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Osteoarthritis as a disease of the cartilage pericellular matrix

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Abstract

Osteoarthritis is a painful joint disease characterized by progressive degeneration of the articular cartilage as well as associated changes to the subchondral bone, synovium, and surrounding joint tissues. While the effects of osteoarthritis on the cartilage extracellular matrix (ECM) have been well recognized, it is now becoming apparent that in many cases, the onset of the disease may be initially reflected in the matrix region immediately surrounding the chondrocytes, termed the pericellular matrix (PCM). Growing evidence suggests that the PCM – which along with the enclosed chondrocytes are termed the “chondron” – acts as a critical transducer or “filter” of biochemical and biomechanical signals for the chondrocyte, serving to help regulate the homeostatic balance of chondrocyte metabolic activity in response to environmental signals. Indeed, it appears that alterations in PCM properties and cell-matrix interactions, secondary to genetic, epigenetic, metabolic, or biomechanical stimuli, could in fact serve as initiating or progressive factors for osteoarthritis. Here, we discuss recent advances in the understanding of the role of the PCM, with an emphasis on the reciprocity of changes that occur in this matrix region with disease, as well as how alterations in PCM properties could serve as a driver of ECM-based diseases such as osteoarthritis. Further study of the structure, function, and composition of the PCM in normal and diseased conditions may provide new insights into the understanding of the pathogenesis of osteoarthritis, and presumably new therapeutic approaches for this disease.

Keywords

Chondron; chondrocyte; type VI collagen; perlecan; aggrecan; osteoarthritis; territorial matrix; decorin; mechanobiology; mechanotransduction; extracellular matrix; intervertebral disc; meniscus

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Introduction

Under normal physiologic circumstances, articular cartilage functions as a nearly frictionless surface while exposed to loads of several times body weight. This remarkable function is attributed to the unique structure and composition that determine the mechanical properties of the cartilage extracellular matrix (ECM). The ECM of articular cartilage is primarily water (60–85% by wet weight). The remaining solid matrix is composed of a crosslinked network of type II collagen (15–22% by wet weight), proteoglycans (4–7% by wet weight), and lesser amounts of several important other collagens (e.g., VI, IX, X, XI) and non-collagenous proteins [1, 2]. The constituents of articular cartilage are organized in a complex porous and permeable ECM that provides the unique capabilities for fluid-pressurization that allow for the long-term load-bearing capabilities of the joint. Under pathologic conditions, such as osteoarthritis, however, the ECM exhibits a myriad of changes in its mechanical function that are associated with increased catabolic activity and inflammation in the joint. In this regard, the role of the ECM in osteoarthritis has been extensively studied and reported in several previous reviews [3–8].

The chondron: The chondrocyte and its pericellular matrix

The ECM changes in osteoarthritis appear to be driven by an imbalance of anabolic and catabolic activities of the chondrocytes, the cell population within articular cartilage. Within the cartilage ECM, chondrocytes are surrounded by a narrow matrix region that is compositionally and structurally distinct from surrounding bulk ECM. This unique region is approximately 2 to 4 μm thick and is called the “pericellular matrix” (PCM) (Figure 1). The PCM then integrates with the surrounding tissue via the “territorial matrix,” connecting the PCM to the “interterritorial matrix” (i.e., the ECM). Together, the chondrocyte and its PCM have been termed the “chondron” [9–12]. This name was derived from “chondrone”, which was coined by Benninghoff in the early 19th century when he observed the altered matrix structure around chondrocytes via polarized light [13]. However, little direct research on the PCM was reported until it was discovered that intact chondrons could be retrieved as a by-product of cartilage homogenization [14]. Using this method, a number of seminal studies were performed by Poole and co-workers to provide the first reports on the composition, metabolic activity, and structure of the PCM [11, 15]. Chondrons were found to contain large amounts of proteoglycans and collagen types II, VI, and IX. Further examination showed that the PCM can be defined primarily by the presence of type VI collagen, fibronectin 1, and the proteoglycans perlecan and biglycan [11, 15–17].

