Review

Cartilage homeostasis in health and rheumatic diseases

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Abstract

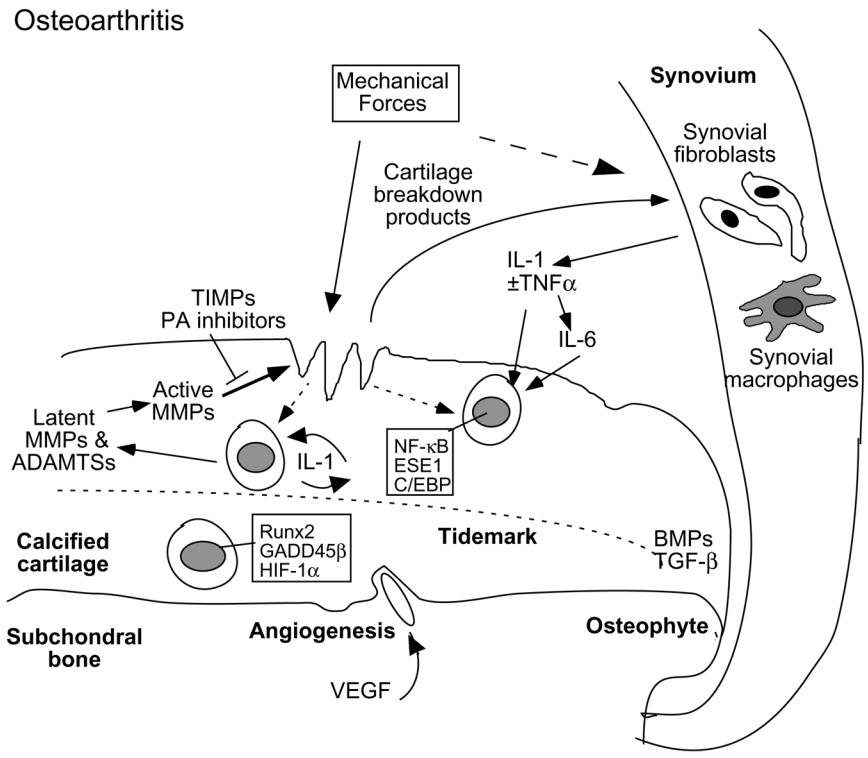
As the cellular component of articular cartilage, chondrocytes are responsible for maintaining in a low-turnover state the unique composition and organization of the matrix that was determined during embryonic and postnatal development. In joint diseases, cartilage homeostasis is disrupted by mechanisms that are driven by combinations of biological mediators that vary according to the disease process, including contributions from other joint tissues. In osteoarthritis (OA), biomechanical stimuli predominate with up-regulation of both catabolic and anabolic cytokines and recapitulation of developmental phenotypes, whereas in rheumatoid arthritis (RA), inflammation and catabolism drive cartilage loss. *In vitro* studies in chondrocytes have elucidated signaling pathways and transcription factors that orchestrate specific functions that promote cartilage damage in both OA and RA. Thus, understanding how the adult articular chondrocyte functions within its unique environment will aid in the development of rational strategies to protect cartilage from damage resulting from joint disease. This review will cover current knowledge about the specific cellular and biochemical mechanisms that regulate cartilage homeostasis and pathology.

Introduction

Adult articular cartilage is an avascular tissue composed of a specialized matrix of collagens, proteoglycans, and non-collagen proteins, in which chondrocytes constitute the unique cellular component. Although chondrocytes in this context do not normally divide, they are assumed to maintain the extracellular matrix (ECM) by low-turnover replacement of certain matrix proteins. During aging and joint disease, this equilibrium is disrupted and the rate of loss of collagens and proteoglycans from the matrix may exceed the rate of deposition of newly synthesized molecules. Originally considered an inert tissue, cartilage is now considered to respond to extrinsic factors that regulate gene expression and protein synthesis in chondrocytes. Numerous studies *in vitro* and *in vivo* during the last two decades have confirmed that articular chondrocytes are able to respond to mechanical injury, joint instability due to genetic factors, and biological stimuli such as cytokines and growth and differentiation factors that contribute to structural changes in the surrounding cartilage matrix [1]. Mechanical influences on chondrocyte function are considered to be important in the pathogenesis of osteoarthritis (OA), but chondrocyte responses to molecular signals may vary in different regions, including the calcified cartilage, and also occur at different stages over a long time course (Figure 1). In rheumatoid arthritis (RA), the inflamed synovium is the major source of cytokines and proteinases that mediate cartilage destruction in areas adjacent to the proliferating synovial pannus (Figure 2) [2]. However, the basic cellular mechanisms regulating chondrocyte responses are very different in OA and RA. Moreover, mechanistic insights from *in vitro* studies ideally should be interpreted in light of direct analysis of human cartilage and other joint tissues and studies in experimental models, inclu-

ADAM = a disintegrin and metalloproteinase; ADAMTS = a disintegrin and metalloproteinase with thrombospondin-1 domains; AGE = advanced glycation end product; CD-RAP = cartilage-derived retinoic acid-sensitive protein; COL2A1 = collagen, type II, alpha 1; COMP = cartilage oligomeric matrix protein; COX-2 = cyclooxygenase 2; DDR-2 = discoidin domain receptor 2; DZC = deep zone chondrocyte; ECM = extracellular matrix; ERK = extracellular signal-regulated kinase; FRZB = frizzled-related protein 3; GADD45β = growth arrest and DNA damage 45 beta; GLUT = glucose transporter protein; HIF-1α = hypoxia-inducible factor-1-alpha; HMGB1 = high-mobility group protein 1; hTNFtg = human tumor necrosis factor transgenic; IGF-1 = insulin-like growth factor 1; Ihh = Indian hedgehog; IKK = IκB kinase; IL = interleukin; JNK = c-jun N-terminal kinase; MAPK = mitogen-activated protein kinase; MIA = melanoma inhibitory activity; MMP = matrix metalloproteinase; mPGES-1 = microsomal prostaglandin E synthase 1; MSC = mesenchymal stem cell; MZC = middle zone chondrocyte; NF-κB = nuclear factor-kappa-B; NO = nitric oxide; OA = osteoarthritis; PGE = prostaglandin E; PPAR = peroxisome proliferator-activated receptor; RA = rheumatoid arthritis; RAGE = receptor for advanced glycation end products; RANK = receptor activator of nuclear factor-kappa-B; RANKL = receptor activator of nuclear factor-kappa-B ligand; ROS = reactive oxygen species; SMAD = signal-transducing mothers against decapentaplegic; SOCS = suppressor of cytokine signaling; SZC = superficial zone chondrocyte; TGF-β = transforming growth factor-beta; TLR = Toll-like receptor; TNF-α = tumor necrosis factor-alpha; VEGF = vascular endothelial growth factor.

