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Review Article

Fibrocartilage hyalinization: A potential therapeutic strategy for articular fibrocartilage

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ABSTRACT

Articular fibrocartilage is commonly observed on the joint surface in osteoarthritis (OA) or cartilage injury, often seen as a result of cartilage degeneration. Compared to hyaline cartilage, fibrocartilage exhibits inferior mechanical properties and biological functions, which contribute to further cartilage degeneration and the progression of OA. Despite this, research on cartilage regeneration has not sufficiently addressed the specific challenges and strategies related to fibrocartilage. Although fibrocartilage formation is an unavoidable outcome during cartilage repair, it offers several benefits in the regeneration process, such as providing a natural cell source and establishing a strong integration with surrounding tissues. Recently, a therapeutic approach focused on the *in-situ* modification of fibrocartilage to promote hyaline cartilage regeneration, referred to as "fibrocartilage hyalinization", has been proposed. Our recent work has demonstrated the feasibility of converting existing fibrocartilage into hyaline cartilage *in vivo* within the injured area. Key elements of this strategy include modifying the extracellular matrix (ECM), targeting fibrotic chondrocytes, and altering the local microenvironment. This review summarizes the current understanding of articular fibrocartilage's characteristics and mechanisms, while also discussing potential approaches and the feasibility of fibrocartilage hyalinization for cartilage regeneration.

Translational potential

The presence of articular fibrocartilage significantly compromises the functionality of adjacent healthy hyaline cartilage, representing a critical challenge in cartilage preservation. Although clinically significant, fibrocartilage management remains poorly understood, with limited strategic approaches currently available. Notably, emerging evidence suggests that fibrocartilage may serve as an intrinsic reservoir for hyaline cartilage regeneration. Building upon this concept, we have developed an innovative cartilage regeneration strategy termed "fibrocartilage hyalinization", representing a paradigm shift in the field of cartilage repair. These findings highlight the urgent need for further investigation into this novel therapeutic approach. We anticipate that the successful implementation of fibrocartilage hyalinization will revolutionize functional cartilage restoration, potentially reducing the reliance on total joint replacement procedures.

1. Cartilage degeneration and fibrocartilage

Cartilage plays various critical roles, such as bearing mechanical loads in articular joints and intervertebral discs, providing lubrication, and supporting the development of long bones during growth [1]. The viscoelastic properties of cartilage arise from its extracellular matrix (ECM) composition, which includes water (70–80 %), collagen (50–75

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%), and glycosaminoglycans (GAGs) (15–30 %). These components provide cartilage with appropriate compressibility, extensibility, and low friction. A decline in these functions is recognized as cartilage degeneration, an irreversible and catastrophic event in articular cartilage, commonly caused by osteoarthritis (OA) and cartilage injury. OA is the leading cause of cartilage degeneration, affecting a large population worldwide and resulting in mobility issues and pain. In the context of chronic inflammatory diseases or wound healing processes, including cartilage injury and OA, tissues continually undergo damage and repair [2], further activating fibroblasts and leading to the deposition of abundant collagen, forming fibrous tissue [3].

Fibrocartilage formation is a significant event during the pathological progression of articular cartilage degeneration [4]. In addition to chronic ECM damage, the intra-articular microenvironment plays a pivotal role in cartilage degeneration. Inflammation originating from OA exacerbates this condition. After cartilage injury, cartilage fragments contribute to further deterioration of the microenvironment [5]. Consistently, fibrocartilage not only induces inflammation and cartilage fragmentation but also causes abnormal cell differentiation, overactivation of immune cells [6], and a deterioration in mechanical properties [7]. In cartilage diseases, chondrocytes residing in the cartilage undergo degeneration and transform into fibrotic chondrocytes in response to stimuli from the microenvironment. The fibrillar collagen secreted by these fibrotic chondrocytes leads to the formation of articular fibrocartilage, which has inferior mechanical properties compared to hyaline cartilage [8], such as the equilibrium aggregate modulus (HA) and equilibrium compressive modulus (E). Furthermore, fibrocartilage exhibits a decreased ability to secrete lubricin, leading to increased friction (μ) between the cartilage articular surface and the opposing cartilage surface.

Cartilage is a tissue devoid of blood vessels, nerves, and lymphatics, which contributes to the insufficient nutrient supply and a lack of circulating stem cells at the injury site, further hindering regeneration [9]. Over the past decades, numerous efforts have been made to achieve structural repair and functional recovery in articular cartilage. Traditional cartilage repair techniques, such as autologous chondrocyte implantation (ACI) and microfracture, fail to replicate the biomechanical properties of hyaline cartilage, which are ultimately replaced by fibrocartilage [10,11]. Cartilage tissue engineering primarily focuses on directly inducing the formation of hyaline cartilage, often overlooking strategies for dealing with fibrocartilage [12]. Notably, fibrocartilage that forms in cartilage defects not only lacks the original function but also accelerates the progression of OA. However, knowledge regarding fibrocartilage remains largely limited, and it is often considered merely a by-product of failed cartilage regeneration. Consequently, fibrocartilage presents a significant challenge in cartilage regeneration. Furthermore, no reasonable or practical solutions have been proposed for dealing with existing fibrocartilage [13]. Therefore, addressing fibrocartilage is critical for the advancement of cartilage regeneration strategies. Recently, our work successfully demonstrated the regenerative potential of fibrocartilage, reprogramming it into hyaline cartilage in situ. We summarized this new cartilage regeneration strategy for fibrocartilage, termed “fibrocartilage hyalinization” [14]. In previous studies, we observed fibrocartilage formation after inducing cartilage defects in rat models. To achieve fibrocartilage hyalinization, we stabilized microtubules to reprogram fibrocartilage, which resulted in a decrease in fibrocartilage and an increase in hyaline cartilage. Notably, our prior studies identified microtubules as a novel factor in cartilage regeneration in both human and rat, highlighting similarities between cartilage regeneration and fibrocartilage hyalinization. Thus, investigating factors that influence cartilage regeneration in the context of fibrocartilage is a promising new approach for cartilage regeneration research. In this review, we introduce the characteristics and mechanisms of articular fibrocartilage and discuss potential strategies focusing on fibrocartilage.

2. Hyaline cartilage and fibrocartilage

In previous studies, two primary types of articular cartilaginous tissues have been identified based on composition and function: hyaline cartilage and fibrocartilage. As shown in Fig. 1, several differences exist between these two types. Hyaline cartilage, the most common type, is located at the joint surface, whereas fibrocartilage is considered a degenerated form of hyaline cartilage. One of the key differences between them lies in their composition [15]. The predominant collagen in hyaline cartilage is collagen type II (Col II) (>90 %), with smaller amounts of Col III, Col IX, Col XI, and Col VI. Col II provides the overall structural integrity of the tissue by counteracting the swelling pressure exerted by negatively charged glycosaminoglycans (GAGs) [16]. Functionally, hyaline cartilage plays a crucial role in load transduction, experiencing forces up to six times body weight and stress levels reaching 10 MPa [17]. Additionally, it facilitates joint mobility by offering a lubricated surface with an exceptionally low coefficient of friction, ranging from 0.001 to 0.0112 [18]. Lubricin (PRG4), a key protein component of joint lubrication, is another specific marker of hyaline cartilage [19]. The formation and development of synovial joints during the embryonic period are closely linked to growth differentiation factor 5 (GDF5), and PRG4 is a specific hyaline cartilage marker derived from GDF5+ lineage chondrocytes in postnatal articular cartilage [20]. In contrast, fibrocartilage exhibits low PRG4 expression, as it originates from migrating stem cells during cartilage degeneration [21].

During OA or cartilage injury, an imbalance between catabolism and anabolism leads to cartilage matrix degradation and fibrocartilage formation, which is a hallmark of degeneration. The fibrocartilage matrix is composed of densely braided collagen fibers rich in Col I but deficient in Col II, resulting in compromised mechanical properties [22]. As previously mentioned, even after microfracture or autologous chondrocyte implantation (ACI), the regenerated tissue is typically fibrocartilage with a low COL II/COL I ratio, which is mechanically inferior to hyaline cartilage with a high COL II/COL I ratio [23]. Despite improvements in cartilage repair strategies, fibrocartilage formation remains a challenge, as the production of fibrotic ECM components leads to scar formation, inflammation, and further degeneration. Furthermore, fibrotic chondrocytes within fibrocartilage are embedded in thick collagen fibers with minimal ground substance.

