expert reviews in molecular medicine

Cartilage catabolism in arthritis: factors that influence homeostasis

Andrew D. Rowan

Preventing the destruction of articular cartilage has long been a goal in the treatment of arthritic diseases, in which a combination of cytokines and growth factors affect the catabolic state of cells within the joint. Normal tissue turnover can be viewed as a balance between degradation and synthesis of the macromolecules that constitute the extracellular matrix. This process is tightly regulated such that highly degradative proteinases are controlled at several levels, including synthesis and secretion, activation and inhibition. Tissue destruction occurs when proteinase-mediated degradation exceeds synthesis, and this is markedly influenced by cytokines and growth factors that stimulate matrix synthesis as well as the production of proteinases and/or their endogenous inhibitors. This review outlines current knowledge of factors that influence cartilage biology, with particular emphasis on chondrocytes and synovial fibroblasts. Recent findings from the delivery of cytokines to affected tissues are also summarised, and the potential impact these observations might have on new therapies for arthritic diseases is discussed.

The goal of generating new and improved treatments for arthritic diseases of the joints has not yet been achieved, although progress is being made. Destruction of articular cartilage is the hallmark of many of these disabling conditions, and an imbalance of pro-inflammatory cytokines over their anti-inflammatory counterparts promotes the disease process. Therefore, an understanding of the effects of the various cytokines and growth factors present during the disease process on the cells and tissues in the joint will greatly assist the development of new therapies. Since tissue destruction is considered the 'end-point' of the disease process, knowledge of the enzymes involved in this destruction is also paramount in new drug design. This review highlights the effects of cytokines and growth factors on cartilage chondrocytes and synovial fibroblasts with respect to cartilage matrix synthesis and repair, and its degradation.

Articular cartilage

Articular cartilage provides a friction-free surface on which the bones of a joint articulate during motion. The joints in the lower body have to support the body weight even at rest. To fulfil these tasks, articular cartilage must be able to withstand the compressive forces that the joint experiences. Two major macromolecules help to provide this function: proteoglycan and

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collagen. Proteoglycan, of which aggrecan is the predominant monomer, has a high sulphated glycosaminoglycan content that attracts water molecules and hence allows the tissue to swell and resist compressive forces (Ref. 1). These proteoglycans are held in the tissue within a fibrous network of triple-helical type II collagen fibrils, which are crosslinked and provide cartilage with its tensile strength. Together, these macromolecules make up ~25% of the wet weight of cartilage, with water accounting for most of the remainder. Other molecules such as minor collagens (types VI, IX, X and XI) (Ref. 2), biglycan, decorin, laminin, tenascin and fibromodulin all assist in maintaining the tissue, through spatially organising components of the extracellular matrix (ECM) (Refs 1, 2, 3). One component of special note is cartilage oligomeric protein (COMP), which is a member of the thrombospondin family of proteins. COMP is present in high amounts in articular cartilage and its breakdown products have been suggested to be a marker for disease. A role for the matrix metalloproteinases (MMPs), as well as serine proteinases, has been demonstrated in this breakdown (Ref. 4). Although its true function remains unclear, COMP is known to interact with collagen, and given its inter-territorial localisation in mature cartilage, a structural role seems probable. This is further supported by the fact that mutations in COMP give rise to structural defects.

Cartilage receives nutrients from the synovial fluid, which is synthesised by the fibroblasts in the synovial membrane. It is a dynamic tissue that is constantly being remodelled as old macromolecules of the ECM are replaced with new. This matrix is maintained and replaced by the resident chondrocytes, which only sparsely populate the tissue. Adequate maintenance of cartilage is essential for chondrocyte viability and, conversely, loss of chondrocytes adversely affects the tissue. Such loss, via apoptosis, is known to be induced by nitric oxide (NO), which itself is produced by pro-inflammatory stimuli such as interleukin 1 (IL-1) and tumour necrosis factor α (TNF-α) (Ref. 5). These observations extend to osteoarthritis (OA) cartilage, where evidence of apoptosis has been found in abnormal tissue, and a significant correlation between apoptotic cell numbers and proteoglycan depletion (with elevated NO levels) has been shown (Ref. 5); activation of the Fas receptor is thought to be the apoptotic trigger (see Ref. 5 and references therein). A feedback loop is therefore created whereby a healthy matrix supports viable chondrocytes and vice versa and, by contrast, loss of chondrocytes through apoptosis favours deterioration of the ECM.

Arthritic disease

Rheumatoid arthritis (RA) is the most common inflammatory arthropathy, having a disease prevalence of 0.5–1.0%. It has a peak age of onset in the sixth decade and is three times more common in women. Although OA is generally more benign than RA, clinical OA of the knee and hips affects 10–20% of the over 65s, and again is more common in women. The combined costs to the UK NHS Executive are £560 million, although the overall cost in the UK is in excess of £1 billion (see Ref. 6 and references therein).

The term RA was coined in 1859 by Sir Alfred Garrod. He was the first to distinguish gout from RA, although OA was still included in the RA heading. The term OA was subsequently used in 1888, but it was not until 1907 that Garrod's son finally made the modern-day distinction between RA and OA. As clinical diagnosis has progressed, specific criteria have begun to be assigned to these diseases, although RA and OA are often still referred to as an inflammatory autoimmune disease and an erosive disease associated with old age, respectively. This classification is obviously over-simplified and some patients might present in the clinic with a combination of both diseases. Controversy also exists as to the precise nature of the initiating factor(s) underlying these diseases, as well as the enzymes that play a major role in the destructive process. A vast amount of research has been undertaken to try to unravel some of these fundamental questions but, although many advances have been made, they remain relatively unanswered. This review focuses on RA but, where possible, information on OA is also documented for comparison.

