Review

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Review

Mechanisms and Regulatory Networks of Extracellular Matrix-Related Proteins in Cartilage Degeneration of Osteoarthritis

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Abstract

Osteoarthritis (OA) is a chronic degenerative disease characterized predominantly by cartilage degradation, wherein extracellular matrix (ECM) proteins play pivotal roles in its pathogenesis. Proteins such as Asporin (ASPN), Cartilage Intermediate Layer Protein (CILP), Chondroadherin (CHAD), Fibulin-3 (EFEMP1), Pannexin 3 (PANX3), and C-terminal cross-linking telopeptide of type II collagen (CTX-II) exhibit aberrant expression patterns in OA cartilage, influencing chondrocyte metabolism, signaling pathways, and matrix homeostasis. This review provides a comprehensive overview of the altered expression and molecular functions of these ECM-related proteins in OA, emphasizing their interactions with key signaling cascades including TGF-β, Wnt, and BMP pathways. Incorporating recent advances from single-cell sequencing and gene editing technologies, we explore how these proteins serve as potential biomarkers and therapeutic targets. Furthermore, the review delves into the impact of post-translational modifications of ECM proteins on OA pathology, aiming to elucidate mechanisms that underpin precise diagnosis and targeted treatment strategies. By synthesizing current findings, this article seeks to advance understanding of ECM protein-mediated regulatory networks in OA and foster the development of innovative interventions for cartilage preservation and repair.

Keywords: osteoarthritis; extracellular matrix; asporin; cartilage intermediate layer protein; chondroadherin; fibulin-3; pannexin 3; CTX-II; TGF-β signaling pathway; matrix proteins

1. Introduction

Osteoarthritis (OA) is recognized as one of the most prevalent chronic joint disorders worldwide, characterized primarily by the progressive degeneration of articular cartilage and disruption of the extracellular matrix (ECM) integrity. The pathological hallmark of OA involves cartilage degradation, subchondral bone remodeling, synovial inflammation, and resultant joint dysfunction, which collectively contribute to pain and disability in affected individuals [1,2]. The etiology of OA is multifactorial, encompassing mechanical stress, aging, genetic predisposition, metabolic factors, and inflammatory processes, yet the precise molecular mechanisms driving cartilage degeneration remain incompletely understood. Central to OA pathogenesis is the imbalance between anabolic and catabolic activities within the cartilage ECM, where excessive matrix degradation outpaces synthesis, leading to the loss of cartilage structural integrity and function [1,3].

The ECM of articular cartilage is a highly specialized and dynamic network composed primarily of collagen fibers, proteoglycans, and non-collagenous proteins, which collectively maintain the biomechanical properties and homeostasis of cartilage tissue. Chondrocytes, the sole resident cells of cartilage, are responsible for synthesizing and remodeling the ECM components, responding to biochemical and biomechanical cues to preserve tissue integrity [4,5]. In OA, chondrocytes undergo phenotypic changes including hypertrophy, senescence, and apoptosis, accompanied by altered gene

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expression profiles that favor catabolic enzyme production such as matrix metalloproteinases (MMPs) and aggrecanases (ADAMTSs), which degrade collagen and proteoglycans, respectively [1,3,6]. This dysregulated ECM turnover is exacerbated by inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which potentiate the expression of degradative enzymes and suppress matrix synthesis, further accelerating cartilage breakdown [2,7].

Among the ECM-related proteins implicated in OA progression, several specific molecules have garnered increasing attention due to their altered expression and functional roles in cartilage degeneration. Asporin, cartilage intermediate layer protein (CILP), chondroadherin (CHAD), Fibulin-3, pannexin 3 (PANX3), and the C-terminal crosslinked telopeptide of type II collagen (CTX-II) represent key ECM constituents or biomarkers whose dysregulation correlates with OA severity [5,8,9]. For instance, COMP (cartilage oligomeric matrix protein) and thrombospondins (TSPs) are non-collagenous glycoproteins that contribute to ECM organization and chondrocyte function. COMP has been shown to promote chondrocyte migration and stabilize the chondrocyte phenotype, suggesting a protective role in cartilage repair, while TSPs participate in cartilage homeostasis and synovial inflammation modulation [5,9]. However, the precise mechanisms by which these ECM proteins influence OA pathophysiology, including their interactions with key signaling pathways such as transforming growth factor-beta (TGF-β), Wnt/β-catenin, and bone morphogenetic protein (BMP), remain to be fully elucidated [6,10,11].