Figure 1



Cellular interactions in cartilage destruction in osteoarthritis. This scheme represents the destruction of the cartilage due to mechanical loading and biological factors. The induction of stress-induced intracellular signals, catabolic cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), chemokines, and other inflammatory mediators produced by synovial cells and chondrocytes results in the upregulation of cartilage-degrading enzymes of the matrix metalloproteinase (MMP) and ADAMTS families. Matrix degradation products can feedback regulate these cellular events. Anabolic factors, including bone morphogenetic proteins (BMPs) and transforming growth factor-beta (TGF-β), may also be upregulated and participate in osteophyte formation. In addition to matrix loss, evidence of earlier changes, such as chondrocyte proliferation and hypertrophy, increased cartilage calcification with tidemark advancement, and microfractures with angiogenesis from the subchondral bone possibly mediated by vascular endothelial growth factor (VEGF) can be observed in late osteoarthritis samples obtained from patients after total joint replacement. ADAMTS, a disintegrin and metalloproteinase with thrombospondin-1 domains; C/EBP, CCAAT enhancer-binding protein; ESE1, epithelial-specific ETS; ETS, E26 transformation specific; GADD45β, growth arrest and DNA damage 45 beta; HIF-1α, hypoxia-inducible factor-1-alpha; NF-κB, nuclear factor-kappa-B; PA, plasminogen activator; TIMPs, tissue inhibitors of metalloproteinases.

ding knockout and transgenic mice [3,4]. The examination of cartilage or chondrocytes from patients undergoing joint replacement has yielded less information in RA patients, in which cartilage damage is extensive, than studies of OA patients. In both, the findings do not reflect early disease. This review will cover current knowledge about the cellular and biochemical mechanisms of cartilage in health and disease derived from studies over the past 10 years.

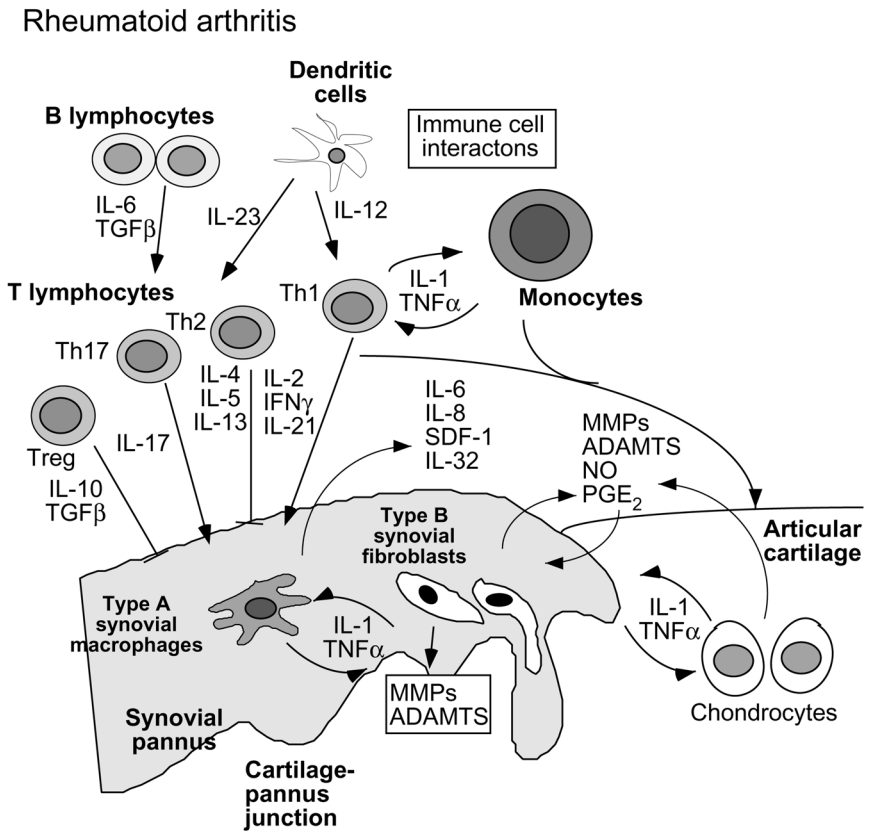
Cartilage in health

Cartilage matrix in healthy articular cartilage

Articular cartilage is composed of four distinct regions: (a) the superficial tangential (or gliding) zone, composed of thin collagen fibrils in tangential array and associated with a high concentration of decorin and a low concentration of aggrecan, (b) the middle (or transitional) zone with radial bundles of thicker collagen fibrils, (c) the deep (or radial) zone, in which the collagen bundles are thickest and are arranged in a radial fashion, and (d) the calcified cartilage zone, located immediately below the tidemark and above the subchondral bone [5,6]. The calcified zone persists after growth plate closure as the 'tidemark' and serves as an important mechanical buffer between the uncalcified articular cartilage and the subchondral bone. From the superficial to the deep zone, cell density progressively decreases, whereas cell volume and the proportion of proteoglycan relative to collagen increase.

