
# Biomaterial Integration in the Joint: Pathological Considerations, Immunomodulation, and the Extracellular Matrix

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# Biomaterial Integration in the Joint: Pathological Considerations, Immunomodulation, and the Extracellular Matrix

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**Defects of articular joints are becoming an increasing societal burden due to a persistent increase in obesity and aging. For some patients suffering from cartilage erosion, joint replacement is the final option to regain proper motion and limit pain. Extensive research has been undertaken to identify novel strategies enabling earlier intervention to promote regeneration and cartilage healing. With the introduction of decellularized extracellular matrix (dECM), researchers have tapped into the potential for increased tissue regeneration by designing biomaterials with inherent biochemical and immunomodulatory signals. Compared to conventional and synthetic materials, dECM-based materials invoke a reduced foreign body response. It is therefore highly beneficial to understand the interplay of how these native tissue-based materials initiate a favorable remodeling process by the immune system. Yet, such an understanding also demands increasing considerations of the pathological environment and remodeling processes, especially for materials designed for early disease intervention. This knowledge will avoid rejection and help predict complications in conditions with inflammatory components such as arthritides. This review outlines general issues facing biomaterial integration and emphasizes the importance of tissue-derived macromolecular components in regulating essential homeostatic, immunological, and pathological processes to increase biomaterial integration for patients suffering from joint degenerative diseases.**

## 1. Introduction

Cartilage erosion and degradation are hallmark features of diseases with increasing incidence such as osteoarthritis (OA) or the autoimmune rheumatoid arthritis (RA).[1–4] Here, the goal of cartilage regenerative medicine is to fully integrate a material within the articular tissue to aid or replace the malfunctioning joints.[5] To regain joint motion and reduce pain for these patients, total joint replacement has been the only option for late-stage disease.

However, due to an increased market interest, enhanced therapeutic options, and improved technologies that enable earlier diagnosis, several new biomaterial approaches have been developed. Yet, many of these biomaterials lack full integration, have a limited life span, and don't fully recapitulate the intricate tissue structure. This has led to few materials reaching the clinical stage before being terminated.[6,7] One promising approach in reconstructing and repairing a variety of tissues, including cartilage, is the use of decellularized extracellular matrix (dECM)-based materials.[8] These materials consist of tissue-derived proteins from harvested organs. They have been stripped of lipids and cellular components that would otherwise contribute to material rejection. While nearly every tissue type has been decellularized and used for different applications, there is little consensus on optimal composition since the contents of the tissue source depend on many physical factors which result in a wide heterogeneity.[8] Compared to synthetic foreign objects, dECM-based biomaterials can reconstruct tissues faster due to their capacity to not merely act as a biomaterial scaffold, but to also neutralize pathogenic signaling.[8,9] In pioneering work from Prof. Eliseeff's lab, a key mechanism to a favorable integration and reconstruction process involved engaging the immune system.[10,11]

Yet, during the tissue remodeling process, several factors could dictate the fate of the implanted material including released extracellular matrix (ECM) components, environmental abnormalities such as loss or gain of hypoxia, and the recruitment of primed immune cells and their subsequent foreign body response (FBR).[12] Immune engagement in diseases with an already active immunoregulatory pathogenesis could compromise the biomaterial integration process. For diseases such as OA and

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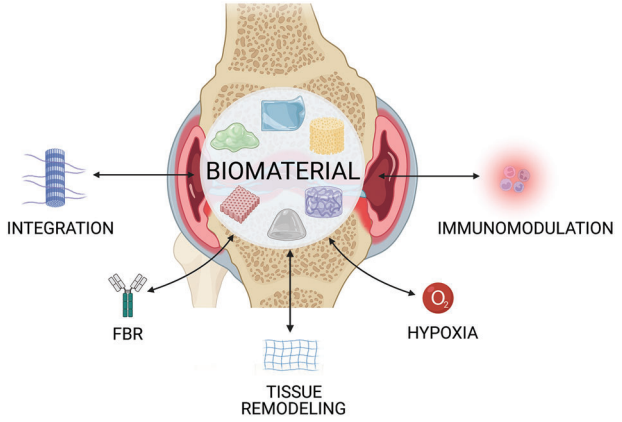


**Figure 1.** Overview figure illustrating the considerations and potential limitations for biomaterials in a pathological joint. Several biomaterial structures are exemplified in the circle.

RA, the goal of implants in general is to support the joint function, and for biomaterials in particular, the objective is to regenerate the cartilage tissue. However, the cartilage tissue and joint organ are highly complex, and a biomaterial aiming to regenerate a full depth cartilage must take numerous factors into considerations. Hurdles include developing a construct that mimics the tissue's mechanical properties and the complex tissue structure since the hyaline tissue phenotype may change during tissue reorganization. Predicting long-term success of cartilage treatments is further challenged by the overall pathological condition, heterogeneity of the disease, patient lifestyle, and other physical factors.[13–15] The aim of this review is therefore to summarize important organ and tissue specific features and highlight pathological and immune-related mechanisms that biomaterials face in patients with OA and RA (**Figure 1**). A particular section deals with how the cartilage ECM components can interact with immune cells, to provide increased awareness of arthritides, and to identify potential targets and strategies to increase tissue integration of developed biomaterials.

## 2. The Pathological Environment Can Influence Biomaterial Integration

In diseases affecting the joints, like RA and OA, all the articular tissues are affected and contribute to the pathogenesis. While much emphasis has been put on cartilage degradation and reduced friction from the synovial fluid, additional factors, including the cartilage-ECM producing cell the chondrocyte, are involved, and engaged in joint pathologies. In this section, we therefore give an overview of cartilage degradation and additional pathological processes that are oftentimes overlooked when investigating biomaterial integration.

### 2.1. The Stratified Cartilage Tissue Architecture during Pathogenesis

Many implanted biomaterials behave differently from expectations based on in vitro models. The architectural importance of hyaline cartilage is directly associated with the function of the tissue, which is especially apparent in weight-bearing joints. The biomaterials field still struggles with questions such as why chondrogenic lab constructs do not produce hyaline phenotypes in different cultures and why hyaline constructs certified in vitro revert to fibrocartilage at longer time points in vivo. Some of the reasons lie not only in the complex tissue architecture of the healthy cartilage with its mechanical resilience-properties that are difficult to reproduce with biomaterials, but also in the tissue being remodeled during pathogenesis.

The dense network of the hyaline cartilage ECM is distinctly stratified based on the depth of the tissue, as can be seen in **Figure 2**. This organization is a part of the unique features that leads to the incredible mechanical resilience of the hyaline cartilage and stems from the tissue being stratified into distinct zones (Figure 2A). The direction of collagen type II (COL2A1) fibers changes from parallel to the surface, to perpendicular as the tissue depth increases (Figure 2B).

Development of OA is characterized by the increasing deterioration of the cartilage surface, reaching further deeper zones as the disease progresses (Figure 2C). Cartilage associated pathologies often begin at the superficial zone that is subjected to the interactions with synovial fluid and its components. This interaction determines the lubrication of the tissue, thus enabling it to withstand shear stress and sustain tensile strength. This in turn suggests the need for lubrication properties in a biomaterial when targeting the early stages of cartilage degeneration. In the cartilage, hyaluronic acid (HA) interactions with lubricin and phospholipids ensure the entrapment of water in the tissue while preserving the underlying zones.[19,20] As the largest, middle zone is responsible for stress and compression resistance; an abundance of structural collagens and glycosaminoglycans (GAGs) is crucial for tissue stability and performance. Here is also where we find the most chondrocytes, which are considered the most active producers of collagens and aggrecan under both normal and OA conditions.[21] The deep zone of the cartilage possesses the most anionic charge due to high proteoglycan (PG) content, thus further contributing toward the mechanical resilience of the tissue. Collagen X is also found here, marking the transition of the cartilage tissue toward ossification.[22] Collagens such as IX, XII, XIII, and XIV are complimentary collagens associated with fibril interactions, although they do not form fibrils themselves. They are considered to bridge the stability of the ECM and help sustain osmotic and mechanical stress.[23–25] Distinct zonal architecture, negative charge of GAGs, and collagen scaffolding all contribute to the resilient properties of cartilage. Numerous reports have stated that mechanical stress is an important modulator of the native articular cartilage, which together with metabolic activities serves to maintain the cartilage homeostasis. Excessive mechanical forces such as constant, cyclical load leads to cartilage damage and development of pathologies such as OA.[26] Replication of the highly ordered nanonetworks of the cartilage remains a big challenge in cartilage tissue engineering.