Recent advances in molecular biology and high-throughput technologies have begun to shed light on the complex regulatory networks governing ECM protein expression and function in OA cartilage. MicroRNAs (miRNAs), small non-coding RNAs that post-transcriptionally regulate gene expression, have emerged as critical modulators of cartilage homeostasis by targeting mRNAs encoding ECM components and degradative enzymes. Specific miRNAs such as miR-140, miR-497-5p, and miR-15a have been identified to influence cartilage ECM metabolism by modulating the expression of MMPs, ADAMTSs, and signaling molecules within the Wnt/β-catenin and NF-κB pathways [1,12,13]. Moreover, epigenetic modifications, including DNA methylation changes at enhancer regions of genes like TGFB1 and WWP2, have been linked to altered gene expression profiles in OA cartilage, highlighting the interplay between genetic and epigenetic factors in disease progression [14].

Importantly, the advent of single-cell RNA sequencing and spatial transcriptomics has provided unprecedented resolution in characterizing the heterogeneity of chondrocyte populations and their microenvironment within osteoarthritic cartilage. These technologies have revealed distinct chondrocyte subtypes with variable ECM production capabilities and responsiveness to inflammatory stimuli, offering new insights into the cellular dynamics underlying cartilage degeneration and repair [4]. Concurrently, gene editing tools such as CRISPR/Cas9 facilitate functional validation of candidate ECM proteins and regulatory factors, enabling the dissection of causal relationships and the identification of potential therapeutic targets [15].

Therapeutically, targeting ECM-related proteins and their regulatory networks holds promise for disease-modifying interventions in OA. Strategies include inhibiting matrix-degrading enzymes (e.g., MMP-13), modulating signaling pathways (e.g., Wnt/β-catenin, TGF-β), and harnessing the regenerative potential of mesenchymal stem cells and their secretomes, often delivered via biomaterial scaffolds that mimic the native ECM environment [16–18]. Additionally, natural compounds like curcumin monoglucuronide and pterostilbene have demonstrated chondroprotective effects by inhibiting ECM degradation and inflammation [19,20]. The integration of molecular insights with novel biomaterials and gene therapies represents a frontier in OA treatment aimed at restoring cartilage homeostasis and halting disease progression.

In summary, the degradation of cartilage ECM is central to OA pathogenesis, with ECM-related proteins playing pivotal roles in maintaining cartilage integrity and modulating chondrocyte function. Aberrant expression and regulation of proteins such as Asporin, CILP, CHAD, Fibulin-3, PANX3, and CTX-II, coupled with dysregulated signaling pathways and epigenetic alterations, contribute to the complex molecular landscape of OA. Emerging technologies in single-cell analysis

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and gene editing are accelerating the understanding of these mechanisms, paving the way for targeted therapeutic approaches aimed at preserving cartilage structure and function in OA patients. This review aims to systematically summarize current knowledge on the roles and regulatory networks of ECM-associated proteins in OA cartilage degradation, highlighting their potential as biomarkers and therapeutic targets.

2. Main Body

2.1.1. ASPN's Structural Features and Expression Regulation

Asporin (ASPN) is a member of the small leucine-rich repeat proteoglycan (SLRP) family, characterized by a distinctive structural organization that includes leucine-rich repeat domains and an aspartate-rich N-terminal region. This unique structure enables ASPN to interact specifically with transforming growth factor-beta (TGF-β), a critical cytokine in cartilage homeostasis and repair. The aspartate-rich domain of ASPN facilitates direct binding to TGF-β, thereby modulating its bioavailability and signaling capacity. In osteoarthritic (OA) cartilage, ASPN expression is markedly upregulated compared to normal cartilage, a phenomenon that is likely driven by a combination of inflammatory mediators and mechanical stressors inherent to the OA joint environment. Inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which are elevated in OA synovial fluid, can induce ASPN transcription in chondrocytes. Additionally, mechanical overload and altered joint biomechanics, common in OA, have been shown to enhance ASPN expression, suggesting that mechanotransduction pathways contribute to its regulation. Genetic studies also support the role of ASPN in OA susceptibility; specific polymorphisms, particularly the D14 allele of the ASPN gene, are associated with increased risk of knee and hand OA in various populations. This allele may influence the structure-function relationship of ASPN, potentially altering its interaction with TGF-β and other matrix components. The elevated ASPN expression in OA cartilage and peripheral blood lymphocytes underscores its potential as both a biomarker and a mediator of disease progression. Collectively, the structural features of ASPN, coupled with its inducible expression by inflammatory and mechanical stimuli, position it as a pivotal extracellular matrix protein influencing cartilage integrity in OA [21–23].