Rheumatoid arthritis

RA is a complex disease and, although the initiating trigger is poorly understood, the disease is considered to have an autoimmune basis. Antigens suggested to be the target of autoimmunity include type II collagen, heat shock proteins and gp39 (Ref. 7). A genetic predisposition to RA has been demonstrated, with an increased susceptibility locus being

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linked to expression of specific HLA-DR4 subtypes (Ref. 8) (see later section entitled 'Other factors'). One widely accepted hypothesis has been that RA is a disease driven primarily by the synovium, which undergoes proliferation to generate the 'pannus' that then invades articular cartilage and promotes its destruction (Ref. 9). At this stage of disease, the synovitis may subside only to reappear later; this cycle of inflammation followed by remission is typical of many RA patients, in whom damage to the cartilage is thought to occur during inflammatory episodes.

Maintenance of the invasive pannus tissue is an integral part of disease progression. The potent angiogenic cytokine vascular endothelial growth factor (VEGF) appears to play a role in this process (Ref. 10). Invasion is reduced by anti-TNF-α therapy; this might result from blockade of a cytokine cascade or a reduction in leukocyte trafficking into the joint (Ref. 11). Synovial invasion of the cartilage is associated with the plasminogen activation system (Ref. 12), and is also a phase in disease when synovial fluid neutrophils and chondrocytes within the cartilage might begin to respond to the predominantly pro-inflammatory stimuli (Ref. 13).

Recent evidence has indicated that tissue destruction and inflammation might not in fact be coupled (Ref. 14), and therefore that sustained degradation of the cartilage ECM might be a later consequence of the inflammation via stimulation of the resident chondrocytes. A variety of pro-inflammatory stimuli are known to induce chemokine production, including monocyte chemoattractant protein 1 (MCP-1), in chondrocytes, which might provide a mechanism by which cartilage actively promotes disease progression (Ref. 15). It is also unclear why activation of synovial fibroblasts persists even after anti-inflammatory therapy. One possibility is that the synovial membrane is gradually repopulated with immature mesenchymal and bone marrow cells with altered properties. This hypothesis is supported by work that has shown elevated expression of the human embryonic growth factor homologues of *wingless* and *frizzled* in RA fibroblasts compared with OA and normal cells, suggesting that the synovium is indeed repopulated with immature cells (Ref. 16). Alternatively, existing cells might undergo (de)differentiation in some way such that they then express these embryonic markers.

Osteoarthritis

OA falls into two categories: primary OA occurs in middle-aged to elderly patients where an active disease process is often presumed to be a consequence of joint 'wear and tear'; secondary OA occurs at any age as a result of trauma or disease. In both situations, the central feature is loss of articular cartilage and a reduced capacity for repair; the chondrocytes themselves appear to be the driving force behind these deficiencies. A focal lesion in the cartilage might lead to abnormal loading of the surrounding chondrocytes, which, in turn, respond by promoting a cascade of slow but persistent degradation of cartilage, ultimately leading to loss of joint function. The cyclical disease course of OA has also been proposed to be the result of sequential cytokine stimulation followed by a feedback inhibition of autocrine cytokine and cytokine receptor production, which affects collagenase synthesis (Ref. 17). Although not considered an inflammatory disease, orthopaedic surgeons often comment on the marked synovial infiltration seen during joint replacement surgery of OA patients, further increasing the evidence for the involvement of pro-inflammatory cytokines such as IL-1 and TNF-α (Ref. 18).

Matrix metabolism

Degradation and synthesis of cartilage macromolecules under normal physiological conditions is kept in equilibrium and can therefore be viewed as a balance (see Fig. 1). Chondrocytes and synovial cells respond to a variety of cytokines and growth factors that stimulate the production of destructive proteinases. All four major classes of proteolytic enzymes (aspartic, cysteine, serine and metallo) are involved in normal turnover and pathological destruction, and the pathway that predominates will alter depending on the resorptive circumstances (Ref. 19). These pathways are not mutually exclusive and it is highly probable that total degradation of matrix components involves several pathways and classes of proteinases.

MMPs are a family of neutral zinc endoproteinases that collectively degrade all the components of the ECM (Ref. 20), and have received considerable attention with respect to arthritic tissue destruction because their expression correlates strongly with collagen degradation (Refs 21, 22), although this is not always the case (Ref. 23). The MMP family