The interterritorial cartilage matrix, which is composed of a fibrillar collagen network that bestows tensile strength, differs from the territorial matrix closer to the cell, which contains type VI collagen microfibrils but little or no fibrillar collagen. The interterritorial collagen network consists primarily of type II collagen fibrils with type XI collagen within the fibril and type IX collagen integrated in the fibril surface with the non-

Figure 2



Cellular interactions in cartilage destruction in rheumatoid arthritis. This scheme represents the progressive destruction of the cartilage associated with the invading synovial pannus in rheumatoid arthritis. As a result of immune cell interactions involving T and B lymphocytes, monocytes/macrophages, and dendritic cells, a number of different cytokines are produced in the synovium due to the influx of inflammatory cells from the circulation and synovial cell hyperplasia. The induction of proinflammatory cytokines produced primarily in the synovium, but also by chondrocytes, results in the upregulation of cartilage-degrading enzymes at the cartilage-pannus junction. Chemokines, nitric oxide (NO), and prostaglandins (PGE_2) also contribute to the inflammation and tissue catabolism. ADAMTS, a disintegrin and metalloproteinase with thrombospondin-1 domains; IFN-γ, interferon-gamma; IL, interleukin; MMP, matrix metalloproteinase; SDF-1, stromal derived factor 1; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T (cell).

collagen domain projecting outward, permitting association with other matrix components and retention of proteoglycans [7]. Collagen XXVII, a novel member of the fibrillar collagen family, also contributes to the formation of a stable cartilage matrix [8].

Compressive resistance is bestowed by the large aggregating proteoglycan aggrecan, which is attached to hyaluronic acid polymers via link protein. The half-life of aggrecan core protein ranges from 3 to 24 years, and the glycosaminoglycan components of aggrecan are synthesized more readily under low-turnover conditions, with more rapid matrix turnover in the pericellular regions. The proteoglycans are essential for protecting the collagen network, which has a half-life of more than 100 years if not subjected to inappropriate degradation. A large number of other noncollagen molecules, including biglycan, decorin, fibromodulin, the matrilins, and cartilage oligomeric matrix protein (COMP), are also present in the matrix. COMP acts as a catalyst in collagen fibrillogenesis [9], and interactions between type IX collagen and COMP or matrilin-3 are essential for proper formation and maintenance of the articular cartilage matrix [10,11]. Perlecan enhances fibril formation [12], and collagen VI microfibrils connect to collagen II and aggrecan via complexes of matrilin-1 and biglycan or decorin [13].

Chondrocyte physiology and function in healthy articular cartilage

Differences in the morphologies of zonal subpopulations of chondrocytes may reflect matrix composition and are ascribed largely to differences in the mechanical environment [14]. The superficial zone chondrocytes (SZCs) are small and flattened. The middle zone chondrocytes (MZCs) are rounded, and the deep zone chondrocytes (DZCs) are grouped in

columns or clusters. *In vitro* studies with isolated SZCs and DZCs indicate that differences in the expression of molecules, such as lubricin (also known as superficial zone protein or proteoglycan-4) and PTHrP by SZCs and Indian hedgehog (Ihh) and Runx2 by DZCs, may determine the zonal differences in matrix composition and function [15-17].

How chondrocytes maintain their ECM under homeostatic conditions has remained somewhat of a mystery since they do not divide and the matrix isolates them from each other, but gene expression and protein synthesis may be activated by injury. Since the ECM normally shields chondrocytes, they lack access to the vascular system and must rely on facilitated glucose transport via constitutive glucose transporter proteins, GLUT3 and GLUT8 [18], and active membrane transport systems [19]. Chondrocytes exist at low oxygen tension within the cartilage matrix, ranging from 10% at the surface to less than 1% in the deep zones. *In vitro*, chondrocytes adapt to low oxygen tensions by upregulating hypoxia-inducible factor-1-alpha (HIF-1α), which can stimulate expression of GLUTs [18], and angiogenic factors such as vascular endothelial growth factor (VEGF) [20,21] as well as a number of genes associated with cartilage anabolism and chondrocyte differentiation [22]. One of our laboratories has identified growth arrest and DNA damage 45 beta (GADD45β), which previously was implicated as an anti-apoptotic factor during genotoxic stress and cell cycle arrest in other cell types as a survival factor in healthy articular chondrocytes [23]. Thus, by modulating the intracellular expression of survival factors, including HIF-1α and GADD45β, chondrocytes survive efficiently in the avascular cartilage matrix and respond to environmental changes.

The aging process may affect the material properties of healthy cartilage by altering the content, composition, and structural organization of collagen and proteoglycan [24-26]. This has been attributed to overall decreased anabolism and to the accumulation of advanced glycation end products (AGEs) that enhance collagen cross-linking [27]. Unless perturbed, healthy chondrocytes remain in a postmitotic quiescent state throughout life, with their decreasing proliferative potential being attributed to replicative senescence associated with erosion of telomere length [28]. The accumulation of cartilage matrix proteins in the endoplasmic reticulum and Golgi of chondrocytes, which have been modified by oxidative stress during aging, may lead to decreased synthesis of cartilage matrix proteins and diminished cell survival [29].

Cartilage in joint disease

The loss of balance between cartilage anabolism and catabolism

Although the etiologies of OA and RA are different, both diseases present states of inappropriate articular cartilage destruction, which is largely the result of elevated expression and activities of proteolytic enzymes. Whereas these enzymes normally are involved in the formation, remodeling, and repair of connective tissues, a shift in equilibrium between anabolic and catabolic activities occurs in OA as a response to abnormal mechanical loading in conjunction with genetic abnormalities or injury to the cartilage and surrounding joint tissues. In RA, the inflamed synovium is the major source of cytokine-induced proteinases, although the episodic intra-articular inflammation with synovitis indicates that the synovium may also be a source of cytokines and cartilage-degrading proteinases in OA [30,31]. However, in OA, these degradative enzymes are produced primarily by chondrocytes due to inductive stimuli, including mechanical stress, injury with attendant destabilization, oxidative stress, cell-matrix interactions, and changes in growth factor responses and matrix during aging.