2.1.2. ASPN's Inhibitory Effect on the TGF-β Signaling Pathway

ASPN exerts a critical inhibitory effect on the TGF-β signaling pathway, which is essential for maintaining cartilage extracellular matrix (ECM) synthesis and chondrocyte anabolic activity. Mechanistically, ASPN directly binds to TGF-β ligands via its aspartate-rich domain, competitively blocking the interaction between TGF-β and its cell surface receptors on chondrocytes. This blockade prevents the activation of downstream Smad proteins, particularly Smad2 and Smad3, which are transcription factors responsible for promoting the expression of cartilage matrix components such as type II collagen and aggrecan. The suppression of TGF-β/Smad signaling by ASPN leads to a reduction in the synthesis of these critical ECM molecules, thereby impairing the reparative capacity of chondrocytes. Consequently, the balance between matrix synthesis and degradation is disturbed, favoring cartilage degradation. This inhibitory role of ASPN has been corroborated by studies demonstrating that increased ASPN levels correlate with decreased TGF-β activity and enhanced cartilage matrix breakdown in OA models. Furthermore, the upregulation of ASPN in OA cartilage is associated with elevated expression of matrix-degrading enzymes, such as matrix metalloproteinases (MMPs), which further exacerbate cartilage deterioration. The negative regulation of TGF-β signaling by ASPN thus represents a key molecular mechanism contributing to the pathogenesis of OA by diminishing chondrocyte anabolic responses and promoting matrix catabolism [21,23].

2.1.3. Potential Interactions Between ASPN and Other Signaling Pathways

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Emerging evidence suggests that ASPN may interact with additional signaling pathways beyond TGF-β, notably the Wnt and bone morphogenetic protein (BMP) pathways, which are also integral to cartilage metabolism and OA pathophysiology. Although the precise molecular mechanisms remain to be fully elucidated, preliminary studies indicate that ASPN could modulate Wnt signaling, a pathway known to regulate chondrocyte proliferation, differentiation, and matrix production. Dysregulation of Wnt signaling has been implicated in OA progression, and ASPN's potential to influence this pathway may contribute to its multifaceted role in cartilage homeostasis. Similarly, BMP signaling, which shares components with TGF-β pathways and promotes cartilage repair and regeneration, might be affected by ASPN through competitive binding or modulation of ligand availability. The crosstalk between ASPN and these pathways could orchestrate a complex regulatory network that fine-tunes chondrocyte behavior and ECM turnover. Understanding these interactions is critical, as it may reveal novel therapeutic targets that address the comprehensive regulatory role of ASPN in cartilage metabolism. Future research focusing on delineating the molecular interfaces between ASPN and Wnt/BMP signaling will enhance our understanding of its contribution to cartilage degeneration and provide insights into integrated regulatory mechanisms in OA [24,25].

2.2.1. CILP Expression Changes in OA Progression and Subtype Specificity

Cartilage intermediate layer protein (CILP), particularly CILP-1 and CILP-2 isoforms, exhibits distinct expression patterns in osteoarthritic (OA) cartilage, with notable elevation in the intermediate layer of affected cartilage. Immunohistochemical analyses have demonstrated that CILP-2 is abundantly expressed in the superficial and middle layers as well as in the pericellular matrix of the deep zone of OA cartilage, with staining intensity positively correlating with the severity of cartilage damage graded by OARSI criteria [26]. This suggests that CILP expression is not uniform but varies with cartilage zonal architecture and disease progression. Moreover, studies reveal that CILP levels are elevated in OA compared to healthy controls and differ among OA subtypes, reflecting heterogeneity in disease pathophysiology [27]. The dynamic regulation of CILP expression is influenced by mechanical loading and inflammatory milieu characteristic of OA joints. For instance, mechanical stress modulates chondrocyte metabolism and extracellular matrix (ECM) remodeling, which in turn affects CILP secretion and deposition. Inflammatory cytokines such as TNF-α can alter matrix metalloproteinase (MMP) activity, leading to proteolytic cleavage of CILP and generation of neo-epitopes detectable in serum, indicating ongoing cartilage degradation [27]. Furthermore, single-cell transcriptomic analyses have identified CILP-positive synovial fibroblast subpopulations that interact with chondrocytes, suggesting a role for CILP in mediating crosstalk between synovium and cartilage during OA progression [28]. These findings collectively underscore the subtype-specific and spatially distinct expression of CILP in OA cartilage, modulated by biomechanical and inflammatory factors, highlighting its potential as a dynamic marker of cartilage degradation and disease heterogeneity.

