Pathogenesis of bone and cartilage destruction in rheumatoid arthritis

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Proinflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor alpha (TNFα), have been implicated in the dysregulation of bone and cartilage remodelling characteristic of rheumatoid arthritis (RA). With respect to bone remodelling, both of these cytokines have been shown to up-regulate the production of the receptor activator of nuclear factor-kB ligand, which acts to enhance osteoclastic bone resorption. TNFα stimulates differentiation of osteoclast progenitors into mature osteoclasts and IL-1 acts directly on osteoclasts to increase the bone-resorbing capacity of these cells. IL-1 and TNFα also adversely affect cartilage remodelling, although IL-1 is more potent on a molar basis. This cytokine not only increases production of factors that stimulate cartilage matrix degradation, but also inhibits the synthesis of type II collagen and proteoglycans. Enhanced understanding of the mechanisms underlying the processes of joint destruction will allow more selective and specific application of therapeutic agents that target these pro-inflammatory cytokines and, thus, more effective management of patients with RA and other inflammatory disorders.

Key words: Bone, Cartilage, Cytokines, Interleukin-1, Osteoclast, Receptor activator of nuclear factor-kB ligand, Rheumatoid arthritis, Tumour necrosis factor alpha.

Rheumatoid arthritis (RA) is characterized by a chronic inflammatory process that targets the synovial lining of diarthrodial joints. As the disease advances, there is evidence of progressive destruction of the structural components of the joints. This inflammatory process targets the articular cartilage, the bone at the joint margins, as well as periarticular and subchondral bone. Histopathological analyses of tissues retrieved from patients with RA and from animal models of inflammatory arthritis have provided insights into the cellular mechanisms by which inflammation of the synovium and pannus contributes to the pathogenesis of the abnormal connective tissue remodelling. Understanding of the regulatory factors responsible for the initiation, perpetuation and destructive capacity of RA synovium has been enabled by the cloning and functional characterization of a variety of cytokines and related inflammatory cell products.

Among these factors, particular attention has been focused on interleukin-1 (IL-1) and tumour necrosis factor alpha (TNFα). Studies by van den Berg and others using animal models of inflammatory arthritis have demonstrated that these two cytokines play critical roles in the perpetuation and destructive capacity of the inflamed synovial tissues [1]. Similarly, both of these cytokines are abundant in inflamed synovial tissues in RA and have been shown to produce marked disturbance of bone and cartilage remodelling leading to destruction of the extracellular matrices of these tissues [2]. Furthermore, the validation of a major role for these cytokines in joint destruction in RA has been provided by the results of clinical studies in which the targeting of these factors has resulted in striking attenuation and, in some instances, almost complete inhibition of tissue destruction. This review will focus on the underlying mechanisms of bone and cartilage loss in RA with particular attention to the role of IL-1, TNFα and related cytokines in these events.

Progression of structural damage in RA

Although RA is a systemic disorder in which functional disability is a multifactorial process, there is an increasing awareness that damage to joint structures, caused by bone and cartilage loss, contributes significantly to the overall functional status of the patient [3–6]. The assessment of cartilage and bone damage in RA has traditionally relied on radiographical analyses in which joint space loss and
Marginal joint erosion serve as surrogate markers of joint damage. The introduction of magnetic resonance imaging (MRI) techniques helped to establish that cartilage and bone loss occur early and that these changes tend to progress throughout the course of the disease [7, 8]. This information has allowed modification of the treatment strategy for patients with RA, reinforcing the rationale for early intervention to prevent joint damage. Indeed, results from several recent studies indicate that therapeutic intervention with so-called disease-modifying anti-rheumatic drugs (DMARDs) [9] or biological response modifiers (BRMs) [10–12] can halt or retard the progression of joint destruction in patients with RA. Notably, several of these therapies target IL-1 and TNFα, providing direct evidence that these factors play an essential role in the inflammatory and destructive processes associated with the RA synovial lesion. However, despite the therapeutic potential these agents may offer, many patients continue to show evidence of joint damage. In order to develop more effective treatment approaches aimed to prevent these complications, it is essential to have a more complete understanding of the complex pathological processes associated with bone and cartilage loss in RA.