Of the proteinases that degrade cartilage collagens and proteoglycans in joint disease, matrix metalloproteinases (MMPs) and aggrecanases have been given the greatest attention because they degrade native collagens and proteoglycans [32-34]. These include the collagenases (MMP-1, MMP-8, and MMP-13), the gelatinases (MMP-2 and MMP-9), stromelysin-1 (MMP-3), and membrane type I (MT1) MMP (MMP-14) [35]. MMP-10, similar to MMP-3, activates procollagenases, is detectable in OA and RA synovial fluids and joint tissues, and is produced *in vitro* by both the synovium and chondrocytes in response to inflammatory cytokines [36]. MMP-14, produced principally by RA synovial tissue, is important for synovial invasiveness [37], whereas the MMP-14 produced by OA chondrocytes activates pro-MMP-13, which in turn cleaves pro-MMP-9 [38]. Other MMPs, including MMP-16 and MMP-28 [32,39], and many members of the reprolysin-related proteinases of the ADAM (a disintegrin and metalloproteinase) family, including ADAM-17/TACE (tumor necrosis factor-alpha [TNF-α]-converting enzyme), are expressed in cartilage, but their specific roles in cartilage damage in either OA or RA have yet to be defined [40-42]. Although several of the MMPs, including MMP-3, MMP-8, and MMP-14, are capable of degrading proteoglycans, ADAMTS (ADAM with thrombospondin-1 domains)-4 and ADAMTS-5 are now regarded as the principal aggrecan-degrading enzymes in cartilage [43,44]. Aggrecanase inhibitors that target ADAMTS-5 have been developed and are awaiting opportunities for clinical trials in OA [45].

OA and RA differ with respect to the sites as well as the origins of disrupted matrix homeostasis. In OA, proteoglycan loss and type II collagen cleavage initially occur at the cartilage surface, with evidence of pericellular damage in deeper zones as the lesion progresses [46]. In RA, intrinsic chondrocyte-derived chondrolytic activity is present at the cartilage-pannus junction, as well as in deeper zones of cartilage matrix [47], although elevated levels of MMPs in RA synovial fluids likely originate from the synovium. There are also differences in matrix synthetic responses in OA and RA. Whereas type II collagen synthesis is reduced in early RA [48], there is evidence of compensatory increases in type II collagen synthesis in deeper regions of OA cartilage [14].

This is in agreement with findings of enhanced global synthesis and gene expression of aggrecan and type II collagen in human OA compared with healthy cartilage [49-51]. Importantly, microarray studies using full-thickness cartilage have also shown that many collagen genes, including collagen, type II, alpha 1 (*COL2A1*), are upregulated in late-stage OA [23,51]. The latter applies mainly to MZCs and DZCs, as revealed by laser capture microdissection, whereas this anabolic phenotype is less obvious in the degenerated areas of the upper regions [52].

Inflammation and cartilage destruction

In vivo and *in vitro* studies have shown that chondrocytes produce a number of inflammatory mediators, such as interleukin-1-beta (IL-1β) and TNF-α, which are present in RA or OA joint tissues and fluids. Chondrocytes respond to these proinflammatory cytokines by increasing the production of proteinases, prostaglandins, and nitric oxide (NO) [2,25]. The first recognition of IL-1 as a regulator of chondrocyte function stems largely from work in *in vitro* culture models showing that activities derived from synovium or monocyte macrophages induce the production of cartilage-degrading proteinases (reviewed in [2,53]).

IL-1, TNF-α, MMP-1, MMP-3, MMP-8, and MMP-13, and type II collagen cleavage epitopes have been shown to colocalize in matrix-depleted regions of RA cartilage [48,54] and OA cartilage [46,55]. In addition, chondrocytes express several chemokines as well as chemokine receptors that may participate in cartilage catabolism [56,57]. IL-1β also induces other proinflammatory cytokines such as IL-17, which has similar effects on chondrocytes [58,59]. IL-32, a recently discovered cytokine that induces TNF-α, IL-1β, IL-6, and chemokines, is also expressed in the synovia of RA patients and contributes to TNF-α-dependent inflammation and cartilage proteoglycan loss [60]. The importance of synergisms between IL-1 and TNF-α and with other cytokines, such as IL-17, IL-6, and oncostatin M, in RA or OA joints has been inferred primarily from culture models [61-63]. The up-regulation of cyclooxygenase-2 (*COX-2*), *MMP13*, and *NOS2* gene expression by IL-1β in chondrocytes and other cell types is mediated by the induction and activation of a number of transcription factors, including nuclear factor-kappa-B (NF-κB), CCAAT enhancer-binding protein (C/EBP), activator protein 1 (AP-1), and E26 transformation specific family members, which regulate stress- and inflammation-induced signaling [64]. IL-1β also uses these mechanisms to suppress the expression of a number of genes associated with the differentiated chondrocyte phenotype, including *COL2A1* and cartilage-derived retinoic acid-sensitive protein/melanoma inhibitory activity (*CD-RAP*/MIA) [64-66]. The role of epigenetics in regulating these cellular events in cartilage is under current consideration [67].

The IL-1R/Toll-like receptor (TLR) superfamily of receptors, which has a key role in innate immunity and inflammation, has received recent attention with respect to cartilage pathology. Human articular chondrocytes can express TLR1, TLR2, and TLR4, and the activation of TLR2 by IL-1, TNF-α, peptidoglycans, lipopolysaccharide, or fibronectin fragments increases the production of MMPs, NO, prostaglandin E (PGE), and VEGF [68-73]. In immune complex-mediated arthritis, TLR4 regulates early-onset inflammation and cartilage destruction by IL-10-mediated upregulation of Fcγ receptor expression and enhanced cytokine production [74]. The IL-18 receptor shares homology with IL-1RI and has a TLR signaling domain. IL-18 has effects similar to IL-1 in human chondrocytes and stimulates chondrocyte apoptosis, although studies do not suggest a pivotal role in cartilage destruction in RA [75,76]. IL-33, an ST2-TLR ligand, is associated with endothelial cells in RA synovium, but its role in cartilage destruction has not been examined [77]. Of recent interest are the suppressor of cytokine signaling (SOCS) molecules, including SOCS3, which is induced by IL-1 and acts as a negative feedback regulator during insulin-like growth factor 1 (IGF-1) desensitization in the absence of NO by inhibiting insulin receptor substrate 1 (IRS-1) phosphorylation [78].

