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A Brief Review of Cellular and Molecular Changes in Chondromalacia

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ABSTRACT

Aims: Chondromalacia is a condition that transparent cartilage on the surface of a bone joint turns soft and swollen and followed by the fibrillation, and degeneration of the cartilage. Its exact cause is unknown. We decided to review the existing literature on cellular and tissue changes in cartilage and use them to help future studies in chondromalacia.

Method and Materials: In this research, a comprehensive search was conducted until March 2025 across databases such as Web of Science, Science Direct, Scopus, Magiran, PubMed, and Google Scholar. The search employed keywords including chondromalacia, articular cartilage, genetics, Extra Cellular Matrix (ECM), chondroitin sulfate, proteoglycan, collagen, mitochondrial dysfunction, and the Ubiquitin-Proteasome System (UPS).

Findings: Chondromalacia represents a critical early stage in joint degeneration that, if left untreated, has the potential to progress to severe joint damage. Early diagnosis and treatment are essential for a good prognosis in patients with chondromalacia and can prevent more serious joint problems.

Conclusion: Studying the molecular system of articular cartilage will not only reveal new pathways that influence the development of cartilage-related diseases, but also pave the way for new therapeutic approaches.

Keywords: Chondromalacia, Genetic, Articular Cartilage, Extra Cellular Matrix (ECM)

Introduction

Most joints in the body are lined with a kind of tissue known as articular cartilage (hyaline cartilage). This resilient, elastic tissue coats the ends of the bones within the joint. As the joint operates, the cartilage aids the bones and enables them to glide smoothly past one another. Articular cartilage is a uniquely specialized tissue that offers a low-friction surface for movement in joints. It comprises a dense Extra Cellular Matrix (ECM) alongside specialized cells referred to as chondrocytes, which make up about 1–5% of the cartilage's volume. These cells are responsible for maintaining the joint cartilage by synthesizing collagen and the extracellular matrix. Because of the lack of blood vessels, nerves, and lymphatic tissue, it has a poor self-repair capacity, and therefore damage to cartilage is a factor in the progression to joint problems [1]. At times, the hyaline cartilage that covers the articular surfaces of bones within a joint may soften and deteriorate. This issue is referred to as chondromalacia. Chondromalacia can occur in any joint, particularly those that have experienced trauma or deformities, such as the knee and patella [2].

Chondromalacia is a condition characterized by the cartilage on the surface of a bone joint becoming dull or even somewhat yellowish-white, as well as soft and swollen, ultimately leading to fibrillation, fissures, fragmentation, or erosion of the cartilage. This can result in joint pain, particularly during physical activities [3]. Chondromalacia predominantly involves the extensor mechanism of the knee joint and is therefore frequently designated as patellar chondromalacia, runner's knee, or patellofemoral pain syndrome. The Outerbridge classification scale is widely employed to evaluate the extent of chondromalacia. This system of

classification is predicated on the identification of various degenerative processes of differing severity within a knee joint, thereby facilitating the categorization of cartilage degeneration into four distinct degrees of progression.

The precise etiology of chondromalacia remains elusive; however, several risk factors have been identified, including obesity, diminished strength of lower extremity musculature, female sex, repetitive strain, misalignment, trauma or injury, arthritic conditions, as well as both molecular and cellular alterations, alongside genetic predispositions. Furthermore, the presence of patellar malignancies may play a role in the pathogenesis of chondromalacia patella [4].

Few studies have been conducted on cellular and molecular changes in chondromalacia, but there have been studies on some other diseases related to articular cartilage, such as rheumatoid arthritis and osteoarthritis. We decided to review the existing literature on cellular and tissue changes in cartilage and use them to help future studies in chondromalacia. The objective of this research is to explore the genetic, cellular and molecular changes of cartilage in chondromalacia. Studying the molecular system of articular cartilage will not only reveal new pathways that influence the development of cartilage-related diseases, but also pave the way for new therapeutic approaches.

Genetic

Genetic factors can contribute to the development of this condition. Some people may have a genetic predisposition to cartilage disorders or structural abnormalities in the knee and other joints that can lead to chondromalacia.

Molecular biology techniques, such as single-gene analysis via polymerase chain reaction or genome-wide analysis through microarrays, can be utilized to identify the molecular markers linked to the onset of chondromalacia. Additionally, methods in bioinformatics and computational biology, including meta-analysis and association studies, can also be employed for this purpose [5, 6].

