osteoblast-like cells, resulting in replacement of the hypertrophic cartilage matrix with bone tissue. Under physiological conditions, chondrocyte apoptosis is therefore largely restricted to the terminal hypertrophic zone and is minimal in the resting and proliferative zones of the growth plate [9].

Extracellular matrix deterioration

Both tissues experience qualitative changes in collagen and proteoglycans due to non-enzymatic glycation and oxidation. In bone, advanced glycation end products (AGEs) increase brittleness. In cartilage, AGEs and collagen fragmentation reduce elasticity and water content. This leads to impaired shock absorption and altered load transmission across the osteochondral unit [10].

Oxidative stress and mitochondrial dysfunction

Reactive oxygen species (ROS) accumulate with age, impairing mitochondrial function in both osteoblasts and chondrocytes. Reduced activity of SIRT1 and AMPK signaling diminishes autophagy, while increased NF-κB activation enhances inflammatory responses. These combined effects accelerate matrix degradation and cellular apoptosis [11-13].

Altered mechanotransduction

In young tissue, mechanical loading stimulates anabolic responses. With aging, osteocytes lose dendritic connectivity and mechanosensitivity, while chondrocytes show reduced responsiveness to growth factors such as IGF-1 and TGF-β. The consequence is a loss of adaptive remodeling capacity in both bone and cartilage [14].

Bone-cartilage crosstalk

Although cartilage is avascular, it relies on diffusion from the subchondral bone microcirculation. Age-related vascular rarefaction and subchondral sclerosis limit nutrient exchange, exacerbating cartilage degeneration. Dysregulation of shared signaling molecules (sclerostin, RANKL, Wnt, BMPs) further disturbs the mechanical and biochemical dialogue between both tissues [15].

Vascular and metabolic interactions

Although articular cartilage is avascular, its health depends on the subchondral bone microcirculation. Age-related vascular rarefaction and sclerosis in the subchondral plate lead to nutrient diffusion impairment toward cartilage, contributing to degeneration. Simultaneously, altered bone-cartilage crosstalk through signaling molecules (e.g. sclerostin, RANKL, Wnt, BMPs) plays a critical role in the parallel deterioration of both tissues [16].

Hormonal and systemic influences

Decline in estrogen, vitamin D, and IGF-1 contributes to joint aging. Estrogen deficiency increases both bone resorption and chondrocyte apoptosis, while reduced $1,25(OH)_2D_3$ impairs matrix synthesis. These systemic factors link osteoporosis and osteoarthritis as parallel manifestations of skeletal aging [17].

Conclusion

Bone and cartilage aging are interdependent processes governed by common molecular and biomechanical mechanisms. Cellular senescence, oxidative stress, inflammaging, and altered mechanotransduction collectively reduce tissue resilience and regeneration. Targeting shared signaling pathways, such as SIRT1/AMPK activation, NF-κB inhibition, and Wnt pathway modulation may represent promising strategies for preserving joint health during aging. Future research should focus on integrated osteochondral models to better understand and counteract age-related degeneration.

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