The function of the PCM and chondron

Significant evidence is now accumulating on the important role of the PCM (and chondron) in regulating the function of the chondrocyte (reviewed in [18, 19]). As every chondrocyte is surrounded by this tissue region, any chemical or physical signals that the chondrocyte perceives may be modulated by the PCM. Although the complete role of the PCM remains to be elucidated, it is apparent that the PCM can serve as a transducer, or “filter,” of both biomechanical and biochemical signals for the chondrocyte [20–23] (Figure 1). Data from a variety of theoretical models and experimental studies of the PCM and cell-matrix

interactions indicate that the presence and properties of the PCM can regulate mechanical and physiochemical environments in cartilage, influencing chondrocyte physiology and cartilage ECM homeostasis [24–38]. By modulating the stress-strain, osmotic, and fluid-flow environments of the chondrocyte, the PCM is believed to serve as an additional regulator of the chondrocyte mechanotransduction process [39–41].

In addition to these biomechanical and mechanobiologic roles, the PCM can regulate cell-matrix ligand binding, growth factor and enzyme sequestration, transport, assembly, and activation, thus influencing major aspects of ECM turnover in cartilage [42, 43]. The presence of a PCM significantly influences chondrocyte gene expression and response to mechanical loading [44–46], while PCM retention and sequestration of various growth factors may play an important role in regulating chondrocyte activity [21, 47–49]. The critical role of the PCM has been recently highlighted in a review of the various protective effects that it may have against the development of osteoarthritis [19]. Thus, it is apparent that alterations in PCM properties, secondary to genetic, epigenetic, metabolic, or biomechanical stimuli, could in fact serve as initiating or progressive factors of osteoarthritis.

The mechanical properties of the pericellular matrix

Over the past two decades, a variety of techniques have been pioneered to quantify the biomechanical and physical properties of the PCM, using either mechanically or enzymatically isolated chondrons, or *in situ* testing methods that combine experimental microscopy and computational modeling (reviewed in [18]). For example, physically extracted chondrons have been tested using osmotic swelling [25, 34], deformation within hydrogels [33, 34, 50], or individual chondron testing using compression [51–53] and micropipette aspiration [54–58]. More recently, methods have been developed for the direct quantification of PCM properties *in situ* through the application of osmotic swelling and 3D confocal microscopy [59] or atomic force microscopy (AFM)-based microindentation [60–67]. With this method, AFM-stiffness mapping showed comparable values for PCM properties as compared to other methods such micropipette aspiration [55] or combined computational modeling and 3D microscopy [68]. These studies have shown that the moduli of the PCM (Young's moduli, $E_Y \sim 40 – 100$ kPa) are two orders of magnitude greater than those of chondrocytes ($E_Y \sim 0.5$ kPa) [54, 69] but as much as an order of magnitude lower than those of the surrounding ECM, depending on the zone of cartilage (aggregate modulus, $H_A \sim 0.1 – 2$ MPa) [70]. With the growing prevalence of mouse models in cartilage and osteoarthritis research, recent studies have shown that the Young's moduli of murine PCM (300 – 1000 kPa) is much higher than that of human PCM, while the surrounding ECM (0.5 – 2 MPa) is similar human values [59, 71]. These differences in mechanical moduli implicate the PCM as a crucial transducer or filter of mechanical signals to the chondrocyte.

The PCM in osteoarthritis

In healthy articular cartilage, the ECM is maintained in a slow, continuous state of turnover – often described as "homeostasis" – a balance of overall anabolic and catabolic activities of matrix synthesis and degradation. These activities are tightly controlled by the

environmental signals (including both biochemical and biomechanical cues) through regulating genetic and epigenetic programming of the chondrocytes. As a transitional zone between the interterritorial matrix and chondrocytes, the PCM, which has a much higher proteoglycan turnover rate [72], can modulate these environmental signals before they reach the chondrocytes and thus play a key role in chondrocyte gene expression and epigenetic state. Consequently, in a pathologic state such as osteoarthritis, changes to PCM properties may not only reflect the disease state but may also influence the regulatory function of PCM and thus chondrocyte activity. Therefore, further study of the PCM remodeling with osteoarthritis may provide new insights into understanding the etiology and pathogenesis of the disease.