The increased production of prostaglandins by inflammatory cytokines is mediated via induction of the expression of not only COX-2 but also microsomal PGE synthase 1 (mPGES-1) [79,80]. In addition to opposing the induction of COX-2, inducible nitric oxide synthetase (iNOS), and MMPs and the suppression of aggrecan synthesis by IL-1, activators of the peroxisome proliferator-activated receptor gamma (PPARγ), including the endogenous ligand 15-deoxy-$\Delta^{12,14}$ prostaglandin J_2 (PGJ_2), inhibit IL-1-induced expression of mPGES-1 [81,82]. Recent evidence indicates that PPARα agonists may protect chondrocytes against IL-1-induced responses by increasing the expression of IL-1Ra [83].

White adipose tissue has been proposed as a major source of both pro- and anti-inflammatory cytokines, including IL-1Ra and IL-10 [84]. Roles for adipokines, identified originally as products of adipocytes, have received recent attention, not only because of their relationship to obesity, but also because they can have pro- or anti-inflammatory effects in joint tissues and may serve as a link between the neuroendocrine and immune systems [85]. Leptin expression is enhanced during acute inflammation, correlating negatively with inflammatory markers in RA sera [86]. The expression of leptin is elevated in OA cartilage and in osteophytes and it stimulates IGF-1 and transforming growth factor-beta-1 (TGF-β1) synthesis in chondrocytes [87]. Leptin synergizes with IL-1 or interferon-gamma to increase NO production in chondrocytes [88], and leptin deficiency attenuates inflammatory processes in experimental arthritis [89]. It has been proposed that the dysregulated balance between leptin and other adipokines, such as adiponectin, promotes destructive inflammatory processes [90]. Recent studies indicate that resistin plays a role in early stages of trauma-induced OA and in RA at local sites of

inflammation and that serum resistin reflects inflammation and disease activity [91,92].

Effects of mechanical loading

In young individuals without genetic abnormalities, biomechanical factors due to trauma are strongly implicated in initiating the OA lesion. Mechanical disruption of cell-matrix interactions may lead to aberrant chondrocyte behavior, contributing to fibrillations, cell clusters, and changes in quantity, distribution, or composition of matrix proteins [93,94]. In the early stages of OA, transient increases in chondrocyte proliferation and increased metabolic activity are associated with a localized loss of proteoglycans at the cartilage surface followed by cleavage of type II collagen (reviewed in [95,96]). These events result in increased water content and decreased tensile strength of the matrix as the lesion progresses.

Chondrocytes can respond to direct biomechanical perturbation by upregulating synthetic activity or by increasing the production of inflammatory cytokines, which are also produced by other joint tissues. *In vitro* mechanical loading experiments have revealed that injurious static compression stimulates proteoglycan loss, damages the collagen network, and reduces synthesis of cartilage matrix proteins, whereas dynamic compression increases matrix synthetic activity [97]. In response to traumatic injury, global gene expression is activated, resulting in increased expression of inflammatory mediators, cartilage-degrading proteinases, and stress response factors [98,99]. Neuronal signaling molecules, such as substance P and its receptor, NK1, and *N*-methyl-D-aspartic acid receptors (NMDARs), which require glutamate and glycine binding for activation, have been implicated in mechanotransduction in chondrocytes in a recent study [100].

Chondrocytes have receptors for responding to mechanical stimulation, many of which are also receptors for ECM components [101]. Among these are several of the integrins that serve as receptors for fibronectin and type II collagen fragments, which upon activation stimulate the production of proteinases, cytokines, and chemokines [102]. Discoidin domain receptor 2 (DDR-2), a receptor for native type II collagen fibrils, is activated on chondrocytes via Ras/Raf/Mek signaling and preferentially induces MMP-13 via p38 mitogen-activated protein kinase (MAPK); this is a universal mechanism that occurs after loss of proteoglycans, not only in genetic models, but also in surgical mouse OA and human OA [103]. On the other hand, in RA the cell-cell adhesion molecule, cadherin-11, is expressed at the interface between the RA synovial pannus and cartilage and facilitates cartilage invasion and erosion in mouse models *in vivo* and in human RA tissues *in vitro* and *ex vivo* [104] in a TNF-α-dependent manner [105]. Recent studies indicate that lubricin is an important secreted product of chondrocytes, synovial cells, and other joint tissues which is downregulated in OA and RA and modulated by cytokines and growth factors [91,92].

Stress responses in cartilage

Injurious mechanical stress and cartilage matrix degradation products are capable of stimulating the same signaling pathways as those induced by inflammatory cytokines [98,106-109]. Along with extracellular signal-regulated kinase 1/2 (ERK1/2), the key protein kinases in the c-jun N-terminal kinase (JNK), p38 MAPK, and NF-κB signaling cascades are activated, particularly in the upper zones of OA cartilage [110]. Furthermore, the engagement of integrin receptors by fibronectin or collagen fragments activates focal adhesion kinase signaling and transmits signals intersecting with ERK, JNK, and p38 pathways [111,112]. Cascades of multiple protein kinases are involved in these responses, including protein kinase Cζ, which is upregulated in OA cartilage and is required for activation of NF-κB by IL-1 and TNF-α [113]. However, it remains controversial whether inflammatory cytokines are primary or secondary effectors of cartilage damage and defective repair mechanisms in OA since these same pathways also induce or amplify the expression of cytokine genes. Interestingly, physiological loading may protect against cartilage loss by inhibiting IκB kinase-beta (IKKβ) activity in the canonical NF-κB cascade and attenuating NF-κB transcriptional activity [114] as well as by inhibiting TAK1 (TGF-β-activated kinase 1) phosphorylation [115]. In addition, genetic factors that cause disruption of chondrocyte differentiation and function and influence the composition and structure of the cartilage matrix may contribute to abnormal biomechanics, independently of the influence of inflammation.