Mechanical forces are also highly relevant to consider for the pericellular matrix immediately surrounding the chondrocyte. During the onset of OA, the spatial organization of the chondrocyte changes, followed by rearrangement of the pericellular matrix.[27] The pericellular matrix is especially dynamic as it is highly accessible to the chondrocyte and readily modified. The

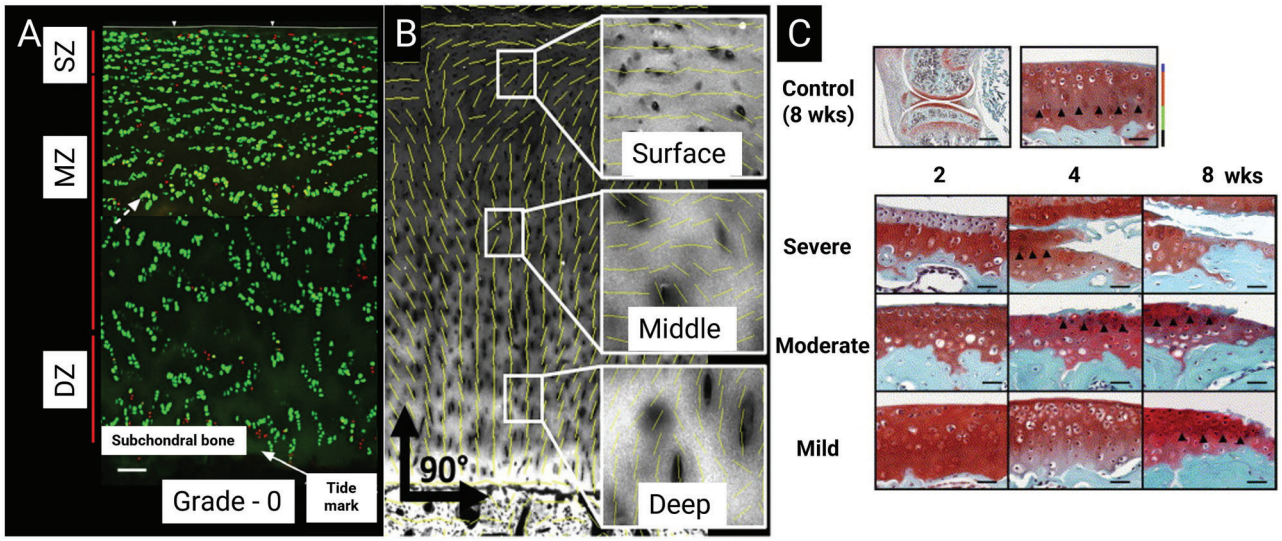


**Figure 2.** The overall structure and composition of the ECM in articular cartilage under normal and OA conditions. A) Representative confocal scanning laser microscopy low power (×10) images of 5-chloromethylfluorescein diacetate- and propidium iodide-labeled chondrocytes viewed in the coronal plane. The approximate thicknesses of the zones (SZ = superficial zone; MZ = mid-zone; DZ = deep zone) are shown by the red bars on the left. B) ECM collagen fiber orientation varies based on the depth of the tissue. C) Histologic representation of the mouse knee joints depicting severe, moderate, and mild OA. A) Reproduced with permissions.[16] Copyright 2020, John Wiley and Sons. B) Reproduced with permission.[17] Copyright 2020, Elsevier. C) Reproduced with permission.[18] Copyright 2005, Elsevier.

matrix molecules are either bound directly to the plasma membrane or to transmembrane receptors that can activate intracellular signaling and subsequent gene activation. It has been suggested that the onset and progression of OA pathogenesis lies in changes in the pericellular matrix, secondary to other stimuli such as genetic or epigenetic changes.[28] Zelenski and colleagues demonstrated that the knock-out model of type VI collagen in mice leads to decreased stiffness and swelling in chondrocytes. Their results suggest that type VI collagen mediates the role of mechanical signal transduction between the pericellular matrix and the cell.[29] For biomaterial integration, and especially for cartilage regeneration, it is important for chondrocyte maintenance to recapitulate this specialized environment in order to achieve long-term biomaterial integration.[30–33]

While synthetic materials are more easily tuned to provide mechanical stability, reproducibility and mechanical strength remain to be resolved for dECM-based materials. Material characteristics may differ depending on the source and its physiological properties including size, age, health status, as well as the chosen processing technique for obtaining the material. Depending on the end-goal of the dECM product, protocols may employ use of harsher or milder chemical agents that may compromise the molecular profile of the cartilage. This includes the potential loss of minor collagens, PGs, and GAGs which contribute to the mechanical resilience of the tissue.[34] In addition to mechanical properties, porosity of the scaffold is another important feature required for cellular growth and the regeneration of the tissue. An optimal balance between the appropriate stiffness of the material prior to and post infiltration should be evaluated for biomaterial integration. Dense scaffolds may require remodeling for cellular integration, prolonging the regenerative process, and evoking immune interactions, while materials with a high degree of porosity may lack the mechanical support that is crucial to the scaffold. Nevertheless, patients with cartilage defects should receive a tailored strategy to fit the mechanical and biomolecular support posed by the native tissue. Newly emerging 3D bioprinting techniques of cartilage scaffolds have made promising progress toward personalized treatments enabling the modifications of molecular parameters according to the patient's needs.[35]

### 2.2. Matrix Component Remodeling during Pathogenesis

The main concern regarding regenerative biomaterials applied to cartilage damage has been the avascular nature of the tissue, as it has a major effect on nutrient transport, cellular communication, and tissue phenotype. However, during the pathogenic remodeling process of cartilage degradation, matrix constituents are broken down into smaller fragments that impact the viscoelastic and mechanical properties of the tissue and affect the crosstalk between the chondrocytes and immune cells. These proinflammatory processes are further major contributors of cartilage degeneration, perpetuating the proteolytic action on the cartilage, either in case of massive inflammation as in RA, or mild and subclinical inflammation, as in OA.[36,37] The enzymes active in these processes include metalloproteases, such as the families of matrix metalloproteases (MMPs) and aggrecanases (a disintegrin and metalloprotease with thrombospondin motifs [ADAMTSs]) that break down collagens and aggrecans.[38,39] Protease-induced degradation breaks down collagen fibers from their native 200 nm diameter to smaller fragments, initiating tissue remodeling and modifying tissue integrity.[40] In **Figure 3**, the degradation of collagen fibrils during OA can be seen, where the larger fibers have been degraded from 200 to 40–60 nm (A), to an ultimate formation of a wool-like structure (B) with entanglement features (C).