Recent research has focused on chondrocyte lineage heterogeneity following cartilage degeneration [24]. Various stem/progenitor cells in the intra-articular joint contribute to cartilage repair, including cartilage stem/progenitor cells (SCPCs), bone marrow mesenchymal stem cells (BMSCs), skeletal stem cells (SSCs), synovial mesenchymal stem cells (SMSCs), and adipose-derived mesenchymal stem cells (ADSCs) [5]. These stem/progenitor cells exhibit different differentiation potentials, often leading to disorganized matrix formation. Under degenerative conditions, stem cell activation contributes to fibrosis, resulting in the formation of low-quality cartilage. For example, Thy1+ (CD90) and Pdgfα+ (platelet-derived growth factor receptor alpha) SMSCs migrate to sites of cartilage damage and transdifferentiate into fibrocartilage in response to early-stage cartilage injury in mice [25]. Similarly, Vegfrα+ (vascular endothelial growth factor receptor alpha) SSCs drive endochondral ossification during cartilage repair [26]. Conversely, Tet1+ (Ten-eleven translocation family protein 1) SSCs promote cartilage regeneration by regulating epigenetic modifications in both OA and cartilage defects in both human and mice. Additionally, Grem1 lineage SSCs maintain hyaline cartilage homeostasis and differentiate into chondrocytes during cartilage degeneration by Grem1-creERT; R26-LSL-TdTomato mice. Upon cartilage injury, quiescent chondrocytes are activated, undergoing proliferation and clustering within the damaged tissue to respond to the altered extracellular matrix (ECM) environment [16]. This process often leads to chondrocyte dedifferentiation or transdifferentiation into fibroblast-like cells, which in turn promotes an increased synthesis of type I collagen (Col I), as observed in

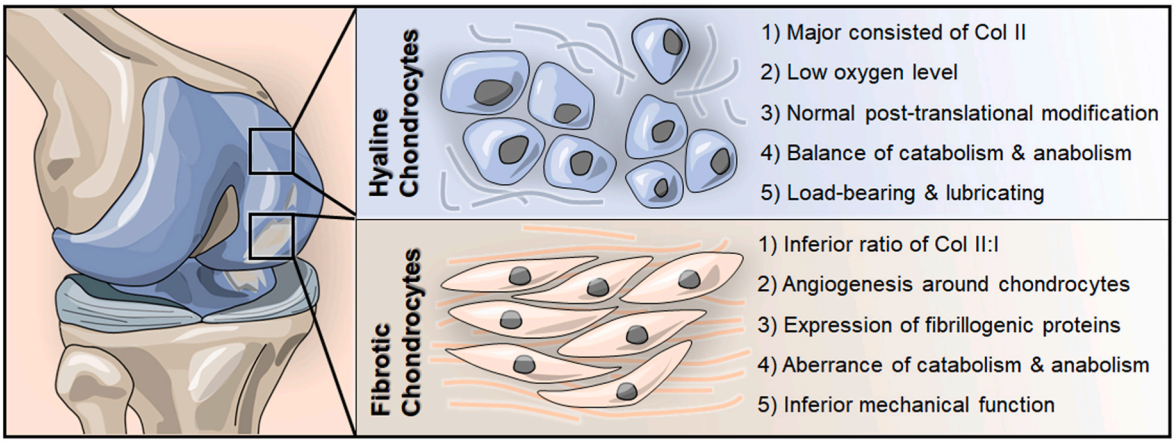

Fig. 1. Schematic of the differences between hyaline cartilage and fibrocartilage.
The structure and pathophysiology between hyaline cartilage and fibrocartilage are different. Firstly, the major component of the matrix in hyaline cartilage is Col II. The percentage of Col I is significantly increased in fibrocartilage. An imbalance between catabolism and anabolism, resulting in the loss of the cartilage matrix, is a hallmark of injuries and degeneration. Low oxygen level and normal post-translational modification are an important basis for the function of hyaline cartilage, which also provides the balance of catabolism and anabolism of chondrocytes. However, increasing angiogenesis around chondrocytes and the expression of fibrillogenic proteins result in the aberrance of catabolism and anabolism of fibrocartilage. The dense matrix of fibrocartilage further contributes to inferior mechanical function, which hardly achieves the function of load-bearing and lubricating.

murine models [27]. Additionally, mesenchymal stem cells (MSCs) have been implicated in the development of fibrotic chondrocytes following cartilage injury [28]. However, the precise composition and organization of the ECM, as well as the differentiation trajectory of chondrocyte lineages under these conditions, remain poorly defined and warrant further investigation.

3. The biological markers of fibrocartilage

Unlike hyaline cartilage, fibrocartilage contains a low percentage of aggrecan and Col II but is rich in Col I. Additionally, Col III is observed in fibroblasts and fibrotic chondrocytes. Since fibrocartilage is considered a transitional tissue, originating from both dense fibrous connective tissue and hyaline cartilage, its cells express α-smooth muscle actin (α-SMA), a non-polymerized form of actin and a key marker of myofibroblasts [29]. Importantly, fibrotic chondrocytes express both hyaline cartilage markers—such as SOX9 (SRY-box transcription factor 9), Col II, PRG4, GDF5, and DCN (decorin)—as well as fibroblast-associated markers, including α-SMA, Col I, Col III, and fibromodulin (Fmod). The mRNA expression ratio of Col II to Col I in fibrocartilage ranges from 0.2 to 1 [30]. Single-cell RNA sequencing (scRNA-seq) of human osteoarthritic (OA) cartilage has confirmed that fibrotic chondrocytes exhibit high expression of fibroblast phenotype markers—including *COL1A1, COL3A1, COL5A1, and* S100A4 *(S100 calcium-binding protein A4)*—while displaying low levels of mesenchymal stromal stem cell (MSC)-specific surface markers and hematopoietic markers, such as *CD106, CD146, ITGA11 (integrin subunit alpha 11), CD34, CD45, and CD133* [31]. A summary of fibrocartilage biological markers is provided in Fig. 2.

Connective tissue growth factor (CTGF; also known as CCN2) plays a crucial role in the development and differentiation of fibroblasts. In mice models, it has been reported that CTGF expression is linked to OA progression and serves as a major indicator of joint fibrosis [32]. The dysregulation of CTGF is frequently associated with excessive transforming growth factor β (TGF-β) activity. Similarly, human chondrocytes exhibited CTGF is regulated by PIZEO1 and related to the mechanical mechanism after cartilage injury. While TGF-β is essential for chondrocyte development, it is also recognized as a key mediator of tissue fibrosis due to its role in ECM accumulation under pathological conditions [33]. Appropriate levels of TGF-β contribute to cartilage repair in OA, but uncontrolled TGF-β expression can lead to excessive cartilage