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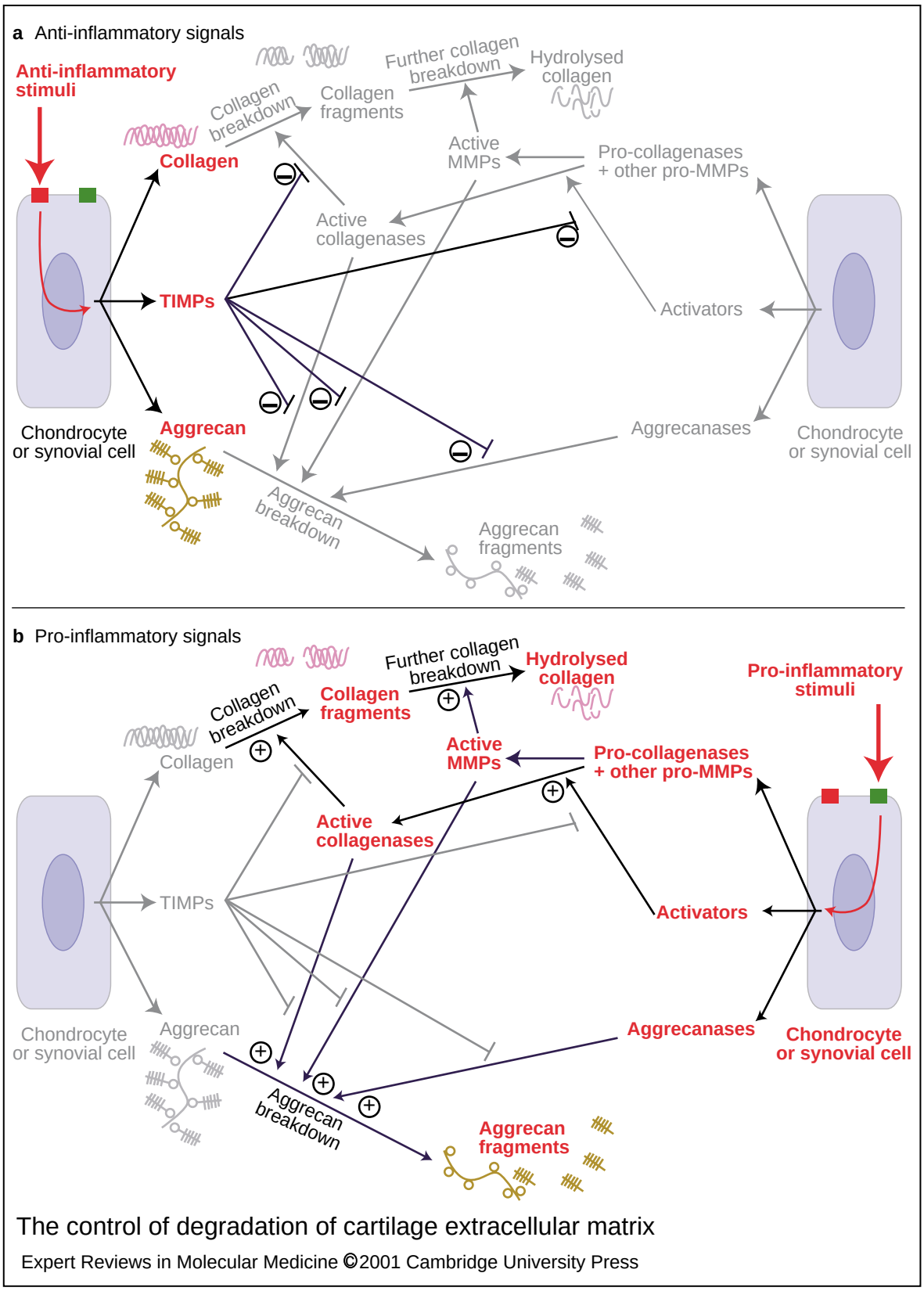

The control of degradation of cartilage extracellular matrix

Figure 1. The control of degradation of cartilage extracellular matrix (*see next page for legend*) **(fig001arn).**

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Figure 1. The control of degradation of cartilage extracellular matrix. Chondrocytes maintain articular cartilage by replacing degraded components via local synthesis, which is balanced with degradation to prevent over-deposition of matrix. In arthritic diseases, this equilibrium is shifted towards degradation. Chondrocytes and synovial cells are stimulated by both (a) anti-inflammatory and (b) pro-inflammatory cytokines, as well as mechanical stress, and cell–cell and cell–matrix contacts, via a variety of cell-surface receptors. These stimuli are transferred to the nucleus via intracellular signalling and mechanotransduction pathways, resulting in activation of gene transcription. Synthesis and secretion of matrix components, including aggrecan and collagen occurs, as well as enzymes such as aggrecanases (e.g. ADAMTS-5), pro-matrix metalloproteinases (pro-MMPs) (including procollagenases) and activating enzymes (e.g. MMP-3, membrane-type MMPs and plasmin). Aggrecanases promote rapid aggrecan loss, and this might be inhibited by tissue inhibitor of metalloproteinase 3 (TIMP-3). Induction of TIMPs, and other inhibitors, via anti-inflammatory agents can block some activating enzymes that otherwise convert pro-enzymes to their active forms. These activating enzymes might in turn also require activation. Once the level of active MMPs exceeds the local supply of TIMPs, they can promote specific cleavage of triple-helical collagen via collagenases, as well as further nonspecific collagen hydrolysis by other MMPs; aggrecan degradation by MMPs might also occur **(fig001arn)**.

contains at least three collagenases [interstitial collagenase/collagenase 1 (MMP-1), neutrophil collagenase (MMP-8), and collagenase 3 (MMP-13)] that can degrade fibrillar collagen (Ref. 20). MMPs are controlled at several levels (Ref. 24), including inhibition by a family of endogenous inhibitors called the tissue inhibitors of metalloproteinases (TIMPs) (Refs 24, 25, 26). MMP inhibition has been the subject of much research in recent years by the pharmaceutical industry in an attempt to find a highly potent, specific and bioavailable inhibitor (Ref. 26). Other metalloproteinases, most notably of the ADAM (for 'a disintegrin and metalloproteinase') family of proteinases, are also expressed in cartilage (Ref. 27), although their roles in tissue maintenance and tissue destruction are still unclear. In particular, a subset of this family known as the ADAMTS (ADAM with thrombospondin motifs) proteins contains members that have recently been found to specifically cleave aggrecan at the site considered to be pathologically relevant (Refs 28, 29, 30). At least one of these enzymes (ADAMTS-5) is also expressed in the synovium (Ref. 31). Although these metalloproteinases are not MMPs, recent evidence indicates that TIMP-3 is a potent inhibitor (Ref. 32).

Cysteine proteinases (cathepsins B and L, which can degrade cartilage and bone) are expressed in RA synovial lining (Ref. 33), and have been implicated in cartilage degradation (Ref. 34). Cathepsin K has received recent attention because it is now thought to be strongly associated with pathological bone and cartilage resorption (Refs 35, 36). Serine proteinases, particularly those associated with the plasmin cascade, have also been implicated in tissue destruction (Refs 12, 37).