The first studies of osteoarthritic changes in PCM structure and composition reported on human and canine chondron morphology, viability, and metabolism. This work demonstrated that early changes in the collagen and proteoglycan distribution within the chondron precede chondrocyte proliferation and cell cluster formation [73]. Osteoarthritic cartilage also exhibited chondron swelling and chondrocyte cluster formation, with a loss of pericellular type IX collagen staining [74] and the prevalence of enlarged chondrons with “loosely-organized” PCM structures [73, 75, 76]. Osteoarthritic cartilage was also associated with the appearance of a sub-population of chondrocytes with multiple elongated cytoplasmic processes [77]. Indeed, using confocal microscopy, it has been observed that some of these cytoplasmic processes were longer than 8 μm, radiating beyond the PCM and extending into the territorial matrix [78, 79]. Together these seminal studies suggest that concomitant loss of PCM structure, composition, and mechanical function are present in osteoarthritis.

Interestingly, several other reports also identified early changes in PCM composition with osteoarthritis. In human cartilage with minor osteoarthritic lesions, focal pericellular deposition of collagens I and III was observed, while at more advanced stages of disease, extensive changes were seen in collagen expression in the PCM, with overlapping localization of collagens I, II and III [80]. More recent studies have also shown the presence of type I collagen in the PCM with osteoarthritis [81]. The protein collagen VI, as a primary component of the PCM, has also been shown to be increased with osteoarthritis [82, 83] (Figure 2), showing zone-dependent changes in expression and immunolabeling [84–86]. Moreover, differential mRNA expression analyses of preserved and lesioned articular cartilage of patients undergoing joint replacement surgery due to osteoarthritis show highly significant upregulated expression of collagen type VI with osteoarthritis pathophysiology [87].

These arthritic changes in PCM composition can significantly affect mechanotransduction in chondrocytes, partly through chondrocyte’s primary cilium, a single cellular organelle that projects from the cell surface into the PCM. The primary cilium has recently been recognized as a potential mechanotransducer of the chondrocyte due to its capacity to interact with matrix proteins such as collagens type II and VI through the receptors including integrins and chondroitin sulfate proteoglycan 4 (also called neuron-glial antigen 2, NG2) [88, 89]. In addition to matrix protein receptors, several putative mechanosensors, including connexin 43 and a variety of ion channels such as the transient receptor potential

vanilloid 4 (TRPV4) are expressed on the primary cilia of the chondrocytes [90]. While connexin 43 is a mechanosensitive adenosine 5′-triphosphate (ATP)-release hemichannel [91] found in chondrocytes [92], TRPV4 induces intracellular Ca^{2+} signaling cascades in response to osmotic or mechanical stimuli [90]. Furthermore, it has been reported that both cilia length and incidence (i.e., overall percentage of ciliated-chondrocytes in cartilage) increase with osteoarthritis severity, implying an altered cilia-mediated signaling in degenerated cartilage [93].

Other PCM molecules, such as nidogens and laminins, are also modulated with disease and appear to influence the calcification process of chondrocytes in osteoarthritis through the reciprocal regulation of RUNX2 and SOX9 [94]. Interestingly, the PCM-specific localization of laminins α5 and β1 was reported to be lost in aged, disrupted cartilage while laminin α1 and perlecan were robustly withheld within the PCM in old mice [16]. These points underpin the complex and delicate homeostatic balance maintained by the PCM in presenting biomechanical signals to the chondrocytes.

Indeed, it has been suggested that degradation of PCM structure may be one of the earliest events during osteoarthritis onset due to the observation of elevated serine proteases, such as high-temperature requirement A serine peptidase 1 (HtrA1), in the synovial fluid from the osteoarthritis patients [95]. HtrA1 has the capacity to digest several major PCM components including aggrecan, decorin, fibromodulin, fibronectin, and biglycan, leading to the chondrocyte's exposure to type II collagen fibrils, which is more highly expressed in ECM compared to the PCM. Increased interaction of type II collagen fibrils with cell surface receptors, potentially through discoidin domain receptor 2 (DDR2), may alter metabolic activity and intracellular signaling cascades in chondrocytes [19, 96–98]. For example, there is mounting evidence showing that binding of DDR2 to type II collagen up-regulates production of matrix metalloproteinase (MMP)-13 in chondrocytes [99], which in turn degrades type II collagen in cartilage matrix, suggesting a potential axis of HtrA1-DDR2-MMP13 degradative pathway in osteoarthritis development [100].