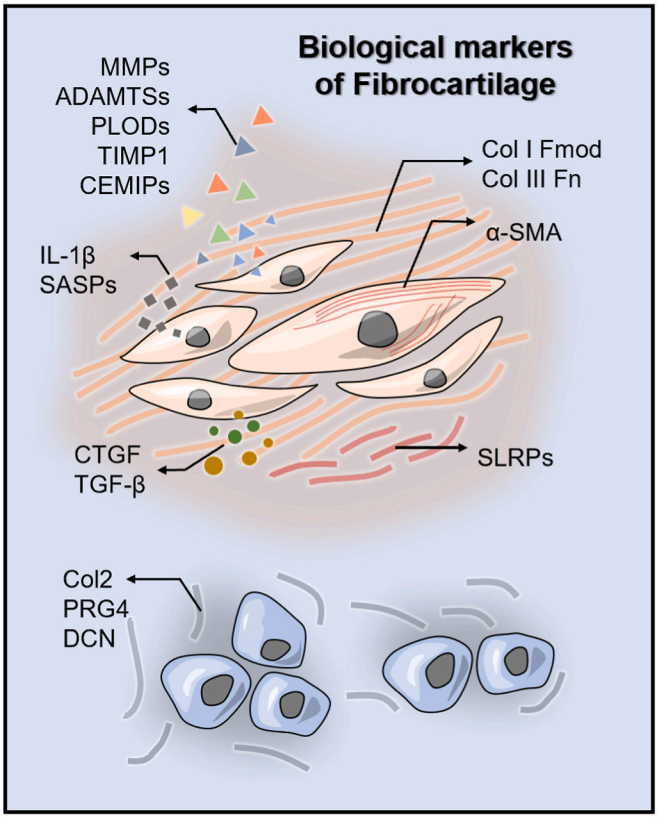

Fig. 2. Biological marker of fibrocartilage
Fibrocartilage is considered a transitional tissue originating from both dense fibrous connective tissue and hyaline cartilage. Thus, Col I, Col III, Fmod, Fibronectin (Fn) are easily observed in the matrix of fibrocartilage. Furthermore, fibrotic chondrocytes contain α-smooth muscle actin (α-SMA), a non-polymerized form of actin and a marker of myofibroblasts. TGF-β, CTGF, and small leucine-rich proteoglycans (SLRPs) play an important role in the fibrosis process of cartilage. The degeneration of the healthy cartilage matrix is an important pathological mechanism of fibrocartilage. Therefore, the increasing inflammatory or degradation factors also can be considered the marker of fibrocartilage, such as IL-1β, MMPs, ADAMTSs, PLODs, TIPM1, CEMIP and so on.

fibrosis [34].

In addition to the classical fibrocartilage markers, several new potential markers have been identified. CEMIP (KIAA1199) has been recognized as a fibrocartilage marker in murine DMM (destabilization of the medial meniscus) models, particularly in cases of chondrocyte proliferation disorders, dedifferentiation, and ECM remodeling. Furthermore, CEMIP promotes chondrocyte transdifferentiation into chondromyo-fibroblasts, which express fibrosis markers such as α-SMA and Col III [35]. Iron accumulation has emerged as a newly recognized hallmark of cartilage degeneration. In human and murine study, transferrin accumulation was verified fibrocartilage, suggesting its potential as a therapeutic target. Moreover, ferroptosis has been observed in the human OA process [36]. Theoretically, iron accumulation differs from ferroptosis, as it is a characteristic of the senescence-associated secretory phenotype (SASP), which, in turn, contributes to cellular senescence and fibrosis progression. The co-identification of multiple iron metabolism and senescence-associated targets represents a potential fibrocartilage biomarker [5]. Recent advances in stem cell research related to the skeletal system have provided a growing number of potential fibrocartilage markers [37]. From an amphibian's developmental perspective, postnatal tissue repair is inherently prone to fibrosis [38]. Consequently, identifying fibrotic phenotypes via stem cell-associated markers has become a central focus in the regenerative medicine field. These markers include THY1, PDGFRα, GLI1 (GLI family zinc finger 1), BMPs (bone morphogenetic proteins), and SHHs (sonic hedgehog signaling). These fibrotic stem/progenitor cells play a role in the cartilage repair process and reside within the fibrocartilage matrix [5]. Therefore, fibrotic stem cell markers hold potential as fibrocartilage-specific biomarkers.

The morphogenesis of articular fibrocartilage is governed by intricate biological processes, involving complex signaling pathways and cellular interactions. Several ECM components in cartilage influence chondrocyte behavior and phenotype, particularly small leucine-rich proteoglycans (SLRPs) [39]. Important members of the SLRP family include decorin, lumican, and fibromodulin, which are essential for collagen fibril organization. Studies on genetically modified mice have shown that mutations in SLRP genes result in significant structural alterations in collagen fibrils. Additionally, the cartilage microenvironment plays a pivotal role in chondrocyte function, particularly during trauma or degeneration. Inflammatory mediators and matrix-degrading enzymes further impact cartilage integrity. Notably, interleukin-1β (IL-1β) has been identified as a key regulator that interacts with Col II and aggrecan, leading to chondrocyte phenotype alterations. Moreover, matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs) are major catabolic factors that contribute to the degradation of hyaline cartilage ECM proteins [40]. Furthermore, other fibrosis-associated markers, including 2-oxoglutarate 5-dioxygenase 2 (PLOD2), procollagen lysine, and tissue inhibitor of metalloproteinase 1 (TIMP1), have been shown to promote fibrillar collagen accumulation and OA-related fibrosis [40–42].

4. Signaling pathways involved in the formation of fibrocartilage

The formation of fibrocartilage is regulated by a complex network of interrelated signaling pathways, including TGF-β/SMAD, Wnt/β-catenin, Hippo, PI3K/Akt, and NF-κB. A summary of these pathways is provided in Fig. 3.

Both the TGF-β/SMAD and Wnt/β-catenin signaling pathways play crucial roles in joint formation during development. TGF-β is a central regulator of collagen fiber production in cartilage and is essential for the differentiation of MSCs into chondrogenic lineages [43]. However,

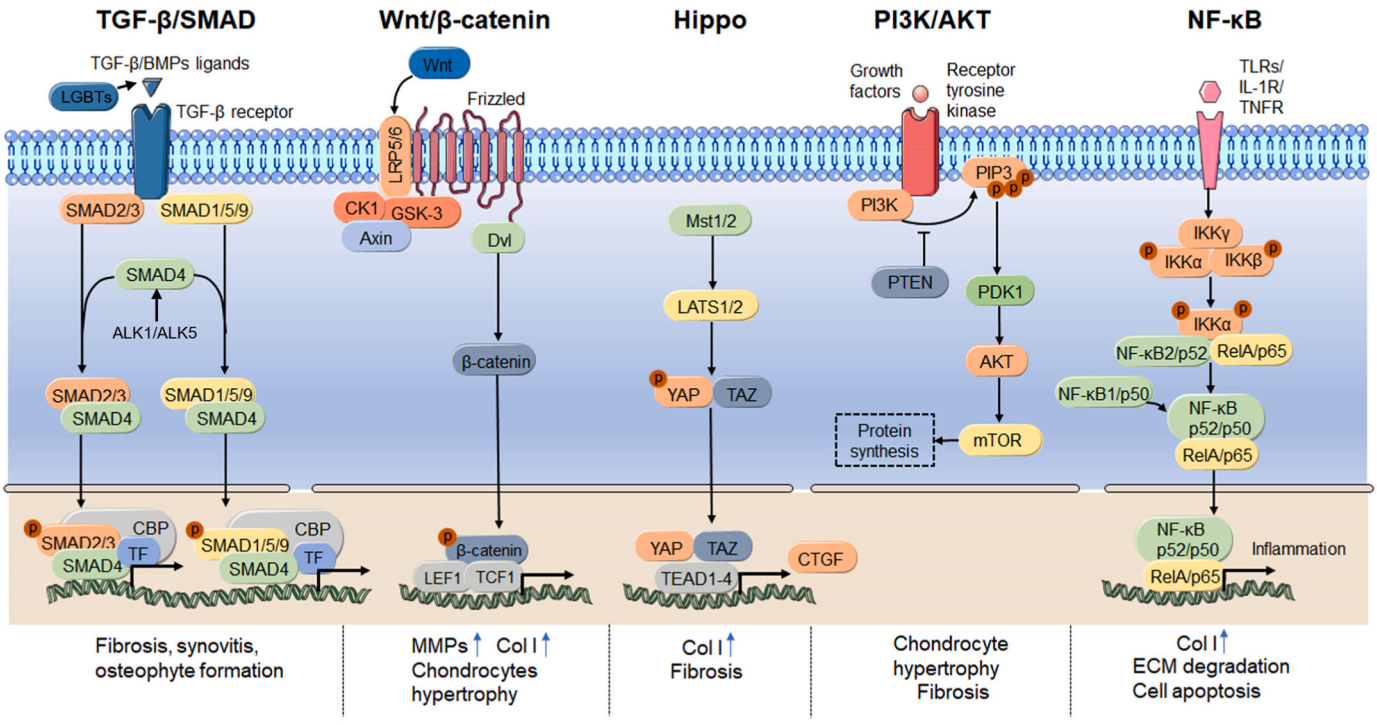

Fig. 3. The signaling pathways related to fibrocartilage

The complex network of interrelated signaling pathways is involved in the generation of fibrocartilage, including TGF-β/SMAD, WNT/β-catenin, Hippo, PI3K/AKT, and NF-κB. The activation of the TGF-β/SMAD signaling pathway can promote the fibrosis of cartilage, synovitis, and osteophyte formation. In the knee joint, the WNT/β-catenin signaling pathway can upregulate the expression of MMPs and Col I and enhance the hypertrophy of chondrocytes. CTGF is the downstream factor of the Hippo/YAP pathway. Thus, the activation of YAP has a positive effect on the expression of Col I and fibrosis. The PI3K/AKT signaling pathway was reported that could promote the fibrosis and hypertrophy of chondrocytes. The NF-κB signaling pathway was identified that related to the increasing Col I, ECM degradation, and cell apoptosis.