The role of MMPs in the pathological destruction of cartilage is promoted by various pro-inflammatory cytokines that perturb the balance between synthesis and degradation of ECM components to favour matrix breakdown (see below and also Fig. 1). Proteoglycan (i.e. aggrecan) loss is a rapid event following pro-inflammatory stimulation but it can be readily replaced once the stimulus is removed. Collagen is more resistant to degradation but is much more difficult to replace (see Ref. 24 and references therein). However, a different situation arises during normal cartilage metabolism (the so-called physiological 'steady-state'). Under these circumstances, degradation of collagen, and indeed probably proteoglycan, occurs within the lysosomal system following phagocytosis, a mechanism shown to occur in fibroblasts (Ref. 38). Although phagocytosis has not been described in chondrocytes, CD44-mediated endocytosis and breakdown of hyaluronate has been reported (Ref. 39), suggesting differences in mechanisms of ECM breakdown among mesenchymal cells. Nevertheless, an equilibrium exists whereby matrix turnover is tightly regulated; any disturbance of the various degradative pathways that prevail might lead to uncontrolled matrix destruction.

Cytokines and cytokine interactions

Cytokines and growth factors have been subdivided into those with pro-inflammatory and those with anti-inflammatory effects; in arthritis, these generally exhibit either catabolic or anabolic effects on cartilage, respectively. Considerable attention has been focused on IL-1 and TNF-α – two pro-inflammatory cytokines that have been regarded as pivotal mediators in inflammatory

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diseases such as RA. However, several other cytokines present in the milieu might also be associated with active disease. The most abundant include IL-1, -6, -8, -10, -11, -13, -17 and -18, TNF-α, granulocyte–macrophage colony-stimulating factor (GM-CSF) and transforming growth factor β (TGF-β). Less-detectable mediators include IL-2, -3, -12 and -15, interferon γ (IFN-γ), oncostatin M (OSM) and leukaemia inhibitory factor (LIF). IL-4 is rarely detected.

It is important to remember that cytokines are capable of acting in synergy, whereby the combined effects of two or more cytokines far exceeds the effects they exert alone. This issue cannot be underestimated, and might occur inadvertently under certain conditions. For example, insulin-like growth factor 1 (IGF-1) has been shown to synergise with TGF-β to induce matrix synthesis (Ref. 40); TGF-β has also been shown to augment prostaglandin E_2 (PGE_2) production in cultured chondrocytes when in the presence of serum (Ref. 41), a result that is most likely explained by the presence of IGF-1 in serum. Hence, culture conditions can significantly alter the responses to cytokines in vitro and careful consideration is required to ensure culture conditions are well defined.

Several antagonist factors might reduce the effects of a given cytokine on cartilage. For example, the effects of IL-1 can be reduced by IL-1 receptor antagonist (IL-1RA), which is a soluble factor that binds IL-1 and prevents it from binding to its cell-surface receptor. This might represent the mechanism of action of the chondroprotective cytokine IL-4, which is known to upregulate IL-1RA (Ref. 42). Many cells also express the IL-1 'decoy' receptor (IL-1RII). It is thought that binding of IL-1 by this receptor does not lead to signal transduction, although this has been challenged recently (Ref. 43) and will require further investigation in the context of experimental data from animal models. There are also various other soluble receptors, which can act as agonists and antagonists [e.g. soluble IL-6 receptor (sIL-6R) and soluble TNF-α receptor (sTNFR), respectively]. These soluble factors are important to consider because they can arise from tissues remote from the cartilage but might have a profound effect on the chondrocytes.

Pro-inflammatory cytokines

A hierarchy of pro-inflammatory cytokines has been proposed to exist in arthritic diseases, whereby IL-1 is the pivotal cytokine at early and late stages of disease and TNF-α is involved in disease onset (Ref. 44). Strong arguments have been proposed for IL-1 as the primary mediator in light of the IL-1β-knockout mouse, which lacks chronic erosive arthritis (Ref. 45). However, other cytokines have also been proposed to be key players, such as IL-15 (Ref. 46). In addition, recent evidence suggests that the T-cell-specific cytokine IL-17 might be the key mediator because it is produced very early in the disease process and is known to induce the production of other pro-inflammatory cytokines (Ref. 47). It is most probable that more than one of these pro-inflammatory cytokines are present in an arthritic joint (e.g. Ref. 48) and that they have varying effects on the disease process, including inhibition of matrix synthesis (e.g. Refs 49, 50), upregulation of matrix-degrading enzymes (e.g. Refs 50, 51, 52, 53, 54), and induction of other pro-inflammatory agents (e.g. Refs 17, 46, 50, 52, 54, 55, 56). This concept of multiple cytokines, perhaps acting synergistically, in arthritic disease has prompted the suggestion that fully effective anti-cytokine treatment will most probably be achieved using a combination therapy (Ref. 57).

Large amounts of NO are produced by chondrocytes activated by pro-inflammatory cytokines (see Refs 5, 58 and references therein). Many studies have shown that NO is at least partly responsible for IL-1-induced effects such as suppressed collagen synthesis. NO production is a consistent feature of arthritic cartilage and synovium and has been associated with matrix degradation and chondrocyte apoptosis. Indeed, inhibitors of NO synthase, which produces NO, help reduce synovial inflammation and result in decreased destruction of cartilage and bone in experimental models of arthritis (Ref. 58).

In general, pro-inflammatory cytokines are potent mediators and exert their maximal effects on cells at relatively low concentrations. This is an important point, especially when considering cell culture experiments in comparison with active disease where, for example, synovial invasion occurs. The localised concentration of a given cytokine at this invasion front might be considerably higher than in the remaining cartilage, and therefore sufficient to affect the local chondrocyte population. Marked differences in cell numbers often occur when comparing cell and tissue culture experiments, such that responses observed in cell culture at a given

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time point might not always be seen in tissue culture.