2.2.2. CILP Inhibition of TGF-β and IGF-1 Signaling Pathways

CILP exerts significant regulatory effects on key anabolic signaling pathways in chondrocytes, notably transforming growth factor-beta (TGF-β) and insulin-like growth factor-1 (IGF-1) pathways, which are critical for cartilage matrix synthesis and homeostasis. Mechanistically, CILP can bind directly to TGF-β and IGF-1 ligands or their receptors, thereby inhibiting downstream signal transduction cascades that promote extracellular matrix production and chondrocyte survival [26]. This inhibitory interaction leads to a reduction in the synthesis of matrix components such as aggrecan and type II collagen, essential for cartilage integrity. The suppression of TGF-β signaling by CILP is particularly detrimental, as TGF-β normally induces anabolic responses and inhibits hypertrophic differentiation and apoptosis in chondrocytes. Similarly, IGF-1 signaling supports chondrocyte proliferation and matrix synthesis, and its inhibition by CILP contributes to impaired cartilage repair capacity. The net effect of CILP-mediated inhibition is a shift toward catabolic

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dominance within the cartilage microenvironment, characterized by decreased matrix synthesis and increased chondrocyte apoptosis, which accelerates cartilage degeneration in OA [26]. Additionally, proteolytic cleavage of CILP by MMPs generates fragments that may further modulate these signaling pathways, amplifying the deleterious effects on cartilage metabolism [27]. Thus, CILP functions as a negative regulator of chondrocyte anabolic signaling, linking its elevated expression in OA cartilage to impaired tissue repair and progression of cartilage degradation.

2.2.3. Potential of CILP as an OA Biomarker and Research Progress

The potential of CILP as a biomarker for osteoarthritis has garnered increasing attention due to its elevated levels in both cartilage tissue and body fluids correlating with disease severity. Serum levels of MMP-cleaved CILP neo-epitopes (e.g., CILP-M) are significantly higher in patients with OA compared to healthy controls, with robust diagnostic accuracy demonstrated by area under the curve (AUC) values exceeding 0.90 in validation cohorts [27]. These findings suggest that circulating CILP fragments reflect ongoing cartilage matrix degradation and could serve as minimally invasive indicators of disease activity. Moreover, longitudinal studies indicate that CILP levels respond to therapeutic interventions, such as TNF-α inhibition in inflammatory arthritis, implying utility in monitoring treatment response [27]. Single-cell and proteomic analyses have further identified CILP expression in synovial fibroblast subpopulations and infrapatellar fat pad secretomes, linking it to distinct OA phenotypes and clinical outcomes [28,29]. Despite promising preliminary data, current evidence is limited by relatively small sample sizes and lack of multi-center validation. Larger clinical studies incorporating diverse patient populations are necessary to establish the sensitivity and specificity of CILP as a diagnostic and prognostic biomarker. Additionally, integrating CILP measurements with other molecular and imaging markers may enhance OA phenotyping and personalized management. In summary, CILP holds considerable promise as a biomarker reflecting cartilage degradation and OA progression, but further rigorous clinical validation is required to translate these findings into routine clinical practice.