Changes in the genome and transcriptome have been documented for many cartilage disorders, particularly OsteoArthritis (OA) and Rheumatoid Arthritis (RA). However, research on genetic variations contributing to individual differences in vulnerability to chondromalacia is limited. A genome-wide association study identified notable links with genetic markers in the Rho GTPase Activating Protein 15 (ARHGAP15) and Melanoma Associated Antigen C2 (MAGEC2) genes. This research revealed two SNPs (rs188900564 and rs144449054) that showed genome-wide significant associations with chondromalacia, enhancing our understanding of the genetic mechanisms underlying this condition [7].

ARHGAP15 functions in a signaling pathway involved in cell motility, cell cycle progression and cytoskeleton reorganization. ARHGAP15 is expressed in various tissues, including bone marrow, skeletal muscle and in B and T cells of the immune system, indicating a role in mediating inflammation, leading to chondromalacia. Overexpression of ARHGAP15 can cause an increase in actin stress fibers and cell contraction [7-9].

The MAGEC2 gene, which enhances the activity of E3 ubiquitin-protein ligases act as an intermediary protein turnover. This gene is not found in normal tissues, apart from the testis, but is present in tumors of different histological types. The genes are located in a cluster on chromosome Xq26-q27. While its biological function is established, the way MAGEC2 impacts chondromalacia remains unclear. Kim et al. proposed that rs188900564 influences the activity of a nearby gene on the X chromosome, rather than MAGEC2, indicating that further research in this area is needed [7].

Articular cartilage structure

There are three types of cartilage found in the body, with articular cartilage being the most prevalent. This type of cartilage serves as a covering for the ends of long bones where movable joints are located. Due to its absence of blood vessels, articular cartilage has a limited ability to regenerate and cannot heal itself [10]. Articular cartilage is composed of an organized ECM of collagen fibers, non-

collagenous proteins, polysaccharides, proteoglycans, and glycoproteins, although 68 to 85 percent of the total weight of the ECM is water [10, 11].

In total, articular cartilage has four layers, which include the superficial zone, the intermediate zone, the deep zone, and the calcified zone. The surface zone lies directly beneath the adjacent surface of the intermediate zone and synovial fluid. This zone contains high-density flattened chondrocytes and collagen fibers parallel to the joint surface [12]. The middle layer is situated beneath the superficial layer. This section consists of denser collagen fibers organized in a random pattern and features low-density rounded cartilage [12]. The deep zone contains 30% to 40% of the chondrocytes arranged in columns perpendicular to the joint surface. Parallel to the cartilage columns in this layer are thick collagen fibers [12]. The calcified region is a narrow layer of mineralized tissue situated between the articular cartilage and the subchondral bone [13].

In chondromalacia, few studies have been conducted on cellular and molecular changes of cartilage structure. Previous studies focused on patellar chondromalacia and have shown that localized lesions in the patellar cartilage have similarities between chondromalacia and osteoarthritis, but in young people, where articular cartilage degeneration occurs due to abnormal mechanical force, the mixed conditions of destruction and repair lead to repair. In contrast, degeneration in the cartilage of patients with osteoarthritis is regressive and presents a completely different histological picture from that of chondromalacia [14].

Chondrocyte

Cartilage is made up of chondrocytes that are responsible for maintaining the ECM and generating the cartilage matrix. Chondrocytes support the cartilage tissues found in joints by producing collagen and the extracellular matrix.

Aging is a contributing factor to the onset of chondromalacia. Changes in articular cartilage associated with aging are linked to the reduced sensitivity of chondrocytes to growth factors, abnormal buildup of Advanced Glycation End products (AGEs), mitochondrial dysfunction, oxidative stress, and a decline in proteostasis [15]. Each of these factors related to aging will be discussed further below.

Loos of proteostasis

A key feature of cellular aging is the decline in proteostasis, which is linked to a dysfunctional Ubiquitin-Proteasome System (UPS), issues with protein folding, and impaired autophagy. Diminished proteostatic function impacts cellular differentiation, survival, and inflammatory responses. In fact, a reduction in proteasomal activity within human chondrocytes can lead to lower levels of certain critical factors essential for the function and maintenance of chondrocytes, such as sox9 and Aggrecan [16].

Changes linked to cellular aging also involve a reduction in the expression of molecular chaperones, leading to stress in the endoplasmic reticulum and cell death in articular cartilage. This occurs after the disruption of proteostasis in the cells of articular cartilage [17].

Another result of loss of proteostasis is the compromise of autophagy pathways. Autophagy is a protective and homeostatic mechanism in normal cartilage, particularly in modulating cellular responses to stress. If autophagic pathways are interrupted, cells may undergo apoptosis, finally leading to cartilage degeneration [18]. Essential regulators of autophagy like Autophagy-related protein-7 (regulator of autophagosome assembly) [19] and key bioenergy sensors such as Sirtuin 1 (Sirt1) and the Active adenosine Monophosphate-activated Protein Kinase (AMPK) signaling pathway [20] can leads to defective chondrogenesis and chondrocyte function [21].