dysregulated TGF-β expression is also considered a key driver of tissue fibrosis. Within ECM, LTBPs bind to TGF-β, which is then activated in response to mechanical stress or injury [44,45]. ALK1 and ALK5 function downstream of TGF-β signaling, determining whether the pathway promotes rat cartilage formation or fibrosis [8,46,47]. Similarly, human chondrocytes exhibited inhibition of TGF-β leads to SOX9 downregulation, while excessive TGF-β activity induces the expression of Col I, Col III, and α-SMA, markers of fibrotic transformation [48]. Moreover, the SMAD1-5-9 pathway, rather than the SMAD2-3 pathway, is activated under conditions of high TGF-β expression, contributing to chondrocyte fibrosis and hypertrophy [49]. Excessive TGF-β also promotes the recruitment of immune cells, such as leukocytes, exacerbating synovitis and cartilage degradation [50]. Therefore, precise regulation of TGF-β signaling is essential for promoting fibrocartilage hyalinization.

Inflammatory pathways, including TNF signaling, IL-1β, and NF-κB, are key contributors to fibrocartilage formation. The TNF signaling pathway is a well-established driver of inflammation and fibrosis in cartilage degeneration, promoting cartilage catabolism. In addition to TNF-α, TNF receptors (e.g., TNFRSF12A, TNFR) contribute to both the inflammatory and fibrotic microenvironments. Similarly, IL-1β suppresses hyaline cartilage synthesis while promoting fibrocartilage formation by inhibiting aggrecan production. The NF-κB pathway plays a crucial role in inflammation and cartilage degeneration in both human and mice OA, as it activates inflammatory cytokines and matrix-degrading enzymes [51,52]. NF-κB signaling is also implicated in fibrosis across multiple tissues and organs. For example, remifentanil treatment has been shown to reduce Col I expression in a rat post-traumatic OA model by inhibiting NF-κB [53]. Moreover, NF-κB signaling has been shown to suppress chondrogenic differentiation, whereas its inhibition promotes cartilage formation. Given these findings, strategies targeting inflammation control may facilitate fibrocartilage hyalinization.

The Wnt/β-catenin signaling pathway is widely recognized for its role in joint development, cartilage homeostasis, and OA progression [54]. Excessive activation of Wnt/β-catenin signaling disrupts cartilage homeostasis by increasing matrix degradation enzymes, such as MMPs [55]. This activation also triggers low-grade repair processes, resulting in fibrotic tissue formation [56]. Furthermore, Wnt/β-catenin signaling induces immune stress, creating an inflammatory microenvironment that synergizes with MMP activity to accelerate cartilage deterioration [57]. The interaction between Wnt/β-catenin and MMPs exacerbates cartilage degradation and fibrosis [58]. In articular chondrocytes, activation of Wnt/β-catenin signaling is associated with the accumulation of fibrillar Col I and calcified Col X, leading to fibrosis and chondrocyte hypertrophy [59]. Given its widespread effects, Wnt/β-catenin signaling is a critical target for understanding cartilage matrix homeostasis and fibrosis.

The Hippo, Yes-associated protein (YAP), PI3K/Akt, and NF-κB signaling pathways regulate multiple cellular processes, including cytoskeletal organization [60,61]. YAP and transcriptional coactivator with PDZ-binding motif (TAZ) are major downstream effectors of the Hippo pathway and are negatively regulated by Hippo signaling [62]. Studies have shown that YAP promotes fibrosis and scar formation during murine wound healing [63], while YAP knockout enhances osteogenesis, an effect mediated by upregulation of β-catenin signaling [64]. Additionally, YAP and β-catenin work together to drive fibrocartilage formation by activating Wnt signaling [64]. Interestingly, our recent work demonstrated that microtubule stabilization significantly downregulates Col I expression and enhances chondrogenesis in human synovial MSCs via YAP inhibition [65]. In articular cartilage stem/-progenitor cells, YAP has been shown to maintain stem cell homeostasis via BIRC2 in mice OA, and may also be regulated by the cGAS-STING pathway. The PI3K/Akt signaling pathway is essential for MSC osteogenic differentiation, whereas PI3K/Akt inhibition favors chondrogenic differentiation [66]. A recent study showed that in a rat OA model, chondrocyte fibrosis and hypertrophy were reduced by activating AMP-activated protein kinase (AMPK) and inhibiting the PI3K/Akt pathway [67].

The pathways discussed above provide a broad framework for understanding fibrocartilage formation, but their regulatory mechanisms remain too general to achieve precise therapeutic control. Given that fibrocartilage hyalinization is an ideal approach for cartilage repair, further research is needed to clarify the fine-tuned regulatory mechanisms governing these pathways. Beyond cytoskeletal pathways, additional signaling mechanisms—including energy metabolism [68], biomechanical signaling [69], metal ion metabolism [70], and pain-related neural pathways [71] have been implicated in cartilage degeneration [55]. Identifying the specific pathways within the fibrochondral regulatory network will be crucial for developing precise therapeutic strategies.

5. Strategies for fibrocartilage hyalinization

A deeper understanding of cartilage physiology and pathology is essential for promoting hyaline cartilage formation in cartilage repair. Given that fibrocartilage can contribute to further joint deterioration, strategies for its elimination or transformation (hyalinization) must be integrated into cartilage regeneration processes. However, while fibrocartilage is often regarded as an undesirable byproduct of cartilage repair, it also possesses beneficial properties that can be leveraged to enhance regeneration. Thus, targeting these beneficial aspects may serve as a key strategy for fibrocartilage hyalinization. 1) Fibrocartilage as an Autologous Biological Scaffold for Cartilage Regeneration: Fibrocartilage can be viewed as a natural, autologous scaffold for cartilage regeneration, offering advantages over exogenous scaffolds, such as immunocompatibility. The early proliferation of fibrotic chondrocytes is considered the initial stage of cartilage regeneration in axolotl limb [2,30]. However, these cells construct a fibrotic ECM, which creates a pathological microenvironment that may impair chondrocyte differentiation. Since fibrocartilage inherently functions as a scaffold, exogenous cell therapy can be used to counteract the disadvantages of fibrotic chondrocytes. Stem cell injection therapy has been shown to alleviate early-stage OA by modulating the microenvironment and repairing microdefects within fibrocartilage in clinical trials. This approach could enhance fibrocartilage's potential as a temporary structural support, ultimately guiding the formation of hyaline cartilage. 2) Fibrotic Chondrocytes as a Natural Cell Source for Regeneration: Fibrotic chondrocytes are derived from various progenitor and stem cell populations, including mesenchymal stem cells (MSCs), skeletal stem cells (SSCs), synovial mesenchymal stem cells (SMSCs), and chondrocytes [5]. Research suggests that human articular chondrocyte fibrosis may be considered a form of dedifferentiation rather than a terminal pathological state [72]. Previous studies have highlighted the role of fibrotic stem cell regulation in cartilage regeneration [73]. Notably, a study demonstrated that treating SSCs with BMP2 and sVEGF-Ra could drive fibrocartilage-to-hyaline cartilage transformation in mice, suggesting that fibrotic chondrocytes have the potential to redifferentiate into hyaline chondrocytes. This finding highlights the possibility of reprogramming fibrotic chondrocytes into a regenerative cell population, rather than eliminating them. 3) Superior Tissue Integration of Fibrocartilage Compared to Bioengineered Cartilage: Compared to bioengineered cartilage, fibrocartilage exhibits superior integration with surrounding native cartilage and subchondral bone. Currently, few biomaterials can fully replicate the compressive strength, abrasion resistance, and shear resistance of hyaline cartilage [4]. Furthermore, many cartilage grafts and biological scaffolds fail due to poor integration with surrounding tissues [12]. As a self-healing repair tissue, fibrocartilage can effectively overcome these integration challenges and provide mechanical support during tissue repair. To capitalize on its natural fusion properties, biomaterial-based therapies targeting fibrocartilage have been explored, including collagen-hydroxyapatite

peptide (CHP) and transferrin-targeted hydrogels, which could serve as effective treatment options.