Reactive oxygen species (ROS) play a critical role in chondrocyte homeostasis, but during aging, trauma, and OA, partial oxygen variations and mechanical stress as well as inflammation induce abnormal ROS production, which exceeds the antioxidant capacity leading to oxidative stress. ROS and attendant oxidative stress impair growth factor responses, enhance senescence through telomere shortening, and impair mitochondrial function [28,116,117]. ROS levels are also induced by activation of RAGE, the receptor for AGEs, which regulates chondrocyte and synovial responses in OA [118]. In chondrocytes, interaction of RAGE with S100A4, a member of the S100 family of calcium-binding proteins, stimulates MMP-13 production via phosphorylation of Pyk2, MAPKs, and NF-κB signaling [119]. RAGE expression and S100A1 release are stimulated in chondrocytes *in vitro* and increased in OA cartilage. Transglutaminase 1, which is induced by inflammation and stress, transforms S100A1 into a procatabolic cytokine that signals through RAGE and the p38 MAPK pathway to induce chondrocyte hypertrophy and aggrecan degradation [120]. In experimental murine arthritis models, S100A8 and S100A9 are involved in the upregulation and activation of MMPs and aggrecanases [121,122]. In addition, high-mobility group protein 1 (HMGB1), another important RAGE ligand and also a chromatin architectural protein, is produced by inflamed synovium and thus acts as a RAGE-dependent proinflammatory cytokine in RA [123]. The differential regulation and

expression of GLUT isoforms by hypoxia, growth factors, and inflammatory cytokines may contribute to intracellular stress responses [124]. COX-2 is also involved in the chondrocyte response to high shear stress, associated with reduced antioxidant capacity and increased apoptosis [125]. Modulation of such intracellular stress response mechanisms may provide strategies for novel therapies.

Biomarkers of cartilage pathology

The recent development of assays for specific biological markers, which reflect quantitative and dynamic changes in the synthetic and degradation products of cartilage and bone matrix components, has provided a means of identifying patients at risk for rapid joint damage and also for early monitoring of the efficacy of disease-modifying therapies. Molecules originating from the articular cartilage, including aggrecan fragments, which contain chondroitin sulfate and keratan sulfate, type II collagen fragments, and collagen pyridinoline cross-links, are usually released as degradation products as a result of catabolic processes. Specific antibodies that detect either synthetic or cleavage epitopes have been developed to study biological markers of cartilage metabolism in synovial fluids, sera, and urine of patients with OA or RA (reviewed in [126-129]). Aggrecan degradation products are assayed using antibodies 846, 3B3(-), and 7D4 that detect chondroitin sulfate neoepitopes, 5D4 that detects keratan sulfate epitopes, and the VIDIPEN and NITEGE antibodies that recognize aggrecanase and MMP cleavage sites, respectively, within the interglobular G1 domain of aggrecan [33]. Similarly, the C2C antibody (previously known as Col2-3/4$C_{Long\ mono}$) has been used to detect specific cleavage of the triple helix of type II collagen [48,129]. Increased ratios of C2C to the synthetic marker, CPII, are associated with a greater likelihood of radiological progression in OA patients [130]. Other markers included COMP [131]; YKL-40/HC-gp39, or chitinase 3-like protein 1 (CH3L1), which is induced in chondrocytes by inflammatory cytokines [132]; and CD-RAP, also known as MIA [133,134]. Such biomarker assays have been used as research tools and are currently under evaluation for monitoring cartilage degradation or repair in patient populations. C-reactive protein, IL-6, and MMP-3 have also been identified as potential biomarkers in both RA and OA patient populations. A single marker has not proven to be sufficient, however, and the major challenge will be to apply such biomarkers to the diagnosis and monitoring of disease in individual patients and to correlate them with structural changes in cartilage identified by magnetic resonance imaging techniques [135].

The genetics of cartilage pathology

Results of epidemiological studies, analysis of patterns of familial clustering, twin studies, and the characterization of rare genetic disorders suggest that genetic abnormalities can result in early onset of OA and increased susceptibility to RA. For example, twin studies have shown that the influence of genetic factors may approach 70% in OA that affects certain joints. Candidate gene studies and genome-wide linkage analyses have revealed polymorphisms or mutations in genes encoding ECM and signaling molecules that may determine OA susceptibility [136-138]. Gender differences have been noted and gene defects may appear more prominently in different joints [136,139]. Gene defects associated with congenital cartilage dysplasias that affect the formation of cartilage matrix and patterning of skeletal elements may adversely affect joint alignment and congruity and thus contribute to early onset of OA in these individuals [140]. Although whole-genome linkage analyses of RA patients have not addressed cartilage specifically, this work has pointed to immunological pathways and inflammatory signals that may modulate cartilage destruction [141].

Genomic and proteomic analyses, which have been performed in cytokine-treated chondrocytes, in cartilage from patients with OA, and in rheumatoid synovium, have provided some insights into novel mechanisms that might govern chondrocyte responses in both OA and RA [57,63,102,142]. When coupled with biological analyses that address candidate genes, gene profiling studies of cartilage derived from patients with OA have also begun to yield new information about mediators and pathways [23,51,143,144]. Similarly, microarray analysis of cocultures of synovial fibroblasts with chondrocytes in alginate has identified markers of inflammation and cartilage destruction associated with RA pathogenesis [145].

Lessons from mouse models

Insight into cartilage pathology in RA has been gleaned from the examination of type II collagen-induced arthritis and other types of inflammatory arthritis in mice with transgenic overexpression or knockout of genes encoding cytokines, their receptors, or activators. These studies have led in part to the conclusion that TNF-α drives acute inflammation whereas IL-1 has a pivotal role in sustaining cartilage erosion [146]. In support of this concept, crossing arthritic human TNF transgenic (hTNFtg) mice with IL-1α- and β-deficient strains protected against cartilage erosion without affecting synovial inflammation [147]. The success of anti-TNF-α therapy in most but not all patients highlights the importance of inflammation in joint destruction.

