Do the Age-Related Changes in the ECM Promote Chondrocyte Senescence or Does Chondrocyte Senescence Promote Age-Related Changes in the ECM?

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Response/Recommendation: Unknown. Therefore, it is critical to investigate chondrocyte mechanical signaling together with concomitant changes in the structural and mechanical integrity of the extracellular matrix (ECM) and, where possible, the pericellular matrix (PCM), in the context of aging, chondrocyte senescence, and age-associated osteoarthritis (OA).

Level of Evidence: Low

Daily joint function relies on the proper assembly and mechanical properties of the cartilage extracellular matrix (ECM), a hydrated composite consisting primarily of a collagen II fibrillar network that entraps the densely packed large proteoglycan, aggrecan.[1] Chondrocytes are responsible for the establishment and maintenance of the ECM, whereas their balanced anabolic and catabolic activities preserve ECM homeostasis. In turn, the ECM provides the biochemical and biophysical environment that allows chondrocytes to sense and respond to external cues.[2] Aging is associated with concomitant changes in intrinsic cellular activities and ECM integrity, resulting in increased chondrocyte senescence and impaired ECM function.[3] To date, understanding of age-related molecular changes within the ECM and their reciprocal effects on chondrocyte aging and senescence remains limited.

Aging-Associated Changes in the ECM.

Chondrocyte senescence drives a metabolic shift from an anabolic to a more catabolic state.[3] After cartilage matures in adulthood, aggrecan undergoes active turnover (half-life ≈ 3.5 years in bulk ECM,[4] and as short as ≈ 10 days in the pericellular domain)[5] yet aging does not markedly reduce aggrecan core protein expression (*ACAN*).[6] In contrast, collagen II fibrils exhibit low expression and minimal turnover once formed (half-life > 100 years).[7] In contrast to its limited impact on gene expression of *COL2A1* and *ACAN*, aging exhibits a much stronger impact on their post-translational modifications during biosynthesis. Aggrecan shows reduced sulfation due to altered biosynthetic processes, leading to decreased length and packing density of chondroitin sulfate glycosaminoglycans (CS-GAGs),[8] as well as a shift in sulfation pattern from C4S to C6S. Meanwhile, increased or sustained expression of lysyl oxidase (LOX) may enhance collagen cross-linking, potentially stiffening individual fibrils.[9] On the catabolic side, aging chondrocytes exhibit persistent release of degradative enzymes such as matrix metalloproteinases (MMPs),[10] along with increased sensitivity to inflammatory cytokines[11] and decreased response to growth factors,[12] tipping the metabolic balance toward matrix degradation.

Beyond cellular changes, the ECM itself undergoes compositional and structural alterations driven by extracellular molecular processes. Under normal homeostasis, fragmented aggrecan gradually accumulates. Reduced aggrecan GAG length, density, and cumulative fragmentation decrease fixed charge density, osmotic pressure and associated nano-scale GAG-GAG repulsion,[13] which in turn reduce the compressive modulus and poroelastic energy dissipation governed by hydraulic permeability.[14] These changes also lower the inherent pre-tension of collagen II fibrils, thereby reducing the apparent stiffness of the fibrillar network.[15] Accumulation of collagen II neo-epitopes further indicates fibrillar degradation, which likely also contributes to reduced fibril stiffness.[16] On the other hand, other molecular processes, such as the increased LOX-mediated cross-linking and associated accumulation of advanced glycation end products (AGEs), may stiffen collagen fibrils and increase their brittleness.[17]

Because tissue-level mechanical behavior reflects the integrated effects of molecular and structural factors across multiple length scales, the net impact of these molecular changes on cartilage mechanical properties are complex. To date, quantitative studies of cartilage mechanics have not shown a consistent trend toward tissue-level stiffening with natural aging. Some reported decreased modulus in human[18,19] and murine[20] cartilage, while others find no significant changes in rats during the normal aging process.[21,22] However, in more advanced degenerative states in OA, cartilage may lose its

hyaline traits and undergo phenotypic changes such as fibrosis, which could lead to an increase in apparent modulus but does not indicate an improvement of tissue function.[23] Collectively, while age-associated changes in cellular activity and ECM molecular composition progressively impair ECM integrity, the net mechanical outcome depends on the phenotypic state and degree of degeneration of cartilage.

ECM Impacts on Chondrocyte Mechanosensitive Signaling.

Given the mechanosensitive nature of chondrocytes, alterations in the ECM are expected to substantially affect chondrocyte behavior and signaling. However, the mechanobiological mechanisms governing reciprocal cell-matrix interactions remain poorly understood. Although it is well established that aged cartilage is more susceptible to osteoarthritis (OA) onset, the specific role of the aged ECM in mediating this susceptibility remains to be elucidated. During aging, chondrocytes exhibit altered mechanosensitive signaling, including dysregulation of RhoA/ROCK,[24] YAP/TAZ[25] and NF-κB[9] pathways, and reduced production of protective proteins such as α-Klotho[26] and the mechanobiological regulator kindlin-2.[27] These changes have been hypothesized to result from ECM stiffening driven by increased LOX-mediated collagen cross-linking.

Despite these insights, aging-associated ECM changes remain incompletely understood, particularly within the pericellular matrix (PCM), the microniche immediately surrounding chondrocytes. The PCM is directly responsible for transmitting biochemical and biomechanical cues to chondrocytes and is highly sensitive to cellular signaling changes.[2] Given that the PCM exhibits faster aggrecan turnover[5] and high susceptibility to catabolic enzymes,[28] it is also considered a disease initiation site in post-traumatic OA models.[29] Alterations in the PCM play a key role in cell-matrix mechanosensing and in the transmission of stress and strain to chondrocytes, contributing to the vicious cycle of cartilage degeneration.[29] Although reductions in PCM micromodulus have been observed in both human and murine models,[29,30] no direct studies have characterized how PCM structural integrity and micromechanics change during natural aging. In the context of aging, further work is needed to rigorously assess structural and mechanical changes in both the bulk ECM and the PCM, and to determine how altered chondrocyte mechanosensitive signaling is modulated by specific changes in ECM structural integrity, mechanics, and in particular, PCM micromechanics, as these all relate to senescence.

Future Directions.

Given the reciprocal interactions between chondrocytes and the ECM, a comprehensive approach is needed to understand how specific cellular or molecular factors regulate cartilage aging:

1. Chondrocyte mechanosensing and signaling in situ: Characterizing chondrocyte behavior, including short-term mechanosensing (e.g., calcium signaling) and transcriptomic responses.
2. ECM integrity and mechanics: Direct assessment of ECM properties, including fibrillar cross-linking, architecture, proteoglycan content, mechanical function, and where possible, PCM integrity and quality.
3. In vitro validation: Using 3D chondrocyte culture systems to test specific hypotheses by assessing cell activities, neo-ECM quality, and their interplay.

Conclusion.

Aging exerts complex effects on ECM mechanical function through alterations in anabolic-catabolic balance, post-translational modifications, and cumulative matrix changes that occur during normal homeostasis. The ECM plays a central role in regulating chondrocyte mechanosensitive signaling, yet the underlying mechanisms require further investigation. Integrated studies that connect senescence-associated cellular changes with reciprocal ECM-cell interactions will be essential for understanding and ultimately mitigating age-associated cartilage degeneration.

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