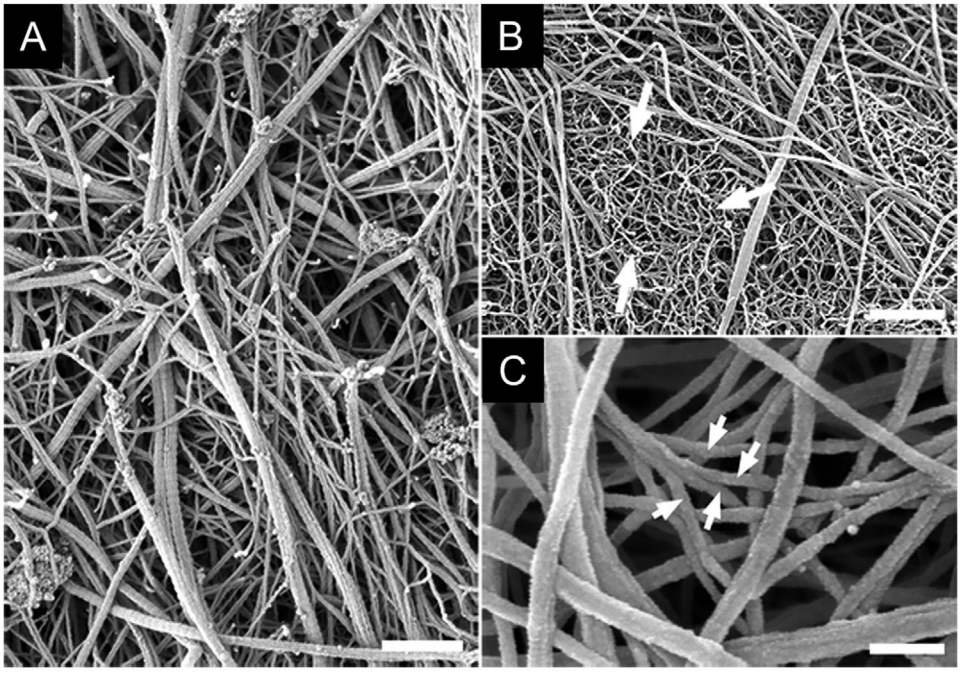


**Figure 3.** Scanning electron microscopy (SEM) images providing an overview of articular cartilage of OA patients after enzymatic depletion of the proteoglycan moiety. A) SEM image of grade 3 osteoarthritic cartilage (knee), exhibiting breakdown of thicker collagen fibers with a diameter of 40–60 nm into thinner fibers down to bundles made of only one prototypic fibril of 18 ± 5 nm in diameter. B) SEM image of grade 3 osteoarthritic cartilage (knee) shows the end-stage of fiber breakdown, that is a wool-like structure (white arrows) with filaments exhibiting a diameter of $d = 13 \pm 2$ nm. C) Degrading articular cartilage larger fibers split into smaller sized fibrils that are often arranged as a highly entangled fibrillary meshwork (white arrows). Scale bars = 500 nm (A,C); 100 nm (B). Reproduced under the terms of the CC-BY 4.0 license.[40] Copyright 2016, The Authors, published by Public Library of Science.

### 2.3. Altered Tissue Environment during Pathogenesis

Due to the avascular nature of cartilage, the native tissue environment is characterized by hypoxia.[41] It is well-established that a hypoxic environment ($\leq 5\%$ $O_2$) benefits cartilage by limiting chondrocyte catabolic activity, enhancing survival, and ECM production.[42–44]

Moreover, the hypoxic environment stimulates chondrocytes to a greater release of PG (**Figure 4**A) and type II collagen (Figure 4B) compared to normoxic growth conditions. The long-time golden standard surgical intervention of bone marrow stimulating procedures aim to promote tissue formation by evoking a tissue healing response.[45,46] Yet, disturbance of oxygen levels have effects on cartilage cell gene expression, chondrogenesis, metabolism, as well as production of integral molecules such as GAGs and various growth factors.[47] Cellular responses to oxygen levels are governed by hypoxia inducible factor (HIF) complexes in both immune cells and chondrocytes. Hypoxia contributes to T-cell stabilization, macrophage polarization, neutrophil survival, and elevated secretion of inflammatory factors.[48,49] Elevated levels of HIF-1$\alpha$ are associated with pathogenesis in the cartilage as it inhibits chondrocyte hypertrophy in OA and increases angiogenesis which contributes to synovitis in RA.[47,50,51] Increased vascularity creates an ossification-favoring environment, thus shifting a cartilage phenotype toward a bone phenotype which is seen in advanced stages of OA.[52] Despite the extensive evidence on cartilage microenvironment and homeostatic networks, these physiological tissue conditions are often neglected when engineering new materials and therapies.[53,54] Taking such tissue requirements in consideration is of great importance to fully assess treatment efficacy, especially for long-term implications.

Environmental dynamics in the cartilage tissue may also explain why biomaterials, cartilage constructs, and implants do not sustain in vitro characteristics and tend to support the production of fibrous cartilage. Milieu changes affect cartilage resident chondrocytes by reprogramming them to adopt fibroblast-like features, consequently, redirecting the majority of collagen production to type I rather than the type II.[56] For instance, using cellular knock-out studies, removing the production of collagen II induces signals for collagen type I production that ultimately alters the structure and function of the ECM.[57] Cartilage repair leads to fibrocartilage formation, which, structurally, differs from the native hyaline phenotype.[58] Unlike the native cartilage, fibrocartilage is unable to sustain mechanical stress over time, resulting in an amplified inflammatory response, scar formation, and continued degeneration of the tissue.[59] Such clinical outcomes for biomaterials in both OA and RA patients underline the need for long-term follow-up and characterization studies on neogenesis and maintenance of hyaline cartilage phenotypes.[46,60,61,62]

### 2.4. Articular Pathologies Engage the Whole Joint Organ

Pathological features in RA and OA include alterations to the joint capsule, to the synovium, to the cartilage, and to the bone

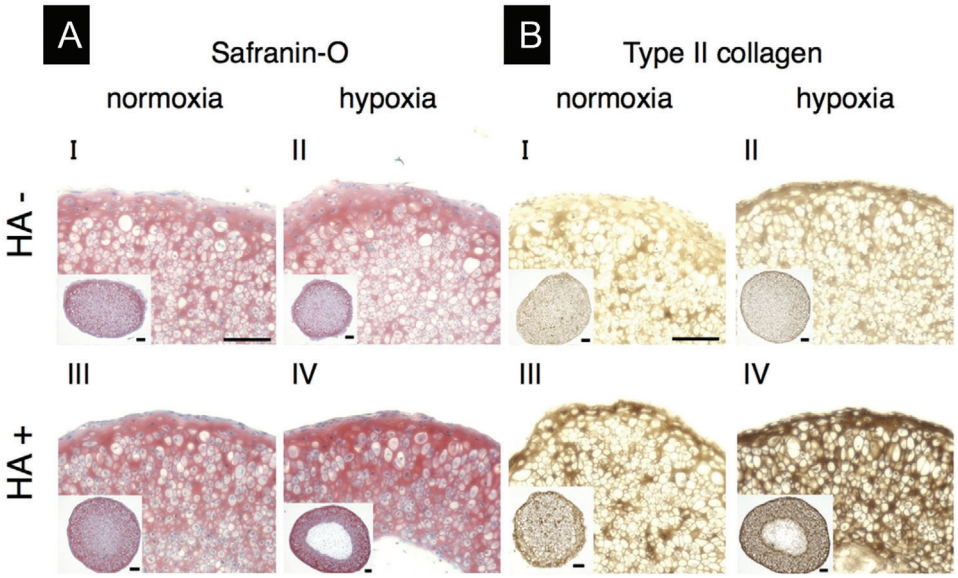


**Figure 4.** Hypoxic environment in articular cartilage regulates the homeostasis of the important extracellular matrix components. A,B) Safranin-O and type II collagen immunostaining in the presence of HA under normal oxygen (normoxic) and low oxygen (hypoxic) conditions. Reproduced under the terms of the CC-BY 4.0 license.[55] Copyright 2016, The Authors, published by MDPI.

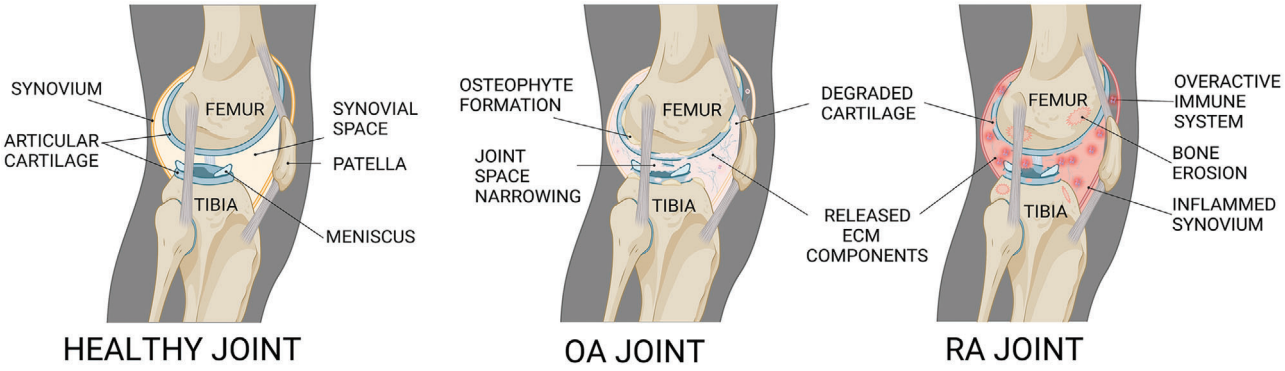


**Figure 5.** Pathologies in arthritic diseases such as OA and RA are evident in the whole joint structure.

tissues (**Figure 5**). These major changes in joint function lead to stiffness and pain. In both RA and OA, the stiffness originates not only from an increased cartilage turnover, but also from an increased bone turnover.[63] In OA, the subchondral bone is greatly affected, with ossification of the growth plate, bone marrow lesions, increased vascularization, and osteophyte formation that stems from changes in chondrocyte signaling. These processes occur in OA over many years. In RA, bone erosions occur not only at the joint margins, but also both periarticularly and systemically, arising from a highly active immune reaction.[64,65] The changes in bone turnover rates and activated signaling pathways may influence the hyaline construct mimicry of a biomaterial and may affect long-term tissue integration, since mineralized collagens can induce osteoformation.[66]