Moreover, because the PCM also serves as a repository for a variety of growth factors and regulatory molecules, the disruption of PCM structure, either due to mechanical injury or by proteolytic activity, may trigger the release of these modulatory proteins, which can function in an autocrine or paracrine manner. For instance, transforming growth factor (TGF)-β is normally sequestered by fibrillin and fibulin in the PCM; however, increased release and activation of TGF-β was observed in injured articular cartilage [41, 101, 102]. It has also been reported that both biglycan and syndecan, a family of transmembrane heparan sulfate proteoglycans, play a critical role in modulating Wnt signaling and phenotypic changes of chondrocyte in osteoarthritis [103–106]. Similarly, perlecan, a PCM-localized proteoglycan [107], modulates fibroblast growth factor (FGF) presentation and binding near chondrocytes through heparin sulfate substitutions [21], altering the proliferation and metabolism of chondrocytes in response to injury.

Abnormal cartilage matrix turnover in osteoarthritis is not only associated with elevated levels of MMPs but also with increased production of aggrecanases such as ADAMTS4 and 5 (a disintegrin and metalloproteinase with thrombospondin motifs) [108, 109], often

occurring secondary to the action of pro-inflammatory cytokines such as interleukin 1 (IL-1) [110]. Furthermore, remodeling of the PCM in osteoarthritic cartilage appears to modify the response of chondrocytes to soluble mediators and matrix proteins [42, 111, 112]. For example, when articular cartilage is degraded following exposure to IL-1, hyaluronic acid (HA) penetrates the cartilage and accumulates in the chondrocyte PCM [113]. In collagen-induced arthritis mouse model, high levels of the aggrecan neo-epitopes, NITEGE (generated by aggrecanases [114]) and VDIPEN (generated by MMPs [115]), are present initially in the chondrocyte PCM, suggesting that stimulated chondrocytes can synthesize and/or activate both matrix-degrading enzymes [116]. Interestingly, it has been reported that NITEGE and VDIPEN are predominantly generated at different zonal regions in healthy tibial cartilage. However, once the spontaneous lesions develop in STR/ort mice, both neo-epitopes co-localize at the PCM and further extend to interterritorial matrices of chondrocytes adjacent to osteoarthritic lesions when the disease advances [117]. In human osteoarthritic cartilage, ADAMTS5 was present in association with cells throughout normal cartilage and was markedly increased in osteoarthritis, particularly in clonal groups in the superficial and transitional zones, where it was predominantly co-localized with HA in the PCM. HA-dependent sequestration of ADAMTS5 in the PCM may be a mechanism for regulating the activity of this proteinase in human osteoarthritis cartilage [118].

Interestingly, despite harboring several matrix-degrading enzymes in osteoarthritis, the PCM appears to possess a certain level of resistance to enzymatic degradation. For example, targeted digestion of articular cartilage with aggrecanase-1 (ADAMTS4), bacterial hyaluronidase, or chondroitinase ABC demonstrated that PCM mechanical properties exhibit high resistance to aggrecan-targeted digestion, despite significant degradative effects on the properties of the cartilage ECM [66]. This resistance to enzymatic digestion may provide a mechanism for enzyme transport from the chondrocyte to the surrounding ECM during normal matrix turnover without mechanical disruption of the PCM.

The mechanical properties of the PCM are strongly associated with its biochemical and structural changes. Using different micromechanical testing methods such as micropipette aspiration or AFM indentation, several studies have revealed that the elastic modulus of the PCM is reduced by 30–50% in osteoarthritic cartilage [55, 56, 65] (Figure 2). Conversely, alterations in PCM properties due to loss of type VI collagen in *Col6a1*$^{-/-}$ mice can accelerate the progression of osteoarthritis in the hip [57] in a joint-specific manner [119]. The loss of PCM properties is accompanied by altered calcium signaling in chondrocytes and increased cell swelling in response to osmotic stress [59]. Deletion of type IX collagen, which is more concentrated in the PCM [120, 121], has been shown to accelerate osteoarthritis progression [96] as well as intervertebral disc degeneration [122], potentially through the exposure and activation of DDR2 in chondrocytes [42, 96, 97]. Of particular interest is the discovery of a genome-wide association between polymorphisms in collagen type VI alpha 4 pseudogene 1 (COL6A4P1, also known as DVWA) with increased risk of knee osteoarthritis, indicating a potential role for alterations in pericellular collagen VI in the initiation of disease [123, 124]. These studies demonstrate the potential for a complex and interrelated role of the PCM as both an indicator as well as a potentiating factor in osteoarthritis and suggest additional studies of gene polymorphisms or mutations in PCM proteins as targets for osteoarthritis research.