In vivo studies have also shown that alterations in cartilage matrix molecules or in regulators of chondrocyte differentiation can lead to OA pathology. The importance of the fine protein network and ECM structural integrity in postnatal cartilage health is well documented in studies of deficiencies or mutations in cartilage matrix genes, including *Col2a1*, *Col9a1*, *Col11a1*, aggrecan, matrilin-3, or fibromodulin alone or together with biglycan, which lead to age-dependent cartilage degeneration similar to that in OA patients [140,148,149]. Deficiency of *Timp3* (tissue inhibitor of metalloproteinases 3) or postnatal overexpression of constitutively active *Mmp13* also promotes OA-like pathology [150,151].

Importantly, surgically induced OA disease models in mutant mice have also implicated ADAMTS5 [152,153], DDR-2 [103], and Runx2 [154] as contributors to the onset and/or severity of OA joint disease. Knockout of IL-1β is also protective against OA induced by destabilization of the medial meniscus [155]. Although single gene defects do not model all aspects of human OA, the loss or mutation of a gene that is involved in the synthesis or remodeling of the cartilage matrix may lead to the disruption of other gene functions in chondrocytes, thus resulting in joint instability and OA-like pathology. Thus, novel mechanistic insights into the initiation or progression of OA may be discovered by identifying intracellular effectors of ECM homeostasis and remodelling *in vitro* and evaluating their functions in animal models of OA disease.

Chondrogenesis, chondrocyte hypertrophy, calcified cartilage, and bone in cartilage pathology

During skeletal development, the chondrocytes arise from mesenchymal progenitors to synthesize the templates, or cartilage anlagen, for the developing limbs in a process known as chondrogenesis [156]. Following mesenchymal condensation and chondroprogenitor cell differentiation, chondrocytes undergo proliferation, terminal differentiation to hypertrophy, and apoptosis, whereby hypertrophic cartilage is replaced by bone in endochondral ossification. A number of signaling pathways and transcription factors play stage-specific roles in chondrogenesis and a similar sequence of events occurs in the postnatal growth plate, leading to rapid growth of the skeleton [64,156-158].

Chondrogenesis is orchestrated in part by Sox9 and Runx2, two pivotal transcriptional regulators that determine the fate of chondrocytes to remain within cartilage or undergo hypertrophic maturation prior to ossification and is also subject to complex regulation by interplay of the fibroblast growth factor, TGF-β, BMP, and Wnt signaling pathways [159-162]. Differential signaling during chondrocyte maturation occurs via TGF-β-regulated signal-transducing mothers against decapentaplegic (Smads) 2 and 3 that act to maintain articular chondrocytes in an arrested state and BMP-regulated Smads 1 and 5 that accelerate their differentiation. Sox9, which is essential for type II collagen (*COL2A1*) gene expression, is most highly expressed in proliferating chondrocytes and has opposing positive and negative effects on the early and late stages of chondrogenesis, respectively. Sox9 cooperates with two related proteins, L-Sox5 and Sox6, which are targets of Sox9 itself and function as architectural HMG-like chromatin modifiers. Moreover, BMP signaling, through the type I Bmpr1a and Bmpr1b receptors, redundantly drives chondrogenesis via Sox9, Sox5, and Sox6. In addition, Runx2, which drives the terminal phase of chondrogenesis [163], is subject to direct inhibition by Sox9 [164]. In cooperation with BMP-induced Smads, Runx2 also upregulates GADD45β, a positive regulator of the terminal hypertrophic phase of chondrogenesis which drives the expression of *Mmp13* and *Col10a1* in the mouse embryonic growth plate [165]. More recently, the findings of our groups suggest that GADD45β contributes to the homeostasis of healthy and early OA articular chondrocytes as an effector of cell survival and as one of the factors induced by NF-κB that contributes to the imbalance in matrix remodelling in OA cartilage by suppressing *COL2A1* gene expression [23] and that the NF-κB activating kinases, IKKα and IKKβ, differentially contribute to OA pathology by also regulating matrix remodelling in conjunction with chondrocyte differentiation [166].

Endochondral ossification, in which the hypertrophic chondrocyte undergoes a stress response associated with ECM remodelling, has been proposed as a 'developmental model' to understand the contribution of exacerbated environmental stresses to OA pathology [167-170]. Changes in the mineral content and thickness of the calcified cartilage and the associated tidemark advancement may be related to recapitulation of the hypertrophic phenotype, including *COL10A1*, *MMP-13*, and *Runx2* gene expression, observed in the deep zone of OA cartilage [167,171]. In addition to *COL10A1* and *MMP-13*, other chondrocyte terminal differentiation-related genes, such as *MMP-9* and *Ihh*, are detected in the vicinity of early OA lesions along with decreased levels of Sox9 mRNA [172]. However, Sox9 expression does not always localize with COL2A1 mRNA in adult articular cartilage [52,173]. Apoptosis is a rare event in OA cartilage but may be a consequence of the chondrocyte stress response associated with hypertrophy [174]. Interestingly, one of our recent studies indicates that intracellular stress response genes are upregulated in early OA, whereas a number of genes encoding cartilage-specific and nonspecific collagens and other matrix proteins are upregulated in late-stage OA cartilage [23]. Moreover, articular chondrocytes in micromass culture show 'phenotypic plasticity' comparable to mesenchymal stem cells (MSCs) undergoing chondrogenesis, by recapitulating processes akin to chondrocyte hypertrophy [175], which one of our labs recently has shown to be subject to differential control by canonical NF-κB signaling and IKKα [166]. This process may also be modulated by Src kinases [176,177].

Additional supporting evidence for dysregulation of endochondral ossification as a factor in OA pathology comes from genetic association studies identifying OA susceptibility genes across different populations [138,170,178]. These include the genes encoding asporin (ASPN), a TGF-β-binding protein with biglycan and decorin sequence homology [179], secreted frizzled-related protein 3 (FRZB), a WNT/β-catenin signaling antagonist [180,181], and deiodinase 2 (DIO2), an enzyme that converts inactive thyroid hormone, T4, to active T3 [182]. The activation of WNT/β-catenin in mature postnatal growth plate chondrocytes stimulates hypertrophy, matrix mineralization, and expression of VEGF, ADAMTS5, MMP-13, and several other MMPs [183]. Findings from microarray analyses of bone from OA patients

[184] and in Frzb knockout mice [185] also suggest that signaling modifications in the calcified cartilage could contribute to increased subchondral plate thickness accompanying tidemark advancement at the border with the articular cartilage and the angiogenesis observed at the osteochondral junction [186]. Moreover, endochondral ossification also contributes to the formation of osteophytes [187-189]. Interestingly, HMGB1 released by hypertrophic cartilage, prior to the onset of programmed cell death, contributes to endochondral ossification by acting as a chemotactic factor for osteoclasts at the growth plate [190], and HMGB1-induced NF-κB signaling is also required for cellular chemotaxis in response to HMGB1-RAGE engagement [191]. Thus, IKK-mediated NF-κB signaling not only may intrinsically influence the differentiation of chondrocytes toward a hypertrophy-like state [166], but also could subsequently drive aspects of intercellular communication culminating in endochondral ossification [190].