Given these advantages, we propose that fibrocartilage should be considered a raw material for hyaline cartilage regeneration. The strategy of converting fibrocartilage into hyaline cartilage, referred to as "fibrocartilage hyalinization," utilizes the existing ECM within lesioned or surrounding areas (including collagen and glycoproteins) while also mobilizing local cells (fibrotic chondrocytes and hyaline chondrocytes) to enhance hyaline cartilage regeneration (Fig. 4) [14]. Two major approaches are central to this strategy are hyalinization and inhibition of fibrosis. Although this review provides a preliminary outlook on fibrocartilage hyalinization, it also explores potential mechanisms and therapeutic approaches (Fig. 5). Notably, our recent studies have identified the feasibility of fibrocartilage hyalinization through cytoskeletal remodeling and microtubule stabilization [14]. These findings underscore the importance of further research into these innovative strategies for cartilage repair.

5.1. Strategies for modifying the original ECM

5.1.1. Post-translational modification (PTM) of collagen II

Collagen synthesis involves multiple steps, including gene expression, translation, post-translational modifications (PTMs), triple-helix formation, secretion, and cleavage of N- and C-propeptides in the extracellular space [74]. PTMs are a hallmark of chronic degenerative diseases, as seen in inflammatory and degenerative conditions, which involve glycation, glycoxidation, carbonylation, and nitrosylation. PTMs of Collagen II (Col II) have been observed in structural cartilage proteins, affecting protein folding, aggregation, and microanatomical organization within the proteoglycan–collagen network surrounding chondrocytes.

During PTM, collagen prolyl-4-hydroxylase (C-P4H) catalyzes the formation of 4-hydroxyproline, a crucial step in the formation of collagen triple helices [75]. C-P4H types I and II are highly expressed in chondrocytes, playing a major role in Col II synthesis by hydroxylating proline residues, which are essential for collagen stability and procollagen secretion in human [76]. Notably, the C-P4H family has been identified as a key factor in collagen modification, but PTMs with enhanced specificity for Col II stabilization are still needed.

Hydroxylated amino acid residues help stabilize the triple-helical molecular structure of human Col II fibers during biosynthesis [77]. Specifically, hydroxylated lysine (HyK) residues facilitate decorin–Col II interactions, indicating that Col II hydroxylation is crucial for cartilage homeostasis [78]. Additionally, Col II glycosylation plays a role in triple-helix formation, directly impacting collagen polypeptide chain synthesis and cartilage integrity [79].

In degenerative microenvironments, citrullinated Col II has been identified, which impairs cellular adhesion and inhibits MSC differentiation and survival via α10β1 and α11β1 integrin dimers [80,81]. It has been hypothesized that citrullinated Col II creates a detrimental cross-talk between different cell lineages, accelerating cartilage matrix degradation, inflammation, and fibrotic stem cell differentiation [82,83]. Additionally, Col II carbamylation, stimulated by inflammatory conditions, has been implicated as a potential trigger of fibrocartilage formation [84].

Given the role of PTM-related proteins in Col II regulation—including stabilization, synthesis, and resistance to MMPs—further research is needed to determine whether collagen modification could enhance Col II content in fibrocartilage and promote its transformation into hyaline cartilage [74]. A promising research avenue involves the targeted delivery of PTM-modifying agents to fibrocartilage, with the goal of restoring hyaline cartilage homeostasis in the ECM.

5.1.2. Regulation of biomechanical communication properties

The biomechanical properties of cartilage are determined by a multiphasic, fiber-reinforced biomaterial structure, which exhibits viscoelasticity, inhomogeneity, anisotropy, and nonlinear mechanical behavior [85]. Mechanical factors play a key role in cartilage formation, tissue morphogenesis, and cell differentiation, and they have also been identified as critical regulators in cartilage development [86]. Mechanotransduction, mechanosignaling, and mechanical microenvironmental changes are crucial for cartilage ECM homeostasis [87,88]. When biomechanical properties become dysregulated, complex molecular processes contribute to OA and cartilage fibrosis, leading to pathological feedback loops.

Mechanotransduction is the primary process by which mechanical stimuli are converted into biochemical or biological signals that regulate cell behavior [88]. However, abnormal mechanical signaling can stimulate fibrosis in cartilage tissues. Several mechanically responsive growth factors contribute to fibrocartilage formation, including FGFs, TGF-β, and YAP/TAZ signaling. FGFs, stored within the pericellular matrix (PCM) and territorial matrix, interact with perlecan and are activated by mechanical overload, triggering fibrosis-related pathways [89]. TGF-β signaling, a key mechanosensitive pathway, is regulated by integrin-mediated mechanotransduction in response to mechanical stress [90]. YAP/TAZ signaling, a critical mechanotransduction pathway, serves as a transcriptional activator in response to ECM stiffness and cellular morphology [91]. YAP/TAZ activation is required for

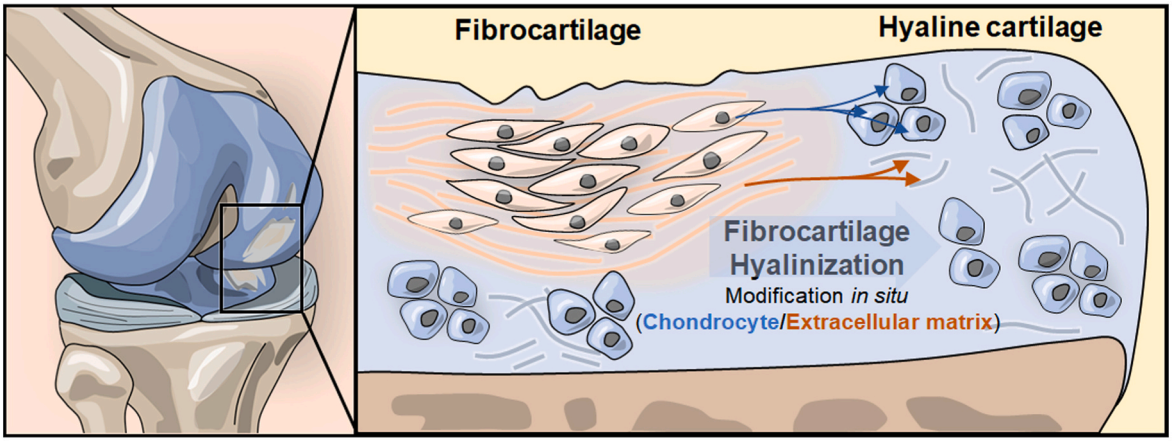

Fig. 4. Schematic of the mechanism of fibrocartilage hyalinization
The strategy of converting the phenotype from fibrocartilage to hyaline cartilage *in-situ* was named "fibrocartilage hyalinization" [14]. The strategy of fibrocartilage hyalinization is consisted of two key points. First, the original fibrotic ECM in the lesion or surrounding areas (including type I collagen and glycoproteins) can be modified to the ECM of hyaline cartilage. Second, local tissues and cells (FCs and hyaline chondrocytes) can be mobilized to improve hyaline cartilage regeneration.