Alternatively, an overactivation of autophagy in chondrocytes contributes to cartilage dysfunction, a phenomenon that remains unclear[22]. Nonetheless, gaining insight into the function of autophagy in chondrocytes appears to hold significant promise for addressing chondrocyte aging and could ultimately serve as an effective treatment

strategy for cartilage and bone disorders.

Mitochondrial dysfunction

Mitochondria play a critical role in providing energy for cells through their vital function of generating Adenosine Triphosphate (ATP) from glucose. When mitochondrial function is impaired, it can disrupt the balance between glycolysis and oxidative phosphorylation, ultimately affecting ATP production, which can lead to permanent changes in metabolism and energy generation. This situation also applies to chondrocytes; when there is mitochondrial dysfunction, it not only hampers ATP production but also disrupts the regulation of various cellular processes, including redox balance, calcium ion (Ca2+) homeostasis, signaling for cartilage cell death, mitochondrial biogenesis, extracellular protein synthesis, and the stability of the extracellular matrix [23]. Research has indicated that abnormalities in mitochondrial function contribute to the development of cartilage-related conditions, including osteoarthritis, degeneration of cartilage, and growth retardation associated with cartilage [23].

Mitochondrial dysfunction can result from mutations in mitochondrial DNA (mtDNA) or in nuclear genes that encode for mitochondrial components. Additionally, it may arise from the negative effects of medications, infections, or the indirect impact of Nitric Oxide (NO), pro-inflammatory cytokines, prostaglandins, and Reactive Oxygen Species (ROS) on the function of the mitochondrial respiratory chain and the synthesis of ATP, leading to cellular dysfunction. In chondrocytes, mitochondrial dysfunction influences various physiological processes, including chondrocyte apoptosis, the generation of oxidative stress, inflammation in chondrocytes induced by cytokines, calcification of the ECM, and the breakdown of the matrix. A rise in ROS and a reduction in superoxide dismutase contribute to mitochondrial dysfunction in chondrocytes. When the production of ROS surpasses the antioxidant capacity of chondrocytes, oxidative stress emerges, leading to disturbances in the Mitochondrial Respiratory Chain (MRC) protein complexes, reduced ATP synthesis, energy storage depletion, compromised matrix synthesis function, and lower chondrocyte viability [24].

Mitochondrial respiratory chain dysfunction occurs with the production of matrix metalloproteinase and pro-inflammatory stimuli, which cause the release of catabolic glycosaminoglycan, thereby disrupting the homeostatic balance of healthy cartilage and increasing cartilage destruction. Direct MRC analysis of chondromalacia chondrocytes has not been performed, butDysfunction in the mitochondrial respiratory chain leads to the production of matrix metalloproteinases and pro-inflammatory signals, which result in the release of catabolic glycosaminoglycans, disrupting the homeostatic equilibrium of healthy cartilage and promoting cartilage degradation. While direct analysis of mitochondrial respiration in chondromalacia chondrocytes has not yet been conducted, research in osteoarthritis has indicated that the activities of complexes I, II, and III, as well as $\Delta\Psi m$, are notably lower in comparison to normal chondrocytes [25, 26]. These attenuations lead to an increase in mitochondrial mass, serving as a compensatory mechanism for diminished electron transport and a subsequent decrease in ATP synthesis. Lower MRCactivity also leads to heightened levels of the inflammatory cytokines TNF-α and IL-1β [27]. Research has indicated that the inhibition of MRC leads to an increased expression of Prosta Glandin E2 (PGE2), a key mediator of inflammation, along with Cyclooxygenase (COX)-2, which is an enzyme that produces prostanoids, in chondrocytes, as well as heightening the inflammatory response to cytokines [28, 29].

AMPK and Sirt1 maintain biological homeostasis in metochondria by suppressing oxidative stress, deregulation of several inflammatory and catabolic responses and suppressing NF-kB activation [30].

Notably, activation of the AMPK/Sirt1/PGC-1a signaling pathway mediated by mitochondrial transcription factor A (TFAM) reverses the impaired mitochondrial biogenesis capacity in cartilage in osteoarthritis patients. However, activation of this pathway has not yet been

validated therapeutically [31].

Other changes resulting from mitochondrial dysfunction in cartilage chondrocytes include inflammatory responses and matrix degradation, which occur through ROS-mediated activation of Mitogen-Activated Protein Kinase (MAPK)/cFos-AP1 [32].