In a similar manner to genetic predispositions to osteoarthritis, the PCM responds to injurious mechanical loading through both matrix turnover and mechanical softening [98, 125]. Proteomic analysis of an *in vitro* cartilage injury model demonstrates elevated loss of collagen type VI during mechanical injury [98]. Similarly, a recent study which used the murine destabilized medial meniscus (DMM) to model traumatic joint injury showed a dramatic decrease in mechanical modulus of the PCM [98, 125]. In addition to direct cellular mechanotransduction, growth factor sequestration in the PCM may serve to modulate chondrocyte response to injury. As noted earlier, perlecan, which is localized to the PCM, can modulate the activity of FGF on chondrocytes. Through deletion of the domain 1 heparan sulfate (HS) in perlecan, Shu and coworkers reported that the progressive degeneration of articular cartilage from DMM-injury could be partially rescued. They concluded that this chondroprotective could be attributed, at least in part, to the preservation of FGF signaling, providing further evidence of the complex interaction between cellular signaling and PCM mechanosensitivity [126]. Future studies to investigate whether mechanical loading either alters the PCM indirectly through chondrocyte-PCM interactions or directly remodels the PCM may establish the role of the PCM in trauma-induced osteoarthritis.

Conclusions

While the role of the cartilage ECM in osteoarthritis has been extensively studied, growing evidence suggests that many of the characteristics and influences of osteoarthritis are present – and possibly initiated – in the PCM. As the primary connection between the chondrocyte and the cartilage ECM, newly synthesized matrix components, enzymes, and growth factors will initially pass through the PCM. Furthermore, the important role that the PCM plays in modulating environmental signals makes it highly sensitive to changes that occur with degradation or osteoarthritis. Thus, further investigation of roles of individual PCM components, how they contribute to chondrocyte mechanotransduction, and how they may serve as potential biomarkers of disease could help to elucidate factors contributing to the progression of osteoarthritis, as well as degeneration changes in other connective tissues such as the meniscus or intervertebral disc that possess PCM-like structures rich in type VI collagen [127, 128].

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Highlights

- The PCM surrounds all chondrocytes in articular cartilage and regulates their interactions with the environment
- Alterations in PCM properties and composition will influence their mechanobiologic response to loading
- Some of the earliest biosynthetic and degradative changes in osteoarthritis may initially manifest in the PCM
- Here we review the potential role of PCM pathology as a potential driver, as well as indicator, of osteoarthritis