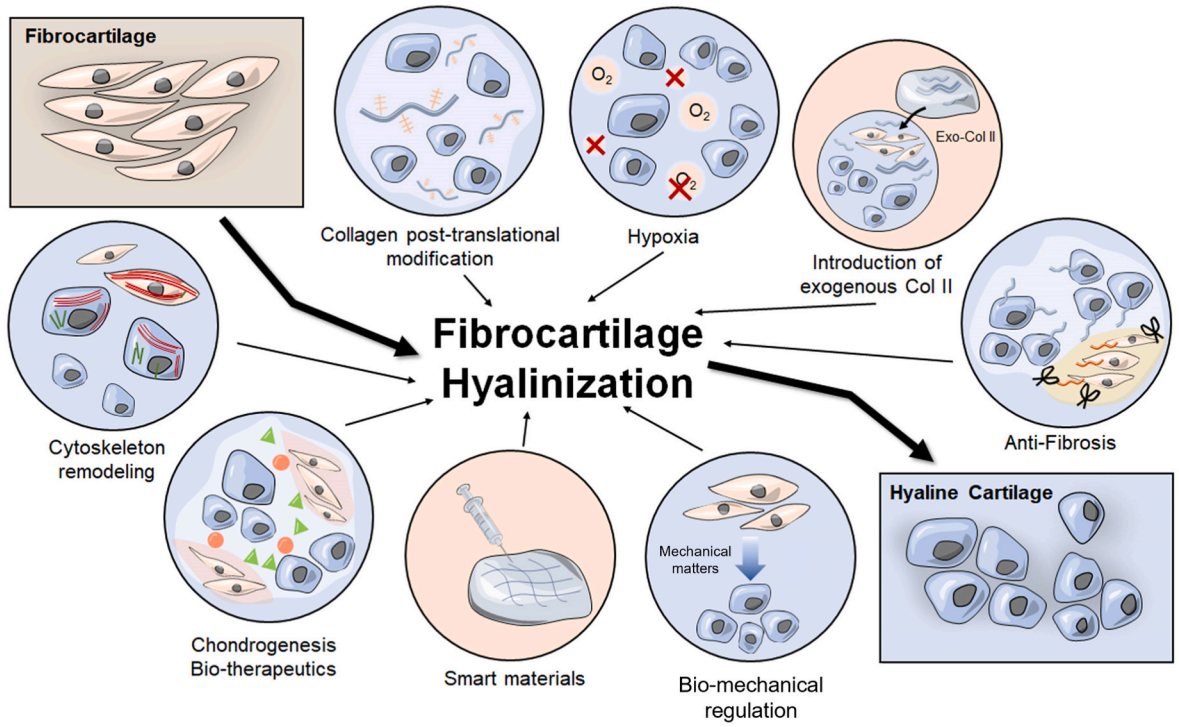

Fig. 5. Schematic of the strategies for fibrocartilage hyalinization
According to the research about chondrogenesis, anti-fibrosis and cartilage regeneration engineering, we proposed the potential methods and mechanisms for fibrocartilage hyalinization. The Strategy for Modification of Original ECM includes collagen post-translational modification, oxygen level regulation, exogenous Col II introduction and anti-fibrosis. The modification of local fibrotic chondrocytes includes cytoskeleton remodeling, chondrogenesis bio-therapeutics. Advanced Cartilage Regeneration Materials for fibrocartilage hyalinization also should be explored for further research.

fibrocartilage formation, as it drives osteogenic transcription factors (Runx2 and Sp7) while repressing chondrogenic transcription factors (Sox9) and cartilage proteins (Col II) [92,93].

In addition to signaling pathways, mechanosensitive ion channels play a significant role in fibrocartilage regulation. Piezo1, a key mechanosensitive ion channel, converts mechanical forces (e.g., shear stress and osmotic pressure) into biological signals [94]. Piezo1 activation modulates various cellular behaviors, including proliferation, migration, and apoptosis [95]. Excessive mechanical loading increases Piezo1 expression, triggering Ca^{2+} influx, which induces murine chondrocyte apoptosis and cartilage degradation [95]. When examining human samples, PIEZO1 increases *Ptgs2* and *Ccn2 (Ctgf)* to induce apoptosis and degeneration in cartilage [95]. Piezo1 inhibition has been shown to enhance chondrogenic marker expression, promote ECM production, and protect chondrocytes from mechanical damage.

Notably, the mechanical properties of fibrotic microenvironments are both a consequence and a cause of fibrosis progression [96]. Changes in ECM elasticity and viscosity over time lead to decreased tissue compliance, exacerbating fibrotic remodeling [97]. During fibrosis development, altered ECM mechanical properties affect force transmission, as increased fibroblast–ECM adhesion leads to stress relaxation behavior within fibrotic tissues [98]. Collagen remodeling enhances fiber density in the fibrotic zone, increasing ECM viscoelasticity and further activating fibroblasts. Fibrocartilage formation is characterized by dense Col I-rich ECM, which dramatically alters its mechanical microenvironment compared to hyaline cartilage. Changes in mechanical properties during cartilage injury and pathological self-repair serve as major barriers to hyaline cartilage regeneration.

Targeting mechanical cues in fibrotic lesions and disrupting fibrosis-promoting mechanical crosstalk are promising strategies for mitigating cartilage fibrosis. Several approaches can be explored to achieve this. Firstly, a detailed assessment of the mechanical properties surrounding fibrocartilage chondrocytes is necessary to determine the optimal conditions for hyaline cartilage formation. Understanding how stiffness, elasticity, and viscosity influence fibrocartilage remodeling will help identify potential therapeutic targets [99]. Ouyang with their fellows [100] redefines current understanding of the mechanism underlying cartilage degeneration process by ion beam-SEM (FIB-SEM) with high-resolution TEM-electron energy loss spectroscopy (HRTEM-EELS). The study reveals novel alteration of calcification from location-specific cartilage in OA development by evaluating chemical environments and multiple mechanical properties. Secondly, biochemical methods can be used to alter ECM characteristics—including stiffness, elasticity, and viscosity—while simultaneously regulating mechanotransduction pathways such as YAP/TAZ, FGFs, TGF-β, and Piezo1. Furthermore, dysfunctional TRPV4 pathway regulates extracellular matrix viscoelasticity to restore chondrocyte homeostasis in osteoarthritis by GSK3β. Col VI regulates mechanotransduction pathway, such as TRPV4, to mediate pericellular matrix properties and chondrocyte volume in mouse articular cartilage [101]. These interventions aim to remodel the mechanical microenvironment within fibrotic cartilage ECM or surrounding fibrotic chondrocytes, thereby promoting a pro-chondrogenic environment. Thirdly, in regards to cartilage tissue engineering and scaffold design, scaffolds used for cartilage regeneration should be biodegradable, biocompatible, and capable of providing optimal mechanical support to facilitate cell proliferation and tissue repair. Notably, cartilage organoids provide a novel and effective potential approach for evaluating biomaterials. Those of organoids, as an advanced platform, provide the mechanical microenvironment of OA to evaluate the mechanical and biological properties of cartilage in vitro. Vainieri et al. [102] demonstrates the demands for cartilage organoid to not only maintain chondrocyte proliferation, but also provide appropriately mechanical microenvironment to response mechanical stimuli. Bioprinting technology offers the potential to fabricate personalized cartilage constructs that mimic native tissue architecture. Ensuring that these regenerative constructs remain biologically active is a critical factor for successful

cartilage repair.

5.1.3. Low oxygen tension of cartilage microenvironment

Healthy chondrocytes reside in a low-oxygen environment within the avascular and anural cartilage tissues. The oxygen content is approximately 6 % in the superficial layer and <1 % in the calcified layer [4]. However, during OA development or trauma, cells within the subchondral bone express angiogenic factors, increasing vascular densities and endothelial cell proliferation. Aberrant neovascularization also results in the upregulation of oxygen levels, leading to a hypoxic defect in the cartilage area. Interestingly, under hypoxia, both healthy and OA chondrocytes highly express Col II and Acan while expressing low levels of Col X and Col I, concomitant with significantly low MMP expression. After isolation from ovine and expansion under hypoxia (3 % oxygen) and normoxia (21 % oxygen), BMSCs showed dramatically superior Col II and ACAN under hypoxia [103]. Moreover, the chondrogenesis of cocultures with a 30:70 chondrocyte:MSC ratio under low oxygen tension has been investigated, demonstrating that hypoxic culture conditions promote chondrogenesis by increasing the collagen II/I expression ratio and matrix synthesis [104]. Herein, we hypothesize that the deprivation of oxygen in fibrocartilage or around fibrotic chondrocytes by biomaterials or chemicals might be effective for converting the phenotype to hyaline cartilage.