Anti-inflammatory cytokines

The anti-inflammatory cytokines typically counteract the effects of their pro-inflammatory counterparts and often promote the synthesis of ECM components. Many of these cytokines favour the differentiation of T cells into T helper 2 (Th2) cells rather than the pro-inflammatory Th1 cells. Differentiation of T cells along the Th2 lineage is generally thought to be a more protective mode of the inflammatory response, owing to their anti-inflammatory 'phenotype'. The effects of anti-inflammatory cytokines include the promotion of matrix synthesis and repair (e.g. Refs 40, 59, 60, 61, 62, 63), induction of protective enzyme inhibitors such as TIMPs (e.g. Refs 64, 65, 66), downregulation of destructive enzymes (e.g. Refs 53, 56, 58, 59, 60), and reduction in the levels of pro-inflammatory cytokines (e.g. Refs 40, 44, 67).

TGF-β has a major role in chondroprotective mechanisms and is known to promote matrix synthesis. Cartilage contains vast stores of TGF-β, as much as 300–500 ng g^{-1} of cartilage, with most of it in the latent, inactive form that requires proteolytic processing (Ref. 68). Various hypotheses have tried to explain the physiological significance of this large excess, and although the mechanism of TGF-β autocrine regulation is still not understood, the presence of such reserves strongly implies a role in cartilage metabolism and a key role for TGF-β activation. A recent report, however, has indicated that TGF-β might also cause synovial hyperplasia and osteophyte formation (Ref. 69).

Also present at elevated levels in cartilage is IGF-1, which appears to have a role in stimulating chondrocyte anabolic activity. This growth factor is sequestered from its cell-surface receptor in the ECM by IGF-binding proteins (IGFBPs) and fibronectin (Ref. 70); this complex system is termed the IGF-1 axis and tightly regulates the bioavailability of IGF-1. IGFBP-3 expression appears to increase with age, paralleling an age-related decline in matrix synthesis, and is also overexpressed in OA cartilage where it could cause metabolic disturbances (Ref. 70). The local increase in matrix synthesis following injury could result from damage-induced IGF-1 release from IGFBP pools. An age-related failure in this system could thus contribute to degenerative disease, and gives some credence to the belief that OA is due to the 'wear and tear' of old age. The protective effects of IGF-1 have been further demonstrated using adenoviral vectors that specifically result in its overexpression (see below).

Recent evidence indicates that some of the cytokines that have been described as anti-inflammatory might not always be so. Members of the IL-6 cytokine family, including IL-6 and OSM, are known to induce TIMP production from chondrocytes and fibroblasts, as well as increase matrix synthesis. These abilities would favour a chondroprotective role for these cytokines, although recent evidence now indicates that this is not always the case (Refs 51, 54, 71). Rather, when in combination with IL-1 these cytokines induced a marked catabolic effect by promoting matrix degradation. A protective role for IL-4 has been described in arthritis (Refs 72, 73), although it is also implicated in asthma.

Links between chondrocytes and matrix

Interactions between chondrocytes and the ECM help to regulate many biological processes important to cartilage homeostasis and repair, including cell attachment, differentiation, growth and survival. The integrin family of cell-surface receptors plays an important role in mediating cell–matrix interactions. Several integrins are expressed on chondrocytes and these serve as receptors for collagens type II and VI ($\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_{10}\beta_1$), vitronectin and osteopontin ($\alpha_V\beta_3$), laminin ($\alpha_6\beta_1$) and fibronectin ($\alpha_5\beta_1$) (Ref. 74). Integrins might be important transducers of mechanical stimuli because they provide a link between the cytoskeleton and the ECM. Such links are critical, for example, for relaying shear-stress-induced signals (Ref. 75). Expression of integrins can be regulated by IGF-1 and TGF-β (see Ref. 74 and references therein). Cross-talk between the integrin signalling mechanisms has recently been demonstrated and is thought to play a role in cartilage homeostasis (Ref. 76). Indeed, an $\alpha_V\beta_3$ antagonist has been shown to reduce inflammation and improve joint integrity in an experimental arthritis model (Ref. 77). Moreover, deregulation of this integrin network might be important in disease progression.

Cell-surface receptor binding is the primary means by which cytokines and growth factors mediate their effects upon cells. In many cases, very limited amounts of cytokine are required to elicit a response. A maximal response to IL-1 in chondrocytes can be achieved when as few

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as 40 cell-surface receptors bind ligand (Ref. 78). Observations such as this clearly suggest that modulation of the number of cell-surface receptors would not have a marked effect on cellular responses. However, where cell-surface receptor expression is limiting, then an increase in expression might alter the responsiveness of a given cell type. This is evident for the TNFRs (which are expressed as two different forms: TNFR55 and TNFR75); normal chondrocytes express mainly TNFR55, but pro-inflammatory cytokines such as TNF-α induce the expression of TNFR75 (Ref. 79). In OA cartilage, differences in TNFR distribution have been found and a role for TNF-α in focal cartilage loss has been reported (Ref. 80); this role is further supported by evidence that levels of TNF-α and TNF-α-converting enzyme (TACE or ADAM-17) are elevated in OA cartilage, suggesting a paracrine/autocrine loop (Ref. 81). A role for CD44, the hyaluronan receptor, on chondrocytes has been demonstrated in the maintenance of cartilage homeostasis (Ref. 82); in particular, this might have implications for aggrecan turnover.

Chondrocytes are able to respond to a wide variety of stimuli, suggesting that they have an extensive repertoire of receptors. When a specific receptor is absent, responsiveness might be conferred by the presence of a soluble receptor. For example, sIL-6R confers IL-6 responsiveness to chondrocytes (Ref. 83), which normally possess gp130, the common signalling subunit for IL-6-type cytokines (Ref. 54). Membrane IL-6R lacks the cytoplasmic signalling domain and hence does not contribute to signal transduction other than by binding to gp130 once it has bound IL-6, as is the case for sIL-6R. Such findings might be relevant to RA since sIL-6R is elevated in RA synovial fluids (Ref. 84) and is known to be produced by the synovium.