Collagen

Collagen is the primary ECMcomponent that organizes itself into cross-striated fibrils, playing a crucial role in facilitating cell growth and ensuring the mechanical strength of connective tissues. Collagen is classified as a glycoprotein and features a distinctive right-handed triple helix structure. This unique configuration is essential for collagen's functions, such as providing elasticity, enhancing bone strength, offering stability and support to cells and tissues, and forming basement membranes, while also impacting biological processes, including cell signaling, differentiation, and motility [33].

Articular cartilage contains many different subtypes of collagen. Healthy hyaline cartilage in joints primarily consists of three main types of collagen (types II, IX, and XI) along with several minor types (types III, IV, V, VI, X, XII, XIV, XVI, XXII, and XXVII). Importantly, type I collagen can be detected in damaged articular cartilage [34].

Research indicates that in chondromalacia, the collagen framework progressively diminishes as the condition worsens, and the extracellular matrix is significantly diminished. However, the biochemical alterations in collagen levels and collagen cross-linking are not marked and are likely not the main contributors to the development of chondromalacia [35].

In chondromalacia, Väätäinen and colleagues discovered that using polarized light microscopy revealed a reduction in birefringence in the upper cartilage of chondromalacia lesions, suggesting a disorganization or loss of collagen fibers in that region. They determined that the collagen framework showed a gradual disorganization correlating with the severity of the patellar chondromalacia lesion, while no alterations in collagen concentration or cross-linking were observed. Research related to osteoarthritis and rheumatoid arthritis indicates that enzymes such as Matrix Metallo Proteinases (MMPs) and cathepsins significantly contribute to cartilage damage through collagen degradation. Specifically, the roles of MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, and MMP-14 in cartilage degeneration have been highlighted. It appears that the activity of these enzymes is also modified in chondromalacia, which necessitates further investigation in this area [35].

Proteoglycan

Proteoglycans are important elements of the cartilage extracellular matrix and play a vital role in the proper functioning of tissue. These molecules consist of a core protein attached to glycosaminoglycan chains. Cartilage proteoglycans are primarily classified into two major families: the Lectican family and the small leucine-rich repeat proteoglycan family. The lectican family encompasses aggrecan, versican, and cartilage junction protein. The small leucine-rich repeat proteoglycan family consists of asporin, biglycan, decorin, lumican, fibromodulin, osteoadherin, proline-/arginine-rich and leucine-rich repeat protein, epiphycan, mimecan, keratocan, opticin, chondroadherin, and chondroadherin-like [36].

Aggrecan is the main type of proteoglycan located in articular cartilage, but in young cartilage, comparable levels of aggrecan, biglycan, and decorin exist at a molecular level [37]. In healthy cartilage, proteoglycans help safeguard the collagen framework under stress. However, in cases of chondromalacia, the articular cartilage undergoes fibrillation, leading to a decreased ability of the collagen structure to retain water-bound proteoglycans within the matrix [35].

Chondroitin sulfate

Chondroitin sulfate is a sulfated glycosaminoglycan that is composed of a long unbranched polysaccharide chain with a repeating disaccharide of N-cetylgalactosamine and glucuronic acid. Chondroitin sulfate has the potential of regulating cartilage formation. In diseases of cartilage destruction, chondroitin

sulfate exhibits anti-inflammatory properties. In fact, chondroitin sulfate is effective in cartilage regeneration and reducing inflammation[38, 39].

In fibrillated lesions of chondromalacia, the concentration of proteoglycans is reduced to 15% of that of normal healthy cartilage [40]. This weakens the rigidity of the articular cartilage, potentially leading to the degradation of the collagen framework and exacerbating the condition. Nonetheless, despite the decrease of proteoglycans in chondromalacia patellae, the levels of hydroxy lysyl pyridinoline cross-links stay consistent.

Conclusion

Chondromalacia represents a critical early stage in joint degeneration that, if left untreated, has the potential to progress to severe joint damage. Early diagnosis and treatment are essential for a good prognosis in patients with chondromalacia and can prevent more serious joint problems. For diagnosis and treatment, we need to understand the cellular and molecular changes of chondromalacia. Current evidence emphasizes that its pathogenesis involves genetic predisposition (such as ARHGAP15/MAGEC2 variants), cellular senescence (loss of proteostasis, mitochondrial dysfunction), and ECM degradation (collagen disorganization, proteoglycan depletion). However, significant knowledge gaps remain, particularly in distinguishing the specific pathways of chondromalacia from those of osteoarthritis or rheumatoid arthritis. Few studies have been conducted in this area, and more studies are needed.

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Author Contributions

MM was the principal investigator and collected the data, analyzed it, and wrote the initial draft. AJ and MH supervised the study. All authors approved the study.

Conflict of Interest

The authors declared there is no conflict of interest for this study.

Ethical Permission

All ethical principles were considered in this study.

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