The synovial cavity is protected by a barrier of fibroblast-like synoviocytes (FLS) and locally resident synovial macrophages.[67,68] FLS are the main cells producing HA and joint lubricants such as proteoglycan 4 (lubricin), as well as matrix components for the synovial ECM such as fibronectin and collagens.[69] FLS infiltrate the synovium during both RA and OA. However in RA these cells have a more active proinflammatory profile, including higher expression of proinflammatory receptors compared to OA.[70,71] A classic characteristic of RA includes synovial hyperplasia caused by aggressive and apoptosis-resistant RA FLS.[72] Changes in FLS function in both RA and OA would directly influence synovial fluid composition, and potentially influence the FBR (described below) to an implanted biomaterial. The natural function of synovial fluid is to lubricate and reduce friction between the hard surfaces.[73–75] It closely resembles plasma in its composition, provides nutrients to the different synovial tissues, and has a high turnover rate. In addition to ECM components, we and others have shown increased concentrations of proteinases, cytokines, and growth factors in the synovial fluid during pathogenesis.[73–76] As this is the natural contact fluid for biomaterials in the joint, it also has

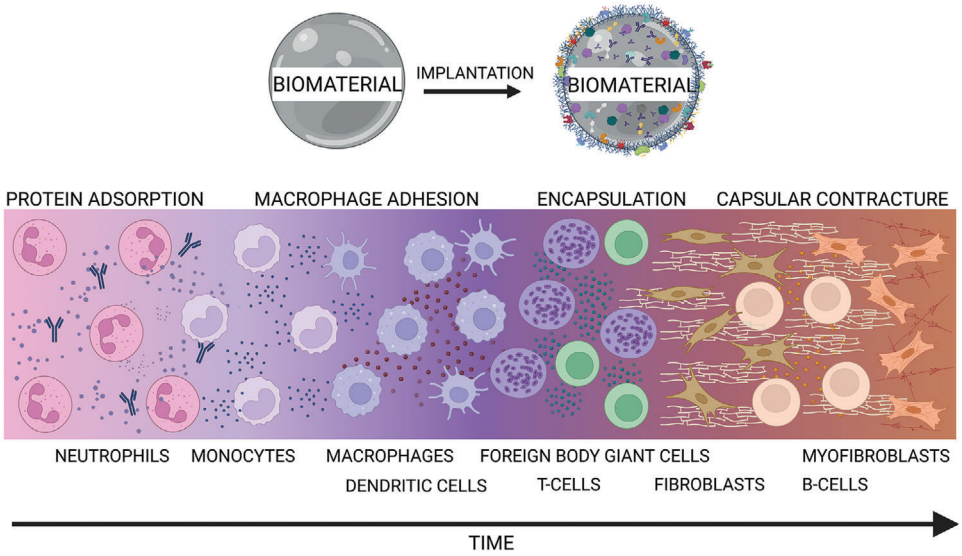


**Figure 6.** Schematic representation of the FBR to biomaterials. The biomaterial is first subjected to protein adsorption and approached by the members of innate immune system such as neutrophils and monocytes. Protein adhesion often leads to monocyte differentiation. This is followed by the process of encapsulation governed by foreign body giant cells, T-cells, and fibroblasts. Capsular contracture occurs as the last stage of FBR and entails B-cells and myofibroblasts.

the capacity to dictate material biocompatibility, integration, and stability.

In addition to the FLS in the synovial lining, a specific type of resident macrophages protects the joint from invading cells as they are able to express proteins associated with tight junctions and are able to form a tight barrier.[67] The membrane that these macrophages form becomes leaky during inflammation, allowing leukocytes such as neutrophils to enter the joint cavity and contribute to disease pathology in both RA and acute inflammatory phases of OA. While this "leaky" phenomenon was noted in RA models, this lining and cells are present in healthy joints, and it has been suggested that these cells could be a target for OA therapies as well.[77] In addition to these macrophages, many different immune components and cells are recruited in joint inflammation of both RA and OA, where $CD14^+$ monocytes and $CD4^+$ T lymphocytes are the most abundant cells in the OA synovial membrane.[78] While these cells contribute to OA and RA pathology, they are also essential for biomaterial incorporation, highlighting the need to understand their involvement and interactions both as individual pathological contributors, as well as their function in tissue repair and biomaterial incorporation.[79]

## 3. Successful Biomaterial Integration Necessitates Balance of Immune Engagement

Full integration of biomaterials demand interactions with the host immune system, determined by the FBR and inflammation. Engineered materials for implants should comply with particular physical and chemical features, be inert, and evoke a limited immunological response from the host. The design of so called "passive" biomaterials was for a long time aimed at avoiding the immune response. In more recent years however, the inflammatory response is instead considered an essential initial reaction in tissue repair and regeneration. The design of a biomaterial can allow for a design aimed at specific biological responses, leading to a beneficial integration process and overall successful biomaterial performance. In this section, we introduce the FBR in general and include a note on how dECM-based materials are able to adjust the FBR toward favorable implantation.

### 3.1. The Foreign Body Response to Biomaterials Determines Integration

Immediately after implantation, proteins, lipids, and sugars from blood cover the external material, recruiting innate immune cells.[80,81] The ensuing immune response depends on factors such as material composition, topography, roughness, and surface chemistry.[81] Early studies demonstrated that the main cells responding to cartilage transplant rejection are monocytes/macrophages, cytotoxic T cells, and natural killer cells.[82,83] This was confirmed in later studies for neocartilage-derived chondrocytes, further emphasizing the essential importance of T-cells and macrophages that has been shown for general biomaterial integration.[10,84,85] Irrespective of material origin, the magnitude and direction of the FBR can dictate a detrimental or—in an optimal setting—a beneficial response. The degree of the host engagement will depend on the extent of the disturbance of the host homeostasis.[86]

Briefly, the sequential order of the FBR after biomaterial implantation includes injury, blood-material interaction, matrix formation, acute inflammation, chronic inflammation, granular tissue development, and finally, development of a fibrous capsule, as illustrated in **Figure 6**.[81] First, the injury to the vascularized connective tissue invokes an inflammatory response aimed to isolate the affected area and subsequently heal the tissue. The resulting change in vascular flow and permeability increases blood flow, fluids, and proteins to the site of the injury. A blood-based

matrix starts to surround the biomaterial in a highly dynamic process, where the initial proteins are exchanged for more surface-active proteins.[81,87,88] In particular, the presence of fibrinogen on the biomaterial surface will control macrophage fusion and the subsequent fibrous capsule formation.[88,89]