Other factors

Several studies have indicated a small but consistent increased risk of arthritic disease in siblings of affected individuals (Ref. 85), although identical twins show little similarity in the timing of disease onset. However, twin studies do support the notion that genetic factors contribute to increased disease risk: monozygotic and dizygotic twins have a disease concordance for RA of 12% and 4%, respectively, which is well above the background disease prevalence of 0.5–1.0% (see Ref. 85 and references cited therein). Polymorphisms in several genes associated with destructive joint diseases have been identified that might contribute to disease pathogenesis, such as an IL-6 polymorphism associated with juvenile chronic arthritis (Ref. 86). Ongoing studies of a polymorphism in the MMP-1 promoter (already shown to correlate with tumour invasion in cancer patients) might shed new light on the role of this proteinase in arthritic disease.

Autoimmunity is also thought to be a dominant factor in the pathogenesis of RA, and autoantibodies to cartilage-specific components have been detected in serum samples of RA patients (Ref. 87). Complement activation occurs adjacent to the cartilage surface, where abundant co-deposits of immunoglobulin and activated complement components such as C1s are present. This component has several novel functions (see Ref. 88), and is thought to participate in the pathogenesis of RA through its collagenolytic activity (Ref. 89), in addition to its role in the complement cascade. A genetic predisposition for RA has been identified in the major histocompatibility complex (MHC) that forms the human leukocyte antigen (HLA) types (see Ref. 8 and references therein). Interactions between antigenic peptide and an HLA molecule determine the immune response, and the HLA molecules associated with RA encode a sequence of amino acids that constitute the 'shared RA epitope'. This epitope has been shown to indicate an increased susceptibility for more-aggressive, erosive RA. Several models have been proposed for how this epitope could lead to antigen-specific T-cell-mediated autoimmunity (see Ref. 8 and references therein).

Gene regulation in cartilage metabolism

Gene regulation through cytokine stimulation is mediated via specific signal-transduction pathways, an area of research that has prompted the search for novel therapeutic targets for many diseases, including inflammatory arthritis. Several transcription factor families, including AP-1, NF-κB and STAT, have been implicated in gene regulation in inflammation (see Ref. 90 and references cited therein). Moreover, the activity of these transcription factors is regulated by mitogen-activated protein kinase (MAPK) pathways. Cross-talk and/or interplay between these pathways might contribute to increased transcription of some catabolic genes (e.g. Ref. 91).

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This level of complexity is compounded when combinations of cytokines appear to have synergistic effects on gene transcription, and this can be problematic when trying to reproduce in vivo effects in vitro.

The advent of potent synthetic inhibitors of factors involved in a variety of signal-transduction pathways has begun to allow a more detailed analysis of the specific pathways that are involved in the regulation of genes considered to be important in the disease process. This applies not only to the degradative enzymes such as the collagenases but also to their inhibitors such as the TIMPs (e.g. Ref. 92). Furthermore, the identification of endogenous regulators of transcription factors such as those for STAT proteins has also allowed more detailed analyses of specific pathways that are utilised in the transcriptional activation of certain genes (e.g. Ref. 93).

Genetic approaches to understanding arthritis

Although pro-inflammatory cytokines and the MMP family of enzymes have been strongly implicated in the pathological destruction of cartilage, considerable controversy still exists as to the identity of a specific cytokine(s) and MMP(s) that are involved in the disease process. In particular, the identity of the collagenase responsible for the destructive turnover of cartilage collagen has been much debated since collagenase 3 (MMP-13) was discovered (Ref. 94). This finding led to a reappraisal of the observations made using murine models of arthritis because rodents appeared to lack the homologue of human collagenase 1 (MMP-1); such a homologue has, however, now been described (Ref. 95). In humans, it is likely that all three collagenases are elevated at some stage in the disease process but that their regulation is not co-ordinated. To date, few studies have assessed multiple MMP expression in diseased tissues, although those that have clearly identify MMP-1 and MMP-13 as being strongly associated with RA synovitis (e.g. Ref. 96).

Transgenic studies

To address some of these issues, transgenic animals have been developed to either overexpress or 'knock-out' expression of MMPs and various cytokines to identify their impact (Table 1). A role for both IL-1 and TNF-α has been demonstrated in these studies. Several MMP-transgenic mice have been developed and interestingly no MMP knockout has been lethal; indeed, several of the knockouts have phenotypes similar to the wild-type animals, suggesting a degree of redundancy within the MMP system. However, one transgenic study has suggested that MMP activation might be a key step in cartilage erosion (Ref. 97).

The major findings relevant to arthritic disease include the following. First, aggrecan cleavage at the 'aggrecanase' site still occurred in stromelysin 1 (MMP-3) knockout mice (Ref. 98), clearly implicating the recently identified aggrecanase (ADAMTS) enzymes (Refs 28, 29, 52) in the specific cleavage of aggrecan; furthermore, in less-aggressive models of arthritis, fewer erosions were found in the MMP-3 knockout mice, suggesting a role for MMP-3 in collagenase activation. Second, the MMP-9 knockout had no obvious phenotypic defects, although there was a delay in long bone growth (Ref. 99). Perturbed vascularisation and ossification of the growth plate appeared to account for the MMP-9 knockout effects, indicating an important developmental role for this enzyme. Third, the MT1-MMP (MMP-14) knockout mice developed dwarfism, osteopaenia and a spontaneous arthritis (Ref. 100), and had severe defects in skeletal development and angiogenesis (Ref. 101). The shortening of bones in these mice is a consequence of decreased chondrocyte proliferation in the proliferative zone of the growth plates. Defective vascular invasion of cartilage promotes enlargement of the hypertrophic zones of the growth plate, which delays the formation of secondary ossification centers. Activation of latent gelatinase A (MMP-2) was also deficient, suggesting that MMP-14 is essential for its activation in vivo. It is unclear whether a nutritional defect might be the cause of some of these observations.