Hypoxia-inducible factors (HIFs) are transcriptional activator families that regulate the cellular response to O2 deprivation or hypoxia. HIF-1α is expressed in both normal and OA articular human chondrocytes and is further induced or stabilized by hypoxia [105]. The relatively high constitutive expression of HIF-1α by chondrocytes is a major reason for adaptation to the avascular-hypoxic environment of cartilage. Furthermore, HIF-1α is a hallmark of chondrogenesis during early skeletogenesis via regulated expression of SOX9 in murine hypoxic prechondrogenic cells [106]. Thus, the overexpression of HIF-1α plays an important role in maintaining chondrocyte function by inducing Col II and ACAN while inhibiting Col I and Col III [107]. Under normoxic conditions, the degenerated HIF-α subunit is hydroxylated by HIF-prolyl hydroxylases (prolyl hydroxylation domain protein [PHD]), relating to the ubiquitin–proteasome pathway and specific prolyl residues [108]. Moreover, PHD is pharmacologically inhibited by the cell-penetrating compound dimethyloxalylglycine (DMOG) in human [109]. The delivery of DMOG *in vivo* significantly enhanced chondrogenesis and reduced hypertrophy in proteoglycan-rich cartilaginous tissue generated by porcine MSCs [110]. However, whether oxygen invasion into cartilage directly activates cartilage fibrosis remains elusive, and no studies have verified whether hypoxia effectively induces fibrocartilage hyalinization. Thus, further investigation is required to assess the effect of hypoxia or HIF-1α in fibrocartilage chondrocytes and the feasibility of hypoxia hydrogels targeting fibrocartilage. In our opinion, targeting DMOG to rescue the disorder of HIF-α from PHD after cartilage injury presents a feasible approach for fibrocartilage hyalinization.

5.1.4. Introduction of exogenous collagen II

The content of Col II determines the quality and function of hyaline cartilage. Interestingly, chondrocytes in the early stage of OA are metabolically active, exhibiting increased synthesis of Col II alongside the liberation of matrix-destructive enzymes. Other studies showed that Col II synthesis increased between 4- and 7-fold during OA but was localized in the deep zone of human cartilage [111]. This phenomenon in OA chondrocytes is considered an attempt to restore the ECM and reform degenerative tissue into hyaline cartilage. In addition to constituting the tissue structure, Col II has demonstrated additional chondrogenic ability in canine chondrocytes by increasing GAG and Col II expression [112]. When examining mice cartilage defect model, an injectable hydrogel with Col II and chondrocytes was investigated, yielding satisfactory results after transplantation [113]. Over the past decade, advanced cartilage tissue engineering has propelled the utilization of Col II in combination with other materials in scaffolds to potentiate chondrogenesis and cartilage regeneration. The decellularized cartilage matrix scaffold (DCMS) is an effective strategy for cartilage regeneration, given its identical composition to native cartilage. Thus, a Col II-rich porcine decellularized cartilage matrix scaffold has been used in porcine cartilage and osteochondral defect models, demonstrating significant benefits in cartilage repair. When MSCs were cultured in the combined scaffold with chondroitin sulfate C and Col II, the expression of chondrogenic genes such as GAG and Col2a1 was upregulated, while osteogenic gene expression decreased [114]. As shown in a rat OA model, since most of these studies were conducted in noninflammatory environments, Sun et al. [115]investigated the effect of squid Col II on cartilage repair in degenerative OA and found that it induces M2 macrophage polarization, which in turn produces specific prechondrogenic proteins (TGF-β and IGF). Furthermore, the mesh size of the Col II fibrillar network is approximately 60 nm, and the proteoglycan network space in cartilage is approximately 20 nm [116]. Attention must be paid to exploring methods to facilitate the entry of Col II molecules through the dense fibrotic ECM barrier. Two key advantages of exogenous Col II induction are: (1) increasing the Col II:I ratio by integrating into the existing ECM and (2) enhancing the chondrogenesis of cells localized in fibrotic tissue. However, the effect of exogenous Col II on fibrocartilage requires further verification.

5.1.5. Anti-fibrosis

Fibrosis is a normal process in wound healing. However, an abnormal wound healing process can lead to excessive secretion and deposition of dense ECM content, resulting in excessive fibrosis. Antifibrosis strategies have been extensively researched in other organs, such as the heart, kidney, and lung. Several signaling pathways and proteins have been identified as potential targets for anti-fibrosis, including the TGF-β signaling pathway, YAP1/EN1 signaling pathway, NF-κB/NLRP3 signaling pathway, CTGF protein, and SPARC protein, among others [117]. These signaling pathways and proteins also hold potential as targets for anti-fibrosis in fibrocartilage. Furthermore, the aberrant synthesis of proteins related to cartilage anabolism, including SLRPs, tenascin-C, and laminin, is significantly associated with the progression of cartilage disease [1,4,16,30]. As biologically active ECM components, SLRPs influence cell behavior, implying their involvement in various biological functions and pathogenic mechanisms in human OA [39]. Additionally, the upregulated fragmentation of SLRPs, such as biglycan (BGN), decorin, fibromodulin (Fmod), keratocan, and lumican (LUM), has been reported from human OA joints compared to nonarthritic joints [118]. The major targets involved in cartilage formation and disease progression of SLRPs are members of the TGF-β superfamily and BMP pathways [119]. Moreover, SLRPs are associated with joint development and integrity, particularly in connective tissues such as tendons and ligaments, due to their role in modulating fibril growth and collagen organization [120]. Understanding the influence and mechanisms of SLRPs in regulating matrix anabolism is crucial for devising strategies for fibrocartilage hyalinization. The changes in collagen matrix composition and fiber turnover are essential for fibrocartilage formation and its transformation into hyaline cartilage. However, the roles of several molecules and the underlying complex mechanisms need further exploration before they can be employed as therapeutic targets for fibrocartilage hyalinization.

5.2. Modification of local fibrotic chondrocytes

5.2.1. Cytoskeleton remodeling

Several studies have reported that the distribution and organization of the cytoskeleton play a crucial role in chondrocyte differentiation by regulating cell focal adhesion [121]. The cytoskeletal components include actin, microtubules, and vimentin intermediate filaments. This highly organized network regulates various cellular processes, including cell shape modulation, organelle movement, cell migration, endocytosis, secretion, cell division, and extracellular matrix formation. Since

articular cartilage is a major load-bearing tissue, the cytoskeleton of chondrocytes is essential for "sensing" mechanical stimulation from the ECM and surrounding tissues. Therefore, cytoskeletal alterations and degradation are crucial factors in the onset and progression of OA and cartilage degeneration. Moreover, cytoskeletal activity and structure significantly influence chondrocyte differentiation. Under physiological conditions, actin monomers (globular/G-actin) assemble into highly ordered filaments (filamentous/F-actin) with polarization characteristics. Cytochalasin D, an actin cytoskeleton disruptor, inhibits the aggregation and polarization of chondrocyte microfilaments, significantly promoting the expression of chondrogenic proteins such as SOX9 and Col II, which are essential for maintaining cartilage function [122]. Furthermore, vimentin is a versatile cytoskeletal protein involved in various key processes of cartilage repair. The vimentin intermediate filament network is critical for maintaining the chondrocyte phenotype, and an imbalance in filament disassembly contributes to articular cartilage degradation, ultimately leading to OA progression [123]. Recent human synovial mesenchymal stem cells studies have demonstrated that microtubule stabilization induced by docetaxel significantly enhances hyaline cartilage-like ECM formation [65]. Based on these findings, microtubule stabilization has been shown to effectively inhibit fibrotic factors while enhancing the hyaline cartilage phenotype in human fibrotic chondrocytes [14]. Moreover, for the first time, microtubule stabilization was successfully utilized as a target to transform fibrocartilage formed in rat cartilage injury into hyaline cartilage [14]. Given that the cytoskeleton is influenced by various factors, including biologically active molecules, the local microenvironment, and biomaterials, cytoskeletal remodeling holds significant potential for fibrocartilage hyalinization therapy.