During the acute inflammatory process that ensues, neutrophils are recruited to the site of implantation. In the case of joint disease, this can be a significant issue, as the tissue would already be primed for a major inflammatory reaction. While the initial neutrophil recruitment is generally considered to subside within 24–48h, advances in neutrophil physiology and involvement in biomaterial rejection/acceptance suggests that their tasks are far more complicated than initially thought.[81] They remain present in the tissue for up to 3 days during the acute inflammatory response, removing debris via phagocytosis.[90] In certain situations, they are also thought to play an important role in orchestrating the recruitment of resolving monocytes and macrophages, as well as mesenchymal stem cells (MSCs) to the site of regeneration.[91] In parallel, the lining macrophages and FLS might also be primed for proinflammation. Since the lining macrophages control the permeability to the synovial cavity, they could aggravate the FBR.[67] The subsequent steps will therefore be the determining factor for implant acceptance or rejection, as the inflammatory reaction either subsides or continues. Continuous recruitment of monocytes and their differentiation into macrophages will determine if their released inflammatory mediators will recruit more cells, degrade the biomaterial, or start the tissue regeneration process. In many cases, after these macrophages have attached to the material, failed attempts to phagocytose the material ensues—termed frustrated phagocytosis—which may lead to their fusion into multinucleated giant cells called foreign body giant cells.[81,92] Oftentimes, recruited fibroblasts will now direct the formation of the fibrous capsule surrounding the material.[81]

The heterogeneous population of macrophages that are present in the tissue and recruited from the blood pose a threat and an opportunity to control the fate of the biomaterial and implant. A predominance of proinflammatory macrophages that recruit more neutrophils and fibroblasts would lead to an aggravated inflammatory response, or to the recruitment of fibroblasts that secrete vascular endothelial growth factor for new vessel formation. Biomaterials are assumed to function as adjuvants, and there are even cases where they have been seen as suspected triggers of autoimmune diseases.[93–98]

Several approaches have been taken to circumvent the FBR. These approaches include controlling the interactions, quantity, and quality of protein adsorption to decrease the formed capsule and increase neoangiogenesis.[99] Tuning the material size, roughness, and shape or using hydrophilic coatings to preferably create a hydrophilic environment can be used.[100–102] Other strategies include modifying the material to increase vascularity and inhibit the capsule formation.[103–105] However, merely including angiogenic growth factors seem to be insufficient to inhibit the FBR, as the inflammatory reaction still remain, and materials that covers both these aspects seem to be more successful.[106,107] Yet, as soon as the immunomodulating drug that controls the acute inflammation runs out, the immune reaction resurfaces, and substantially longer drug release would be needed to protect against chronic inflammation.[108–111] In the case of arthritides, stemming the inflammation and the local joint pathology by regulating immune cells in general would be highly beneficial, as the local pathology in the joint space contribute to the complex synovial microenvironment. A tissue already predisposed for a proinflammatory reaction could induce a more detrimental FBR instead of a reaching a complete and long-term tissue integration. Questions therefore remain as to how the host immunology beyond the FBR can be optimally utilized for full tissue integration.

### 3.2. Immune-Engaging dECM-Based Biomaterials to Enhance Integration and Limit FBR

By presenting natural physical and biochemical cues, dECM biomaterials are proposed to act as prohealing and limit FBR. The approaches have been to either use pure dECM-based materials, or coat artificial materials with dECM, in order to neutralize the environment and fully utilize immune-directed integration processes. As the materials included are completely natural, the dECM-based materials are proposed to be immune-privileged and able to better avoid rejection.[112,113] In the work of Sadtler et al., they showed that an ECM-based scaffold created a microenvironment conducive to a prohealing environment, including T helper 2 cells that released anti-inflammatory cytokines and tuned macrophages toward a healing phenotype as well. Since the plethora of dECM materials are composed of different biochemical macromolecules and biochemical signals, a generalized FBR for these materials is difficult to conclude. In addition to specific biochemical cues, the chosen decellularization processes, resulting tissue architecture, rigidity, and other physical attributes will dictate the FBR to a dECM-based material. More research on individual components, in both health and disease, are needed for dECM-based materials to fully reach their potential in biomedical applications. An example of such advances in biomaterial strategies comes from Tiruvannamalai Annamalai et al., who showed that by including collagen type II in microtissues consisting mainly of agarose, MSCs were able to survive for longer when differentiated into chondrocytes.[114] It was also shown that these cells then produced sGAGs to a higher extent after 21 days in culture as compared to pure agarose microtissues. Further, Corradetti et al. demonstrated that by grafting chondroitin sulfate on the surface of a collagen scaffold, they enhanced the proregenerative environment even further (**Figure 7**).[115] While these examples show that biomaterials can be coated with specific ECM components to drive regeneration, decellularized tissue in general mainly consists of collagen fibrils, yet other proteins can also be retained to induce cellular signaling.

## 4. ECM Components Modulate Immune Functions

Implants based on the ECM components elicit an immune response of the host by directly binding receptors on the immune cells to modulate their function.[116] These induced responses vary vastly based on the state of the biomacromolecule, its structure, and splicing. Both OA and RA, as a broad mechanism, involve the recognition of danger/damage-associated molecular patterns (DAMPs), also called alarmins.[117–119] DAMPs in both

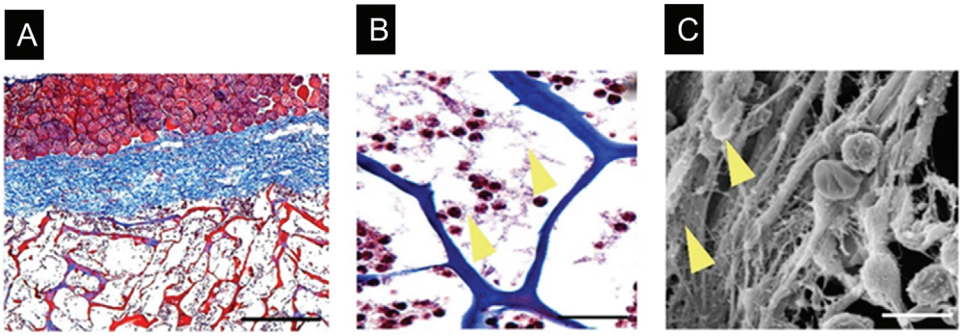


**Figure 7.** Infiltrating cells 1 day after implantation of collagen-chondroitin sulfate (CS) modified scaffolds. A) Masson's-stained section revealed a massive infiltration of cells through the entire scaffold's thickness coming from the surrounding vasculature (Scale bar = 200 µm); B) Magnification Masson's-stained section and C) an SEM image highlighted a high level of fibronectin on the scaffold surface (yellow arrows) (scale bars = 40 and 15 µm, respectively). Reproduced under the terms of the CC-BY 4.0 license.[115] Copyright 2017, The Authors, published by Springer Nature.

pathologies initiate and stimulate the immune system via pattern recognition receptors, engaging both innate and adaptive immune responses. These DAMPs can all originate from the cartilage ECM. Understanding how ECM components interact and modulate the function of immune cells could be a new strategy to drive this response toward new cartilage formation. In this section, we further highlight structural ECM components, and their pathogenic roles under joint inflammatory conditions, and include some examples of their use as biomaterial components.

### 4.1. Collagens

In the articular cartilage, the collagen network provides structural support for the tissue as well as supports the other protein networks yielding high resistance to mechanical loads.[22] In hyaline articular cartilage, collagen type II represents 90% of the collagen mass.[59] They bind to integrins $\alpha$1-, $\alpha$2-, $\alpha$3-, and $\alpha$10$\beta$1 to induce effects and initiate signaling cascades.[120,121] Collagens are highly immunocompetent, and from a biomaterial perspective, they have been extensively researched due to their abundance as structural components.