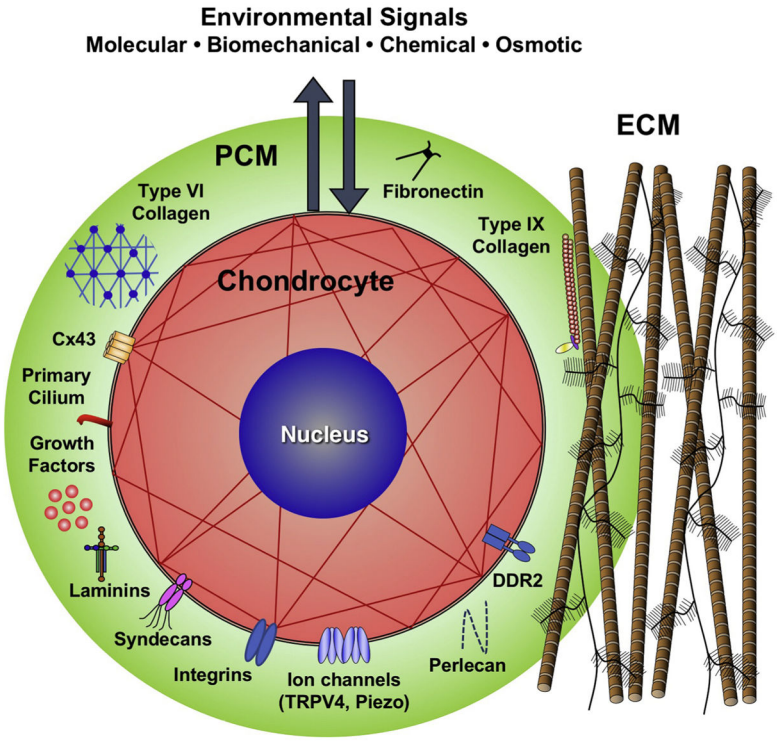

Figure 1. Schematic of the chondrocyte, which together with its surrounding pericellular matrix (PCM) forms a chondron, embedded within the cartilage ECM

The PCM is rich in proteoglycans such as perlecan and is characterized by the presence of collagens type VI and IX, as well as several other matrix macromolecules (fibronectin, laminin, etc.). Because the PCM surrounds the chondrocyte, it is believed to serve as a transducer, or “filter”, of the biomechanical milieu through regulation of the stress-strain, osmotic, and fluid-flow environments of the chondrocyte. In addition to this mechanobiologic role, the PCM can regulate cell-ECM ligand binding, growth factor and enzyme sequestration, transport, assembly, and activation, thus influencing major aspects of ECM turnover in cartilage

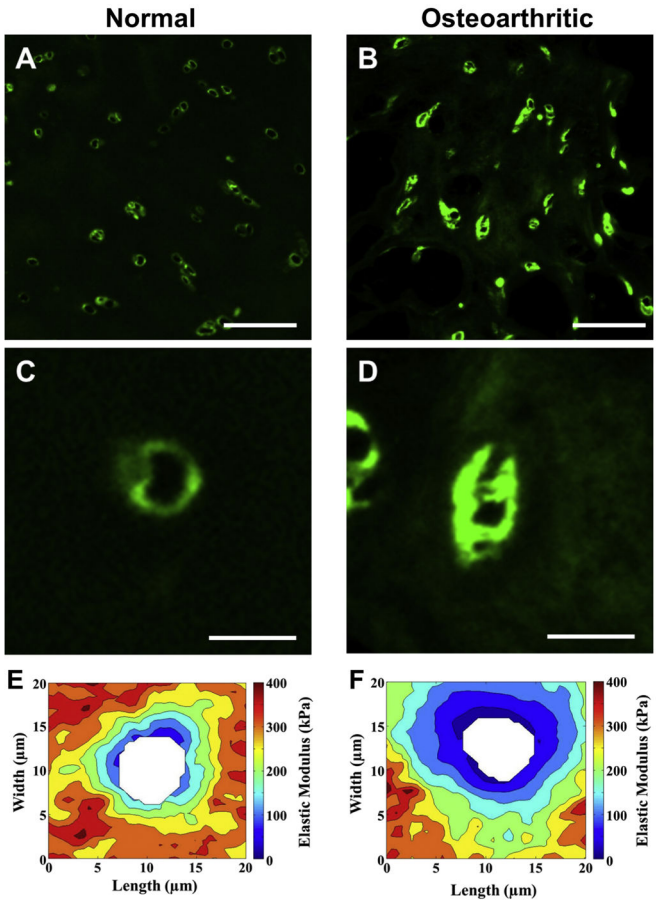

Figure 2. Alterations in the morphology and mechanical properties of the PCM with osteoarthritis

(A, B) Representative images of immunofluorescence labeling of type VI collagen in cartilage from (A) macroscopically normal and (B) osteoarthritic knee joints. Scale bar = 100 μm (C, D) Immunofluorescence labeling revealed altered structure and expanded regions that were positive for type VI collagen in the PCM of osteoarthritic cartilage. Scale bar = 25 μm. (E, F) Elastic mapping of the moduli of the ECM and PCM, from normal (E) and osteoarthritic (F) cartilage, showing a loss of mechanical properties with osteoarthritis. Modulus maps are presented on the same graded coloring scale, and cell-sized voids are depicted in white [Adapted from [65], with permission].