2.3.1. CHAD's Structural and Functional Roles in Cell-Matrix Adhesion

Chondroadherin (CHAD) is a cartilage-specific leucine-rich repeat (LRR) protein that plays a pivotal role in maintaining cartilage integrity by mediating cell-matrix adhesion and preserving mechanical stability. Structurally, CHAD belongs to the small leucine-rich proteoglycan (SLRP) family, characterized by tandem LRR motifs that facilitate protein-protein interactions. CHAD binds directly to collagen fibers within the extracellular matrix (ECM), particularly type II collagen, which is the predominant collagen in cartilage. This interaction is critical for anchoring chondrocytes to the surrounding matrix, thereby influencing cellular behavior and mechanotransduction pathways essential for cartilage homeostasis. The binding of CHAD to collagen not only stabilizes the ECM architecture but also modulates chondrocyte adhesion, proliferation, and differentiation, contributing to the maintenance of cartilage tissue resilience under mechanical stress. Despite these recognized functions, the expression pattern and regulatory dynamics of CHAD in osteoarthritis (OA) remain poorly defined. Current literature lacks comprehensive, systematic investigations into CHAD expression changes during OA progression, leaving its precise role in cartilage degeneration ambiguous. Given the centrality of cell-matrix adhesion in cartilage physiology and the known involvement of other ECM components in OA pathogenesis, elucidating CHAD's expression profile and functional alterations in OA could provide novel insights into disease mechanisms. Future studies employing quantitative analyses of CHAD in healthy versus osteoarthritic cartilage, alongside mechanistic experiments exploring how CHAD modulates chondrocyte-matrix interactions under pathological conditions, are warranted to clarify its contribution to OA development and progression . This knowledge gap underscores the importance of targeted research to determine whether CHAD could serve as a biomarker or therapeutic target in OA.

2.3.2. Potential Functions of Fibulin-3 in Matrix Remodeling and Inflammatory Responses

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Fibulin-3 (EFEMP1) is an extracellular matrix glycoprotein implicated in tissue remodeling and inflammatory processes, with emerging evidence suggesting a significant role in cartilage homeostasis and osteoarthritis (OA) pathophysiology. Fibulin-3 is known to be involved in the organization of elastic fibers and ECM architecture in various tissues, and its expression is upregulated in OA cartilage, correlating positively with disease severity. Clinical studies have demonstrated elevated serum and urine levels of fibulin-3 in patients with knee OA, with higher concentrations observed in late-stage disease, indicating its potential as a diagnostic and prognostic biomarker [30,31]. Functionally, fibulin-3 modulates chondrocyte behavior under inflammatory conditions; for example, in vitro studies show that fibulin-3 expression increases in chondrogenic cells stimulated by tumor necrosis factor-alpha (TNF-α), a key pro-inflammatory cytokine in OA. Fibulin-3 promotes chondrocyte proliferation yet suppresses both chondrogenic and hypertrophic differentiation, suggesting a complex regulatory role in cartilage remodeling [32]. Mechanistically, fibulin-3 partially inhibits the TGF-β/Smad3 signaling pathway by reducing Smad3 phosphorylation and interacting with the TGF-β type I receptor, thereby influencing ECM synthesis and degradation balance. However, direct evidence linking fibulin-3 to the regulation of matrix-degrading enzymes such as matrix metalloproteinases (MMPs) remains limited and inconclusive. Although fibulin-3's modulation of TGF-β signaling may indirectly affect MMP expression, experimental validation is necessary to clarify this relationship. Moreover, fibulin-3's role in cartilage calcification and mineralization processes, which contribute to OA progression, is suggested but not fully elucidated. Given these findings, fibulin-3 emerges as a multifunctional ECM protein involved in matrix remodeling and inflammatory responses in OA, but further studies are essential to delineate its precise molecular mechanisms, especially regarding its influence on ECM-degrading enzymes and calcification pathways. Such insights could facilitate the development of fibulin-3-targeted therapeutic strategies to modulate cartilage degeneration and inflammation in OA [30,32].