#### *4.1.1. Collagen Type I*

Collagen type I has been extensively used as a tool for engineering 3D networks in vitro and possess easily tunable topological and mechanical properties for specific purposes.[122,123] Early studies showed that collagen-based scaffolds only induce a minimal immune response, and much research has gone into investigating this material in tissue engineering and regenerative medicine.[112,122] Biomaterials containing more collagen type I than collagen type II have been used to repair hyaline cartilage damage, however, they been shown to be insufficient for long-term replacement.[124]

The conserved amino acid repeats Gly-Pro-Hyp of collagen interact with the leukocyte-associated immunoglobulin-like receptor 1, whose activation inhibits the proinflammatory function of natural killer cells, effector T cells, B cells, and dendritic cell precursors.[125] While intact collagen I provides structural support in the cartilage and may not evoke an immune response, macrophages have a high affinity to collagen type I through several receptors, including macrophage scavenger receptors, which recognize and bind degraded collagen fibrils to identify and clear a damaged tissue.[126] It was shown that the murine macrophage cell line RAW 264.7 adhere easily to heat-denatured or collagenase-modified type I collagen. Instead they adhere poorly when cultured on fibrillar type I collagen appearing rounded and loosely adherent (**Figure 8**).[126] Similarly, U937 macrophages (human-derived cell line) selectively establish a more extended contact surface with damaged collagens fibrils compared to collagens isolated from a control tissue.[127] Collagen density and pore size in a 3D-collagen scaffold regulated cytokine production from THP-1-derived macrophages: cytokine concentration increased when cells were cultured in 3D collagen matrices with high fibril density.[128] These studies suggest that the attempt of macrophages to repair the damage is affected by the modification of the collagens fibrils, their density, and rearrangement. As mentioned previously, chondrocytes adopt fibroblast-like features when their surrounding environment changes, in this case if surrounded by more collagen type I than II. This also redirects the chondrocyte's production toward collagen type I, a more fibrocartilage structure, rather than the physiological collagen type II.[56] Using collagen type I in a biomaterial could therefore be both detrimental by activating macrophages, yet simultaneously might reduce other proinflammatory signaling.

#### *4.1.2. Collagen Type II*

Despite its higher abundance in hyaline articular cartilage, less effort has been put into engineering collagen type II-based biomaterials. While natural hyaline cartilage contains a large amount of type II collagens, from a materials perspective, it is less rigid, and it is more difficult to produce solid structures than type I collagen.[59,129] The pathogenic bioactivity of type II collagen has been demonstrated in several disease models, including OA and RA. Fragments of collagen type II produced after protease cleavage by collagenase not only induce the expression of MMPs and prodegradative cytokines such as interleukin (IL)-1 and TNF-$\alpha$, but also enhance collagenase activity by engaging integrin receptors.[130] Early in the inflammatory processes,

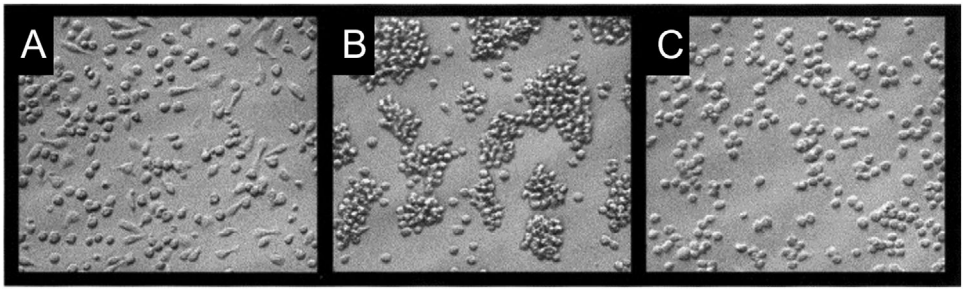


**Figure 8.** Macrophages cultured on type I collagen. RAW 264.7 macrophages were plated on A) uncoated tissue culture plastic, B) fibrillar type I collagen, and C) monomeric type I collagen. A) Reproduced with permissions.[126] Copyright 2000, Elsevier.

circulating monocytes differentiate into macrophages upon DAMP stimulation and infiltrate the damaged tissue. Macrophages are systemically activated in RA with a peak in the early phase of the inflammation, attempting to repair cartilage and at the same time contributing to cartilage degradation.[131,132] In the early phase, M0 macrophages, under the stimulation of INF-$\gamma$ and TNF-$\alpha$, differentiate into M1 proinflammatory phenotype. In the later stage, when the adaptive immune response enters the game, an anti-inflammatory and prochondrogenic phenotype is promoted by the differentiation of M0 to anti-inflammatory M2 state. M1 macrophages affect the cartilage deterioration by releasing cytokines like IL-6, IL-1$\beta$, TNF-$\alpha$, and oncostatin, leading to downregulation of collagen type II; the latter, instead, activates M2 macrophages engaged in cartilage repair.[132–135] Type II collagen can also activate M2 macrophages engaged in cartilage repair. Therefore, type II collagen isolated from squid has been proposed as a new material for cartilage repair: it promotes macrophage polarization toward a pro-chondrogenic gene expression.[136] Yet, collagen type II is also the target of autoreactive T cells in human RA and in the murine model of collagen-induced arthritis.[137] Interestingly, in RA, the T-cell epitope is present in a nonglycosylated form of collagen type II, whereas the glycosylated protein is present in the healthy cartilage, and avoids recognition by T-cells.[138] In addition, as mentioned previously, in the absence of collagen type II, chondrocytes produce more collagen type I, which ultimately alters the structure and function of the ECM.[57] These versatile functions of collagen type II should be taken into consideration before introducing it into a biomaterial, as despite its function in the healthy cartilage, it could provoke an immune reaction during tissue reconstruction.

### 4.2. Proteoglycans

PGs are a large family of polymer proteins found either extracellularly on the chondrocyte surface, anchored to the membrane, or in the extracellular space.[139] PGs are increasingly added to biomaterials in order to improve biological functions, where some have progressed to clinical applications.[140] The attention stems from their capacity as vital regulators of key cellular functions due to their intense decoration with reactive sulfide groups. However, from a chemical perspective, they have been challenging to incorporate as the conjugation processes can alter their biological activity.[141] Heparan sulfate PGs for instance are, in addition to presenting growth factors to cells, vital for generating long-range gradients for morphogens during the tissue regenerative process.[139] This gradient is also known to attract neutrophils to a damaged site.[142] Neutrophils removed by irradiation in a mouse model of inflammatory arthritis decrease the amount of PGs compared to the nonirradiated mice, suggesting that neutrophils, participate in and promote cartilage repair.[143] PGs' interactomes are being mapped to elucidate their connections with matrix components, cytokines, growth factors, and cell signals to clarify their numerous cell-regulating properties.[144,145] Their main mode of action is to induce autophagy—the crucial process of maintaining metabolic homeostasis.[146] This includes regulating metabolic functions independently of access to nutrients, which has recently been reviewed for endothelial and tumor cells by Neill et al.[147] They therefore comprise highly interesting regulatory constituents of the avascular cartilage.

#### *4.2.1. Aggrecan*

The main cartilage PG is aggrecan, a high molecular weight (>2500 kDa) aggregate and a protein heavily glycosylated by chondroitin sulfate and keratan sulfate chains.[148–150] As a structural component it equips the tissue with weight-bearing properties due to water-attracting properties through its negatively charged keratan sulfate and chondroitin sulfate GAG side chains.[151] As a bioactive component in cartilage, it can promote chondrogenesis, a property that also has been shown to be retained as a coating for biomaterials.[152–156]

Yet aggrecan is also highly immunogenic, and it is considered one of the potential autoantigens in patients with RA.[157–160] An aggrecan residue cleaved by ADAMTS has been shown to interact with toll-like receptor (TLR) 2 and can thereby act as a DAMP contributing to pain symptoms in arthritic joints.[161,162] In addition, both the core protein and polysaccharide constituents can be modified and fragmented by reactive oxygen species, highly active signaling molecules and tissue destructing biochemical signals in arthritis.[163] Aggrecan injection in BALB/C mice induces a progressive polyarthritis with high production of autoantibodies immediately followed by a massive proliferation of autoreactive $CD4^+$-T cells, triggered by B-cells antigen presentation.[164–166] In particular, the G1 domain of aggrecan is responsible for activating a cellular immune response, which has been demonstrated both in ankylosing spondylitis and RA.[167] These MMPs cleave aggrecan to generate the neoepitope

VDIPEN, which has been found in areas with extensive PG depletions in a mouse model of arthritis.[168] In both RA and OA, MMPs in cartilage can be activated by elastase released from neutrophils.[169,170] As aggrecan is highly abundant in cartilage, it is not surprising that it has many different functions both in health and disease, and its bioactivity holds promise as a component to enhance biomaterial integration.

#### 4.2.2. Small Leucin-Rich Proteoglycans

The small leucin-rich PGs (SLRPs) maintain cartilage tissue integrity by cross-linking the collagens in the ECM.[139,171–173] In a recently published review on the overall roles of SLRPs, Zeng-Brouwers et al. outlined some interesting findings regarding how the SLRP controls sterile inflammation toward anti- or pro-inflammatory responses, by regulating which coreceptors these factors signal through.[174] These proteins play important roles as signaling molecules in both inflammatory and autoinflammatory diseases and as such, has great potential as immunocompetent biomaterial structures.