Changes in the periarticular and subchondral bone also occur in both RA and OA and may contribute to cartilage pathology. Receptor activator of NFκB (RANK), a member of the TNF receptor family, RANK ligand (RANKL), and the soluble receptor osteoprotegerin regulate osteoclast differentiation and activity and are important mediators of bone destruction in RA. IKKβ-mediated, but not IKKα-mediated, NF-κB signaling is associated with inflammation-induced bone loss [192] and is also critical for the survival of osteoclast precursors by suppressing JNK-dependent apoptosis in response to RANKL signaling [193]. IL-17 induces RANKL, inducing bone destruction independently of IL-1 and bypassing the requirement for TNF in inflammatory arthritis [58]. Although RANK and RANKL are expressed in adult articular chondrocytes, a direct action in cartilage has not been identified [194]. Since cartilage destruction is not blocked directly by the inhibition of RANKL, at least in inflammatory models, indirect effects may occur through protection of the bone [195,196], as suggested by recent studies in experimental models [197,198]. A link between RANKL and WNT has been suggested by findings in hTNFtg mice and RA tissues, in which decreased β-catenin and high DKK-1, a WNT inhibitor, were demonstrated in synovium and in cartilage adjacent to inflammatory tissue [199] (reviewed in [200]). In contrast, increased β-catenin was observed in OA cartilage and conditional overexpression in mouse cartilage leads to premature chondrocyte differentiation and development of OA-like phenotype [201]. Interestingly, Runx2-dependent expression of RANKL occurs in hypertrophic chondrocytes at the boundary next to the calcifying cartilage in the developing growth plate [202].

Mesenchymal progenitor cells in cartilage and their use in tissue engineering

MSCs from bone marrow and other adult tissues, including muscle, adipose tissue, and synovium or other tissue sites, which have the capacity to differentiate into cartilage, bone, fat, and muscle cells, are under investigation as sources of cartilage progenitor cells for cartilage tissue engineering [203-206]. Studies *in vitro* indicate that the same growth and differentiation factors that regulate different stages of cartilage development may be able to promote cartilage repair [207-209]. IGF-1 is a potent stimulator of proteoglycan synthesis, particularly when combined with other anabolic factors, including BMPs [210,211]. Moreover, *ex vivo* gene transfer of anabolic factors such as BMPs, TGF-β, and IGF-1 has been explored as an approach to promote differentiation of autologous chondrocytes or MSCs before implantation [212,213]. Recently, endochondral ossification has been achieved with murine embryonic stem cells in tissue-engineered constructs implanted in cranial bone of rats [214].

BMP-2 and BMP-7 (osteogenic protein 1) are currently approved for multiple indications in the area of bone fracture repair and spinal fusion, but the capacity of BMPs and TGF-β to induce chondrocyte hypertrophy in cartilage repair models and to promote osteophyte formation may prevent controlled repair of articular cartilage *in vivo* [207]. Since the injection of free TGF-β or adenovirus-mediated delivery of TGF-β promotes fibrosis and osteophyte formation, while stimulating proteoglycan synthesis in cartilage, the local application of molecules that block endogenous TGF-β signaling, such as the soluble form of TGF-βRII, inhibitory SMADs, or the physiological antagonist latency-associated peptide 1 (LAP-1), has been proposed as a more effective strategy [188]. Additional strategies include gene transfer of Sox9, alone or together with L-Sox5 and Sox6, into MSCs *ex vivo* or into joint tissues *in vivo* to more directly promote the expression of cartilage matrix genes [215,216]. Strategies to stably express interfering RNAs *in vivo* could also provide a means of blocking dysregulated ECM remodelling or inappropriate endochondral ossification of articular chondrocytes.

Despite intensive investigation of cartilage repair strategies and the increased understanding of the cellular mechanisms involved, many issues remain to be resolved. These include the fabrication and maintenance of the repair tissue in the same zonal composition as the original cartilage, the recruitment and maintenance of cells with an appropriate chondrocyte phenotype, and integration of the repair construct with the surrounding cartilage matrix [217]. These issues are also compounded when cartilage loss is severe or when chronic inflammation exists, as in RA.

Conclusions

Laboratory investigations *in vitro* and *in vivo* regarding the role of the chondrocyte in remodeling the cartilage matrix in the RA and OA joint have identified novel molecules and mechanisms and provided new understanding of the contributions of known mediators. In RA, mediators involved in immunomodulation and synovial cell function, including cytokines, chemokines, and adhesion molecules, have primary roles in the inflammatory and catabolic processes in the joint,

but they may also, directly or indirectly, promote cartilage damage. Despite our increasing knowledge of the mechanisms regulating the responses of chondrocytes to anabolic and catabolic factors involved in developing and adult cartilage, the development of disease-modifying therapies for OA patients has been elusive. In RA, in which significant advances have been achieved in our understanding of the cellular interactions in the RA joint involving macrophages, T and B lymphocytes, and synovial fibroblasts, there is still a need for therapeutic strategies that prevent the extensive cartilage and bone loss, despite the clinical success of anti-TNF therapy for RA. Further work using the principles of cell and molecular biology, such as those described in this review, will be necessary for uncovering new therapies for targeting cartilage destruction in both degenerative and inflammatory joint disease.

Competing interests

The authors declare that they have no competing interests.

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