2.3.3. PANX3's Role in Chondrocyte Differentiation and ATP Signaling

Pannexin 3 (PANX3) is a channel-forming glycoprotein that has garnered attention for its regulatory functions in chondrocyte differentiation, metabolism, and extracellular ATP signaling, all of which are critical for cartilage homeostasis and osteoarthritis (OA) pathogenesis. PANX3 forms multiple channel types, including hemichannels, gap junctions, and endoplasmic reticulum (ER) calcium channels, enabling it to mediate diverse cellular processes. Notably, PANX3 regulates intracellular calcium signaling through its ER Ca2+ channel activity, which is modulated by phosphorylation at serine 68 (Ser68). This post-translational modification, induced by ATP stimulation and PI3K/Akt signaling, promotes osteoblast differentiation and is also relevant in chondrocyte maturation, as phosphorylated PANX3 localizes to ER membranes in prehypertrophic and hypertrophic chondrocytes [33]. Functionally, PANX3 acts as an ATP release channel at the cell surface, influencing purinergic signaling pathways mediated by P2X and P2Y receptors. These pathways are critical for chondrocyte proliferation, differentiation, and metabolic regulation. In osteoarthritis models, PANX3 expression is altered, and its dysregulation has been implicated in cartilage matrix degradation and inflammation. Specifically, in temporomandibular joint OA, PANX3 facilitates ATP release that activates the P2X7 receptor, triggering inflammatory cascades and matrix-degrading enzyme expression, thereby exacerbating cartilage damage [34]. However, the precise mechanisms by which PANX3 influences chondrocyte apoptosis and inflammatory responses in OA remain incompletely understood. The interplay between PANX3-mediated ATP signaling and downstream purinergic receptor activation, particularly the P2X/P2Y receptor axis, requires further elucidation to clarify its contribution to OA pathology. Moreover, whether PANX3 exerts protective or detrimental effects in different OA contexts, such as age-related versus injury-induced disease, is an area of active investigation [35]. Overall, PANX3 emerges as a critical modulator of chondrocyte function through its dual roles in calcium homeostasis and ATP-mediated purinergic signaling, representing a promising target for therapeutic intervention aimed at preserving cartilage integrity and mitigating OA progression. Future research should focus on delineating the molecular pathways

 doi:10.20944/preprints202510.2364.v1

linking PANX3 channel activity to chondrocyte survival, inflammation, and matrix remodeling in osteoarthritic cartilage.

3. Conclusions

In conclusion, the intricate roles of extracellular matrix (ECM)-related proteins such as Asporin, CILP, CHAD, Fibulin-3, PANX3, and CTX-II in osteoarthritis (OA) cartilage degeneration underscore a complex regulatory network that modulates chondrocyte metabolism and matrix homeostasis primarily through pathways including TGF-β and IGF-1 signaling. From an expert perspective, it is evident that these proteins do not act in isolation but rather participate in multilayered interactions that influence the pathophysiology of OA at various molecular and cellular levels. The current body of research, while illuminating, remains incomplete regarding the precise expression dynamics, molecular mechanisms, and interplay among these proteins, particularly in the context of distinct OA subtypes and the impact of post-translational modifications.

Balancing the diverse research findings reveals both consensus and gaps. For instance, studies consistently highlight the dysregulation of these ECM proteins as pivotal to cartilage matrix breakdown and impaired repair processes. However, discrepancies arise in delineating their specific contributions across OA phenotypes, reflecting the disease's heterogeneity and the complexity of cartilage biology. This heterogeneity necessitates a nuanced approach that integrates emerging technologies such as single-cell RNA sequencing and spatial transcriptomics. These advanced methodologies hold promise for unraveling the spatiotemporal heterogeneity of chondrocyte populations and the dynamic functional states of ECM proteins within the cartilage microenvironment. Such insights are critical for refining our understanding of OA pathogenesis and for identifying precise molecular targets.

Moreover, the advent of gene editing tools like CRISPR-Cas9 has revolutionized functional validation studies, enabling the dissection of causal relationships between ECM proteins and OA progression. This technological leap facilitates the development of targeted therapeutic strategies aimed at modulating the activity or expression of these proteins to restore cartilage homeostasis or halt degeneration. Nonetheless, translating these findings into clinical practice demands rigorous validation and an appreciation of the systemic and local tissue contexts in which these proteins operate.

Looking forward, the clinical application of ECM-related proteins as biomarkers offers a promising avenue for improving OA diagnosis and management. Their potential utility in early detection, disease stratification, and monitoring therapeutic responses could significantly enhance personalized medicine approaches. To achieve this, future research must prioritize longitudinal studies that correlate protein expression patterns with clinical outcomes, alongside investigations into the effects of post-translational modifications that may alter protein function or stability.

In summary, the evolving landscape of ECM protein research in OA highlights a multifaceted regulatory framework essential for cartilage integrity and function. A balanced synthesis of current evidence, coupled with innovative technological applications, will be pivotal in overcoming existing knowledge gaps. This integrative approach is poised to drive the development of novel biomarkers and targeted therapies, ultimately advancing precision medicine in OA and improving patient outcomes.

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