*4.2.2.1. Perlecan*: Perlecan is an essential signaling component of the pericellular matrix closest to the chondrocytes, as mentioned previously. Through its heparan sulfate side chains, perlecan can interact with several ligands and cell surface receptors, thereby affecting cell adhesion, growth, and survival.[175–178] Their wide function depends on the cleavage of the heparan sulfate chains by different proteases.[179,180] With its proximity to the chondrocyte, the finding that perlecan can facilitate autophagy or mitophagy in tumorigenesis is highly interesting also in OA, where a dysregulated autophagic process has been suggested as a disease mechanism.[181] Perlecan seems to mainly play a role in leukocyte migration. In the junctional epithelium, perlecan was found to be the primary ECM molecule in the intraepithelial stroma, which leukocytes used as a migration scaffold.[182] Such properties are highly interesting for using perlecan as a bioactive biomaterial component.

*4.2.2.2. Decorin and Biglycan*: Decorin (50–200 kDa) and biglycan (42–45 kDa) belong to class I SLRPs and share 55% homology.[139] Biglycan has been implicated as a danger signal in inflammation, where high levels of soluble biglycan were found in advanced OA and RA synovial fluid.[183] Treating chondrocytes with biglycan produced mRNA of proinflammatory mediators by signaling via TLR 4.[183,184] Decorin null mice develop more severe OA in the destabilization of the medial meniscus model and develop prominent osteophytes, suggesting a potential role as a bone-cartilage crosstalk molecule.[185] A greater proportion of soluble GAGs were released in the media from harvested mouse explants. However, explants stimulated with IL-1$\beta$ did not show an altered expression of either anabolic or catabolic genes. Decorin was shown to delay the loss of fragmented aggrecans and fibrillation of the cartilage surface and was shown to provide an important anchoring molecule in cartilage degeneration.[173,185] Further anti-inflammatory properties include it's function as a barrier in preventing the adhesion of neutrophils on intact bovine articular cartilage.[186] Yet, intact decorin contains both the protein core and GAG chain, and can trigger proinflammatory responses in macrophages.[187] Potential cartilage regenerative properties were shown in experimental cell studies, where macrophages were able to cleave decorin and release a chemotactic agent for mesenchymal stromal cells.[188]

*4.2.2.3. Fibromodulin*: Fibromodulin has been used in biomaterials due to its capacity to reprogram human fibroblasts into multipotent cells.[189] Fibromodulin modulates collagen II fibrils, and fibromodulin null mice develop higher histological arthritis scores.[190–194] Its mechanism lies in its abilities to act as a sequester of the TGF-$\beta$/BMP proinflammatory superfamily and prevent their binding to cellular receptors.[192,195] In line with such anti-inflammatory properties, research also suggests that fibromodulin functions as a barrier to prevent cell adhesion and subsequent cartilage damage. Similar to decorin, administration of fibromodulin can prevent the adhesion of neutrophils and fibroblasts to articular cartilage surfaces.[186,196] Yet in RA and OA, it can activate the classical and alternative pathways of complement via direct binding to C1q and C3b, thereby being able to interact with both the classical and alternative complement pathways.[197,198] Such data suggests that biomaterials containing fibromodulin should pay particular attention to the protein corona adhesion early in the FBR reaction.

### 4.3. Fibronectin

Fibronectin's natural function is to form a fibril network that serves as a template for proper collagen fibrillogenesis, and as a key constituent of the pericellular matrix, it can engage chondrocyte integrin receptors.[199,200] When used in a biomaterial setting, fibronectin bound to the fibrous surface of an implant induced chondrogenesis.[201] Due to alternative splicing events, fibronectin is cleaved into different isoforms during pathogenic remodeling. Such fragments are highly present in the synovial fluid of both OA and RA patients.[202,203] Depending on the origin of the fragment, they engage specific chondrocyte receptors. Certain fragments can induce proinflammatory cytokine production and MMP-expression by signaling through TLR2.[204,205] In monocytes, such a TLR activation leads to MMP 9 induction and release together with IL1-$\alpha$, IL-1$\beta$, IL-6, IL-8, TNF-$\alpha$, and NO.[205–208] At high concentrations, a specific 29 kDa fragment of fibronectin activates protein kinases and induce MMP expression by signaling through integrin $\alpha_5\beta_1$. However, at lower concentrations, signaling by this specific fragment instead induced matrix synthesis.[206] In addition, fibronectin III domains potently induce aggrecanase activity by signaling through TLR 4, which further contribute to cartilage degradation.[209] However, the demonstrated chondrogenic properties when used as a biomaterial suggest a potential for harnessing the matrix synthetic abilities and a beneficial short-term role, but long-term studies are needed to confirm fibronectin's complete bioactivity as a biomaterial component.

### 4.4. Hyaluronic Acid

HA is a linear, charged, hydrophilic polymer containing sulfated substituents, and due to the presence of uronic acid exhibits a negative charge.[210] It has been widely studied both as

a viscoelastic supplement in OA as well as a biomaterial component. As mentioned previously, HA is partially responsible for the lubrication and viscoelasticity of the cartilage and synovial fluid. Endogenous HA is found in both cartilage tissue and the synovial fluid bathing the joint space. As a bioactive component, HA has been shown to regulate several cellular functions and biological processes by signaling via cell surface receptors such as CD44, RHAMM, LYVE-1, Layilin, and TLRs.[176] HA signaling through CD44 induces both anabolic and catabolic gene expressions.[211] The CD44 receptor serves as the critical link between hyaluronan-PG aggregates and the chondrocyte cell surface.[212] The binding of high-molecular-weight (HMW) HA at the cell surface represents the quiescent, nonactive state of chondrocytes. The binding of the long-chain HA does not induce cell signaling.[213] Intact, HMW HA has shown anti-angiogenic and anti-inflammatory properties.[214] In contrast, multiple studies have shown that low molecular weight HA promotes proinflammatory signals in immune cells.[215] HA at high molecular weight can be cleaved in fragments of different sizes by hyaluronidases or free radicals,[216–219] which in turn can augment the production of NO in chondrocytes in a CD44-dependent mechanism.[211] Small HA oligosaccharide binding and signaling via CD44 also induces stimulation of genes involved in matrix degradation.[220] This includes induction of MMPs and elevated aggrecanase levels via the NF-$\kappa$B signaling pathway, while simultaneously inducing matrix repair genes including type II collagen, aggrecan, and HA synthase 2. In both human and bovine chondrocytes, treatment with HA oligosaccharides results in NO production similar to IL-1 treatment.[221] Smaller fragments also activate the TLR2/4 receptor and CD44 on dendritic cells.[222,223] HA and several different PGs can regulate dendritic cells maturation and chemotactic activity.[224–226] In addition, HA, as well as chondroitin sulfate, promote the maturation of monocyte-derived immature dendritic cells and can induce overexpression of antigen-presentation and costimulatory molecules important for T-cell activation.[225] Studies showed that 120 and 1260 kDa HA treatment did not induce the production of NO, suggesting that the cutoff for proinflammatory HA signaling is below 120 kDa. Supporting these findings are studies from RA patient-derived chondrocytes and healthy peripheral blood monocytes, where 1680 kDa fragments did not increase the expression of proinflammatory cytokines.[227] The mechanism underlying the polymer length-dependent HA signal transduction is suggested to be due to the oligosaccharides serving as competitive receptor antagonists that displace HMW HA from the cell surface to induce cell signaling events,[228–230] and differential clustering of HA receptors triggered by their multivalent interaction with HA.[231,232] It is clear that the length of HA has a profound impact on chondrocyte function both in health and disease, which should be taken into consideration when designing biomaterials that include HA components. HA utilize the hydrophilic nature of the material and strong hydrogen bonding interactions for prolonged water retention in the joint space and to lubricate the cartilage surface.[233] This lowers the friction coefficient for joint movement and supports the resistance to loads and mechanical forces.[234] Its innate structural contribution to the cartilage has made it an attractive biomaterial for tissue engineering scaffolds, although its role in de novo tissue formation remains questionable.[235,236]