Other genes relevant to cartilage that have been targeted in knockout studies include ADAM-17 and ADAMTS-1, although experiments to assess the effects on cartilage remain to be reported. Loss of ADAM-17, the enzyme responsible for releasing TNF-α from the cell surface, results in mice with respiratory distress and abnormal lung development, implicating this enzyme in lung morphogenesis (Ref. 102). ADAMTS-1-null mice have growth retardation and impaired female fertility (Ref. 103).

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Table 1. Effects of cytokine transgenes on experimental arthritis (tab001arn)

Gene	Genotype[a]	Findings	Refs
IL-1α	O	Full signs of destructive arthritis	112
IL-1β	K	Normal inflammatory but defective acute-phase responses; resistance to CIA and protection against cartilage destruction in streptococcal-cell-wall arthritis	113, 114
TNF-α	O	Chronic arthritis (inhibited by antibodies to IL-1RI)	108
TNFRI	K	Milder CIA at a reduced incidence; however, once the joint is affected, the disease progresses to the same end-stage as in wild-type mice	115
IL-6	K	Inflammatory cell infiltration in knee joints diminishes, but cartilage proteoglycan loss is enhanced during the early acute phase	116
		Only a transient inflammation during AIA, and no chronic synovitis in zymosan-induced arthritis	117
EGF	O	Growth retardation and reduced IGFBP3 levels; accumulation of pre-hypertrophic chondrocytes in the growth plate and abnormal osteoblast proliferation	118
IFN-γR	K	CIA occurs earlier than in wild-type mice	119
FcR	K	Joint swelling reduced in AIA although sustained inflammation evident; chondrocyte death and matrix erosion absent	97
		Inflammation and cartilage destruction prevented	120

[a] O indicates the gene is overexpressed, and K indicates that the gene is knocked out.

Abbreviations: AIA, antigen-induced arthritis; CIA, collagen-induced arthritis; EGF, epidermal growth factor; FcR, Fc receptor; IFN-γR, interferon γ receptor; IGFBP-3, insulin-like growth factor binding protein 3; IL-1, interleukin 1; IL-6, interleukin 6; IL-1RI, type I IL-1 receptor; TNF-α, tumour necrosis factor α; TNFRI, TNF-α receptor I (TNFR55).

Gene therapy in arthritis

Another approach that has begun to receive much attention recently is that of adenoviral overexpression of (anti-inflammatory) cytokine genes in the joint to study the effects of individual cytokines on cartilage homeostasis and to ameliorate disease (Table 2). The viruses are attenuated so as to be infectious but unable to replicate. Recombinant adeno-associated viral (rAAV) vectors might be advantageous for in vivo gene therapy for arthritis because of their ability to transduce both fibroblasts and chondrocytes (Ref. 104). These studies have confirmed the protective nature of TGF-β and IGF-1, which has prompted the notion that such vectors could be used in the targeted repair of cartilage injury (Refs 59, 60). However, caution should also be used when interpreting such studies with a view to treating human disease. Another study using TGF-β recently reported synovial hyperplasia and osteophyte formation (Ref. 69) – findings that cast some doubt on the use of this growth factor as a reparative agent for cartilage damage.

Clinical implications

While researchers have been trying to understand the factors and mechanisms underlying the disease processes, clinicians have been equally busy treating an ever increasing number of patients. This increase in number is partly due to improvements in general medical care, changes in lifestyles and the fact that many populations are increasing in age. Together, these factors are having considerable impact on the long-term

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Table 2. Effects of adenovirus-transfected mediators on experimental arthritis (tab002arn)

Factor	Cell/tissue targeted[a]	Effect on matrix components	Refs
BMP-2	Chondrocyte	Stimulated proteoglycan synthesis even following IL-1 stimulation	62
Plasmin inhibitor	RA synovial fibroblast	Reduced cartilage matrix degradation; reduced cartilage invasion	12
c-Fos	Chondrocyte[b]	Decreased proteoglycan synthesis and TIMP-1 expression, with an increase in MMP-3; decreased type II collagen expression with elevated MMP-1	121
OSM	Synovium	Increased synovial cell proliferation, with pannus-like appearance and infiltration of mononuclear cells; increased matrix deposition	71
TGF-β1	Chondrocyte	Increased matrix synthesis while maintaining type II collagen phenotype	59
		Restored proteoglycan synthesis following IL-1 stimulation	62
	Cartilage	Increased proteoglycan and collagen synthesis	60
	Synovium	Synovial hyperplasia and chondroosteophyte formation at the cartilage–syonvium junction	69
IGF-1	Cartilage	Induced proteoglycan synthesis but did not have anti-inflammatory or chondroprotective effects	122
		Induced matrix synthesis; maintained long-term chondrocyte phenotype in culture	61
	Chondrocyte	Stimulated proteoglycan type II and collagen synthesis; restored proteoglycan synthesis following IL-1 stimulation	62
iNOS	Chondrocyte	Reduced IGF-1; stimulated proteoglycan synthesis	123
IL-4	Chondrocyte	Prevented chondrocyte death and cartilage erosion; enhanced proteoglycan synthesis and reduced MMP expression; reduced IL-1β and nitric oxide production from synovium; inflammation unaffected	124
	Joint	CIA model: reduced disease prevalence and paw swelling; attenuated synovitis and delayed disease onset	125
IL-4, IL-13	Fibroblast (xenograft)	Significantly reduced disease severity	126
IκBα	Synovial fibroblast	Blocked IL-6, IL-8 and MMP production	127
	Chondrocyte	Blocked IL-6, IL-8 and MMP production	127
CTGF	Chondrocyte	Stimulated expression of aggrecan and collagen types II and X	63
IL-1RII	Keratinocyte graft[b]	CIA model: reduced clinical and histological parameters of disease; reduced IL-6 expression	111

[a] Although a specific cell or tissue is described in the studies, the virus is likely to primarily infect synovial cells. However, specific differences between studies might be a result of a more localised infection (e.g. cartilage versus synovium).
[b] This was a stably transfected line.