5.2.2. *Biotherapeutics of chondrogenesis*

Growth factors, including TGF-β, fibroblast growth factors (FGFs), and insulin-like growth factor-1 (IGF-1), have been extensively studied in cartilage repair due to their strong proliferation potential and anabolic properties [124]. Temporally coordinated TGF-β3 and dynamic compression have been shown to promote the formation of neocartilage with compressive properties similar to native cartilage by bovine cells [125]. However, dysregulated TGF-β signaling can lead to undesirable effects, such as fibrosis and osteophyte formation in joint tissues [126]. Among the FGF family, FGF18 specifically interacts with FGFR3 in chondrocytes, playing a crucial role in chondrogenesis and skeletal development by promoting proliferation and ECM production in healthy mice chondrocytes [127]. Recombinant human FGF18, sprifermin, has been shown to enhance cellular proliferation, increase SOX9 expression, and improve the Col II:I ratio [128]. Additionally, sprifermin has been verified to reduce fibrotic ECM deposition and promote the secretion of hyaline cartilage-like ECM, making it a promising candidate for fibrocartilage hyalinization. IGF-1, a key anabolic factor in cartilage, plays an essential role in maintaining cartilage homeostasis by balancing proteoglycan synthesis and breakdown in chondrocytes [129]. It also stimulates proteoglycan production in a dose-dependent manner, as evidenced by upregulated [35S]-sulfate incorporation [130]. Although these growth factors have demonstrated efficacy in cartilage repair models of OA and trauma, their effects on fibrocartilage remain unclear. Recently, small-molecule drugs such as kartogenin (KGN) and halofuginone (HF) have gained attention due to their low immunogenicity and ease of production. KGN binds to filamin A, disrupting its interaction with the transcription factor core-binding factor β subunit (CBF-β), and induces chondrogenesis by regulating the CBF-RUNX1 transcriptional program [131]. Additionally, KGN loaded with collagen hybridizing peptide (CHP) has been shown to target fibrocartilage and reprogram fibrotic processes in situ, indicating its potential as a strategy for hyalinization. Intra-articular injection of KGN significantly enhances the restoration of full-thickness cartilage defects, particularly promoting rabbit hyaline cartilage formation [132]. Conversely, HF has been reported to attenuate OA progression by inhibiting subchondral bone TGF-β activity and aberrant angiogenesis, making it a potential preventive therapy for mice OA models [133]. Furthermore, antifibrotic drugs have shown efficacy in other organs, such as the lung, liver, and kidney, but their application in fibrocartilage remains largely unexplored. For instance, pirfenidone exhibits strong anti-inflammatory and antifibrotic effects by inhibiting Col I synthesis, downregulating TGF-β and TNF-α, and reducing fibroblast proliferation [134]. Chan et al. demonstrated that pirfenidone administration increased safranin-O staining in growth plate cartilage following cartilage injury in a mouse model [135]. Several growth factors and drugs have achieved promising or even remarkable results in preclinical studies. However, their effects on existing fibrocartilage or fibrotic chondrocytes require further investigation. These biological therapies for chondrogenesis and fibrocartilage hyalinization provide valuable insights for researchers and clinicians in the field of cartilage repair.

5.3. *Advanced Cartilage Regeneration Materials for fibrocartilage hyalinization*

Current cartilage repair strategies, such as debridement, lavage, microfracture, and autografts, have shown efficacy but remain limited by poor integration with surrounding cartilage, insufficient nutrient supply, and the formation of fibrous tissue instead of hyaline cartilage. To enhance cartilage regeneration, injectable hydrogel-based scaffolds have gained significant attention. These hydrogels offer a biocompatible, biodegradable, and highly hydrated 3D structure that mimics the native hyaline cartilage ECM. Additionally, they enable cell encapsulation and controlled delivery of bioactive molecules through stimuli-responsive release mechanisms. Shi et al. developed a photo-crosslinked injectable hydrogel using an ultraviolet-reactive, rapidly cross-linkable matrix integrated with KGN encapsulated in biodegradable PLGA nanoparticles, effectively promoting porcine hyaline cartilage formation [136]. Considering the fluctuating inflammatory environment in arthritis, Karp et al. designed a hydrogel scaffold based on triglycerol monostearate (TG)-18 encapsulating the corticosteroid triamcinolone acetonide (TA). This hydrogel exhibited controlled disassembly and drug release in response to enzyme concentrations during arthritis flares [137]. Building on these advancements, further research is needed to develop cross-linked hydrogels specifically targeting fibrocartilage characteristics, such as high expression of MMPs and fibrotic proteins. Given the high expression of transferrin in fibrocartilage—a positively charged protein due to its role in iron transport—we previously designed a fibrocartilage-targeting, negatively charged thermosensitive hydrogel for sustained drug delivery, which successfully promoted fibrocartilage hyalinization in a cartilage defect model [14]. Other critical properties of hydrogels, such as tissue integrability and cartilage penetration, also require further attention. Effective penetration and retention of bioactive drugs within dense cartilage ECM remain significant challenges for regeneration. Hammond et al. conjugated a growth factor to a cationic nanocarrier using reversible electrostatic interactions with anionic cartilage tissue, enabling targeted delivery into chondrocytes and prolonged retention within articular cartilage after intra-articular injection [138]. Additionally, decellularized cartilage matrix scaffolds (DCMS) are different from traditional scaffolds and hydrogels, have unique features such as retaining natural extracellular matrix (ECM) components, maintaining the microstructure and mechanical properties of the native tissue, reducing immunogenicity, and preserving bioactive factors [23]. DCMS are divided into three types by the origins of the matrix, which consist of autologous DCMS, allogeneic DCMS, and xenograft DCMS. Several limitations in autologous DCMS remain to be solved, such as difficulty in cultivation, prolonged production cycle and excessive cost. Our pervious porcine study shows allogeneic DCMS induces hyaline-like cartilage in full thickness cartilage defect models. In comparison of autologous DCMS, xenograft DCMS shows the highest potential to clinical transformation, such as extracellular matrix of cartilage from pigs was made

into DCMS for rabbits. Thus, DCMS is a satisfactory and cost-effective strategy for cartilage repair. In summary, future biomaterials designed for fibrocartilage hyalinization should possess the following key properties: 1) Injectable formulation for minimally invasive application. 2) Capability to encapsulate and release bioactive factors or cells. 3) Targeting and adhesion properties specific to fibrocartilage. 4) Ability to penetrate the dense ECM barrier of fibrocartilage for effective drug or factor delivery.

6. Future perspectives

Achieving fully functional hyaline cartilage remains a primary goal in cartilage regeneration. Fibrocartilage formation is a crucial physiological and pathological response to cartilage injury and OA. A deeper understanding of the mechanisms underlying fibrocartilage formation is essential for advancing regenerative strategies. Moreover, elucidating the role of cartilage fibrosis in joint disease is critical for developing more effective therapeutic approaches. In addition to the methods discussed in this review, insights from fibrosis-related diseases in other organs, such as the liver, lungs, and kidneys, may provide valuable strategies for fibrocartilage treatment. We also believe that integrating fibrocartilage hyalinization with cartilage tissue engineering, arthroscopic surgery, and joint-preserving osteotomy will enhance functional cartilage restoration and reduce the need for total joint replacement.

7. Conclusion

This review highlights the differences between hyaline cartilage and fibrocartilage and discusses the pathological characteristics of fibrocartilage in articular cartilage injury and OA. The transition from fibrocartilage to hyaline cartilage presents a significant challenge in cartilage regeneration. However, fibrocartilage itself offers certain advantages for repair, including: 1) it serves as an autologous biological scaffold for cartilage regeneration. 2) fibrotic chondrocytes could be reprogrammed in situ. Based on these advantages, we propose a novel strategy termed “fibrocartilage hyalinization," which aims to: 1) reprogram fibrotic chondrocytes into hyaline chondrocytes in situ and 2) implant stem cells into the fibrotic ECM for regeneration. This strategy has the potential to significantly advance cartilage repair research and facilitate clinical translation, as fibrocartilage is commonly encountered in clinical settings. Additionally, the use of fibrocartilage animal models could redefine treatment paradigms. In conclusion, the concept of fibrocartilage hyalinization represents a promising approach for cartilage repair, warranting further investigation and validation in future studies.

Contribution

JWL and DQS conducted the conception and design. JWL and HMJ performed the drafting of the main part of article. GHT, ZYL, ZZL, ZYS, and XQX participated the drafting of some session of article. DQS and JWL conceived the project and designed the study. JWL, HMJ and DQS performed the edition and final approval of the article.

Data statement

All data relevant to the study are included in the article.

Declaration of competing interest

None declared.

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