## 5. Current Biomaterial Approaches for Articular Cartilage Repair

A plethora of cartilage treatments have focused on repairing, replacing, or regenerating tissue function together with increasing the mobility and overall well-being of the patient.[237]

Natural material injection therapies such as platelet-rich plasma (PRP) and/or ECM components such as HA, have been extensively investigated for both OA and RA patients.[238,239] These studies provide relevant data of the roles and functions necessary to understand important clinical needs of biomaterials. PRP injections typically include a cocktail of various cytokines, chemokines, metabolites, growth factors, and other soluble proteins that are thought to aid in the reversal of proinflammatory cascades providing pain-relieving and anti-inflammatory properties.[239–242] Nonetheless, several studies have shown the importance of leukocyte exclusion in PRP to avoid an amplification of the unwanted inflammatory effects.[243,244] Due to the variety of factors composing PRP, a precise mode-of-action mechanism remains to be elucidated and despite providing some relief in patients, other studies have found no significant benefit from PRP administration.[245,246] In contrast, the mechanism for HA has been thoroughly studied and is mainly used as a viscosupplementary agent, as outlined above.[247]

Recent years have seen a particular interest in cell-based approaches such as autologous chondrocyte implantation (ACI) and MSC transplants. The recent use and implications of these techniques for cartilage repair have been described in detail previously.[248–252] In short, cell-based reparative techniques exhibit excellent chondro-inductive and regenerative properties but lack the intrinsic mechanical strength of the cartilage tissue.[253–256] Instead, here we would like to draw focus to the current status of clinically relevant ECM component-employing strategies. The summary of currently active clinical trials involving biomaterial-based modalities for cartilage defect treatment is provided in **Table 1**.

An emerging option to use biologics and small molecule drugs has been making its way into clinical trials as promising disease-modifying osteoarthritis drug.[251] A recent review by Latourte et al. provides an excellent overview of clinically relevant molecules targeting molecular pathways involved in synovial joint homeostasis and resident cell networks.[257] Nonetheless, the inherent structural function of the cartilage tissue and the complexity behind the signaling cascades that are involved in rheumatic diseases emphasizes the need for multifunctional approaches.[258,259] Active clinical trials employing combination treatments are becoming more common compared to single material approaches. While the safety, regenerative capacity, and long-term effects of integrative ECM-based implants and biomaterials remain to be determined, the trend reflects a surge in composite materials where structural support and regenerative properties are key, likely paving the way toward multimodal therapies.

## 6. Outlook and Conclusion

Before a biomaterial is even considered, the lack of homeostatic conditions in a pathological tissue environment must be emphasized. Diseases such as OA and RA exacerbate the cartilage

**Table 1.** Summary of currently active clinical trial studies employing ECM-derived biomaterials for articular cartilage treatment.

| Product/Material | Strategy | Estimated Duration | Participants | Age | Phase | Identifier |
|---|---|---|---|---|---|---|
| NOVOCART 3D | ACI + 3D collagen type I scaffold | 2017–2026 | 42 | 13–17 | | NCT04186208 |
| | | 2013–2023 | 263 | 14–65 | 3 | NCT01656902 |
| | | 2018–2021 | 30 | 18–66 | 3 | NCT03219307 |
| | | 2017–2024 | 100 | 14–65 | 3 | NCT03319797 |
| | | 2013–2026 | 233 | 18–65 | 3 | NCT01957722 |
| HYALOFAST | 3D fibrous layers of HYAFF | 2015–2025 | 200 | 18–60 | N/A | NCT02659215 |
| GelrinC | Polyethylene glycol di-acrylate (PEG-DA) + denatured fibrinogen hydrogel | 2017–2023 | 181 | 18–50 | N/A | NCT03262909 |
| ProChondrix CR | Laser-etched, cryopreserved, cadaver derived osteochondral allograft | 2019–2026 | 80 | 18–60 | | NCT03873545 |
| | | 2020–2040 | 500 | Child, Adult, Older Adult | | NCT04301258 |
| Decalcified Bone Scaffold | Decalcification bone scaffold | 2018–2023 | 60 | 18–50 | N/A | NCT03321812 |
| HST-003 | Human ECM secreted by fibroblasts under hypoxic conditions | 2021–2024 | 20 | 18–50 | 1 | NCT05082831 |
| BioPoly RS | HA+ UHMWPE patellar implant | 2016–2026 | 35 | 21+ | N/A | NCT02991300 |
| | | 2011–2021 | 38 | 21+ | N/A | NCT01473199 |
| MACI | Autologous cultured chondrocytes on porcine collagen membrane | 2018–2025 | 45 | 10–17 | 3 | NCT03588975 |
| NuTech Affinity Membrane | Amniotic membrane patch | 2016–2020 | 10 | 18–55 | N/A | NCT02837484 |
| BioCartilage | Scaffold with Collagen Type II and cartilage matrix elements | 2019–2023 | 15 | 19+ | N/A | NCT03696394 |
| Chondro-Gide | Bilayer porcine collagen I/III membrane | 2020–2025 | 234 | 18–55 | N/A | NCT04537013 |
| DeNovo NT | Human juvenile cartilage pieces | 2012–2021 | 90 | 18–55 | N/A | NCT01670617 |
| | | 2011–2021 | 160 | 18+ | | NCT01329445 |
| JointRep | Deacetylated chitosan (polyglucosamine) scaffold | 2021–2025 | 185 | 18–65 | N/A | NCT04840147 |

N/A refers to trials without FDA-defined phases, such as trials of devices.

remodeling process by engaging the immune system and intensifying catabolic effects. For immuno- and medically-compromised patients, the possibility of implant failure, halted medical treatments, and peri-implant inflammation are all considered risk factors for successful implant treatment.[260–262] In this review, we have aimed to shed light on some issues facing biomaterials from a pathological perspective, including immunomodulation by specific ECM components.

While there are successful treatment approaches for many RA patients that aid in suppressing their autoimmune reaction, unfortunately, the incapacity to halt disease progression in OA remains a major challenge and is currently considered to be a disease of highly unmet clinical need.[263] The treatment potential of a biomaterial designed to intervene at an early stage of these diseases would need to be evaluated for their effects on pathogenic remodeling processes, their ability to promote regeneration and cartilage healing, and their ability to avoid fibrocartilage formation. Other issues further complicate these matters, such that females are more prone to develop both RA and OA, which is rarely taken into consideration when developing and evaluating biomaterials. The knowledge of the differences in the immune system processes between genders highlights the need for appropriate models and the design of materials with the specific patient population in mind. In addition, many studies were made with immortalized cell lines from either mouse or humans, which can behave drastically different compared to primary cells. While much is known about the mechanisms of the immune system's tissue remodeling process of the cartilage, how these processes also impact pain—a major factor in both RA and OA—would determine patients' overall acceptance of a new biomaterial. Long-term studies are necessary to evaluate not only a material's ability to restore joint function, but also the overall treatment capacity of such a material.

In conclusion, pathogenic tissue remodeling and regenerative processes alter the environment by releasing matrix components, induce abnormalities in chondrocyte function, and recruit immune cells for a subsequent reaction to an implanted material. The promising approach using dECM-based materials has shown a path toward the potential to incorporate treatments strategies and enhance tissue regeneration. Long-term studies are necessary that can evaluate cartilage stability, bio- and immuno-compatibility, and overall joint function to understand how developed materials can retain their characteristics and interaction with tissues over time in slow progressing diseases such as OA. Based on lessons from previous research, it is likely that composite materials and multiple-action treatments will become

dominant therapy strategies for multimodal pathologies such as OA and RA.

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## Conflict of Interest

U.v.M. and A.S. declare no conflict of interest. C.C. has received a patent for the use of intra-articular injection of liposomal preparations of adenosine and A2AR agonists for the treatment of osteoarthritis. In addition, C.C. is among the founders of Regenosine, a company incorporated to develop adenosine receptor-related therapies for osteoarthritis.

## Keywords

biomaterials, cartilage, extracellular matrix, immune systems, implants, osteoarthritis, rheumatoid arthritis

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