Abbreviations: BMP-2, bone morphogenic protein 2; CIA, collagen-induced arthritis; CTGF, connective tissue growth factor; IGF-1, insulin-like growth factor 1; IκBα, inhibitor of nuclear factor kappa B; IL-1, interleukin 1; IL-1RII, type II IL-1 receptor; IL-4, interleukin 4; IL-13, interleukin 13; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; OSM, oncostatin M; RA, rheumatoid arthritis; TIMP, tissue inhibitor of metalloproteinase; TGF-β, transforming growth factor β.

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management of arthritis sufferers, not least financially.

During the past ten years, several synthetic MMP inhibitors have been developed for the treatment of arthritic disease (see Ref. 26). Enthusiasm was increased when the first full-length crystal structure of a collagenase (MMP-1) was determined (Ref. 105) to assist such developments. However, despite considerable improvements in bioavailability and avoidance of gut modification, MMP inhibitors have generally not been very successful, because of lack of efficacy. Furthermore, adverse side effects of these inhibitors, presumably due to inappropriate inhibition of metalloproteinases other than those thought to be involved in the disease process, have also been reported. Metalloproteinases, including the MMPs, have many normal physiological roles and considerable debate has arisen as to whether a broad-spectrum inhibitor or a highly specific inhibitor should be used (Refs 26, 106). This is an important and fundamental issue and is biased by how data are interpreted. Some MMP inhibitors have been used with limited success in cancer treatment, but none has yet been used successfully to treat arthritic patients. Whether a specific enzyme responsible for tissue destruction in RA or OA will be identified is also a highly debated point, but is of considerable importance in minimising side effects.

One of the major landmarks in the treatment of RA has been anti-TNF-α therapies; in studies of such therapies ~70% of patients showed some benefit (Ref. 107). However, the remaining 30% of apparent non-responders presumably have a disease that is mediated by another pro-inflammatory agent, assumed by many to be IL-1. This is supported by data from a TNF-α-overexpressing transgenic mouse model, where treatment with antibodies to IL-1RI completely prevented the otherwise spontaneous arthritis (Ref. 108). A combinational therapy with both anti-TNF-α and anti-IL-1 has therefore been proposed (Ref. 57). This is further supported by the finding that elevated levels of the natural anti-inflammatory agent IL-1RA can occur in RA (Ref. 109). Furthermore, treatment with IL-1RA has been shown to be efficacious against arthritic joint disease (Ref. 110), and the decoy receptor IL-1RII blocks experimental arthritis (Ref. 111). These observations might therefore indicate the most promising avenues to pursue towards providing a markedly better prognosis for patients with arthritic conditions, and might ultimately be complemented by gene therapy techniques using attenuated adenovirus to deliver highly efficacious anti-inflammatory mediators.

Unfortunately, these new treatments are expensive. The medical services could find themselves in the predicament of being able to offer a good chance of stopping disease progression in some patients (but not all), but probably at the expense of treating a much larger number of patients who would obtain some benefit from the more traditional treatments already available. This situation therefore suggests that there is still a need for small-molecule drugs that prevent joint destruction. Financial constraints aside, researchers and clinicians alike continue to strive towards being able to offer improved treatment for these chronic and disabling diseases.

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Further reading, resources and contacts

Newcastle Rheumatology: information about the research projects in rheumatology in Newcastle, UK

http://www.ncl.ac.uk/rheumatology

Arthritis Research Campaign: the major funding organisation for rheumatological research in the UK

http://www.arc.org.uk

Arthritis & Rheumatism: the highest-rated, peer-reviewed rheumatological journal

http://www.interscience.wiley.com/jpages/0004-3591/

Arthritis Research: a relatively new research journal available online

http://www.arthritis-research.com

Cytokine and Growth Factor Reviews: publishes excellent articles, available on the web

http://www.elsevier.com/locate/cytogfr

General sites about arthritis and various treatment regimens

http://www.arthritis.about.com/health/arthritis
http://www.healthtalk.com
http://www.arthritisinsight.com

The MEROPS database (Ref. 128) has helped to reform the nomenclature of proteinases. Many have more than one trivial name; in addition, some cannot be conveniently separated by their catalytic activity and are thus not neatly covered by the International Union of Biochemistry and Molecular Biology (IUBMB) enzyme nomenclature system. It is now strongly recommended that researchers use the MEROPS identifier when discussing a particular proteinase to avoid possible confusion. This database is constantly being updated as new proteinases are described.

http://www.merops.co.uk

An excellent and easy-to-read rheumatological textbook for medical students:

Athanasou, N.A. (1999) Colour Atlas of Bone, Joint and Soft Tissue Pathology, Oxford University Press, Oxford, UK.

A useful overview of the MAPKs that are utilised by many pro-inflammatory cytokines:

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Evans, C.H. et al. (2001) Future of adenoviruses in the gene therapy of arthritis. Arthritis Res 3, 142-146, PubMed ID: 21196423

• Lessons from animal models of arthritic disease

Goldring, M.B. (1999) The role of cytokines as inflammatory mediators in osteoarthritis: lessons from animal models. Connect Tissue Res 40, 1-11, PubMed ID: 20231415

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Features associated with this article

Figure
Figure 1. The control of degradation of cartilage extracellular matrix (fig001arn).

Tables
Table 1. Effects of cytokine transgenes on experimental arthritis (tab001arn).
Table 2. Effects of adenovirus-transfected mediators on experimental arthritis (tab002arn).

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