Mechanisms of focal bone loss in RA

Two important questions can be raised with respect to the pathogenesis of focal bone erosions in RA. The first relates to the cell type responsible for bone resorption and the second relates to the definition of the mechanisms that underlie the disturbance in bone remodelling that accounts for the progressive bone loss. The signals for activating the physiological bone remodelling cycle are initiated by cells lining the trabecular bone surfaces. These cells, which are of osteoblast lineage, as well as cells within the adjacent bone marrow stroma, receive the hormonal or cytokine signals that begin the remodelling cycle. Following activation, these cells release additional cytokines and chemokines that are responsible for the recruitment and induction of osteoclasts, which are the principal cell type responsible for bone resorption under physiological conditions. The bone lining cells are also involved in the preparation of the bone surface for recognition by osteoclast precursor cells [through a process that is believed to involve release of matrix metalloproteinases (MMPs)] [13, 14]. The osteoclast precursor cells are derived from haematopoietic precursors of the monocyte–macrophage lineage and are present within the bone marrow or are derived from a pool of circulating cells. After completion of the resorption phase, the bone surface is repopulated by osteoblasts or preosteoblasts, which then differentiate into mature osteoblasts. These cells deposit bone matrix, which undergoes mineralization to form the new bone surface. After completing their tasks, the osteoclasts and osteoblasts are believed to undergo apoptosis. In the physiological remodelling cycle, the amount of bone that is removed during the resorption phase is exactly matched by the amount of bone that is laid down during the formation phase. This process of remodelling permits adaptation of the skeleton to changing biomechanical environments and repair of microdamage. The erosive changes that occur in association with the inflammatory synovial lesion in RA are indicative of an imbalance between bone resorption and formation. This imbalance leads to progressive focal articular bone loss.

A number of phenotypic markers have been used to identify osteoclasts and to distinguish these cells from their precursors as well as other bone cell types [15, 16]. These include the presence of multinucleation and the expression of carbonic anhydrase and a proton-pump ATPase that permit generation of an acidic microenvironment for dissolving the mineral phase of bone. Osteoclasts also produce acid proteases, including tartrate-resistant acid phosphatase (TRAP) and cathepsin K, that degrade the organic bone matrix. In addition, they express receptors involved in cell attachment, such as vitronectin and calcitonin receptors. The expression of calcitonin receptors is a particularly useful marker of the osteoclast phenotype since they are not expressed on macrophages or other haematopoietic cells. Expression of the calcitonin receptor coincides with the terminal differentiation of the osteoclast into a fully competent resorbing cell [17].

In our studies we have examined the phenotype of bone-resorbing cells at the bone–pannus interface using in situ hybridization and immunohistochemistry [18]. Multinucleated cells expressing mRNA for TRAP, cathepsin K and the calcitonin receptor were found in resorption lacunae in regions where the pannus invaded into bone. These findings lend further support to the concept that cells with phenotypic and functional properties of osteoclasts mediate a component of the pathological bone loss associated with the inflamed RA pannus. Others have provided evidence that additional cell types, including activated synovial fibroblasts or macrophages, may contribute directly to the pathogenesis of focal bone erosions [19].

More recently, several lines of evidence have added further support implicating osteoclasts as the principal cell type responsible for focal bone loss in RA. These data are derived from animal models in which osteoclast differentiation or activity has been impaired, either by deletion of genes that are required for osteoclast formation, or by targeting a newly described cytokine, receptor activator of nuclear factor-κB ligand (RANKL), which is necessary for osteoclast differentiation and activation [20–23]. In these models, which involve animals that lack the ability to form osteoclasts or in whom osteoclast differentiation and activity have been blocked by an inhibitor of RANKL, known as osteoprotegerin (OPG), there is minimal evidence of focal bone erosion. These findings provide further support that osteoclasts are the major cell-type mediating focal bone loss in inflammatory arthritis.
Regulation of bone remodelling

As depicted in Fig. 1, there are three potential regulatory sites in the pathway of osteoclast differentiation and activation. On trabecular bone surfaces, the initial site of regulation of the resorption phase of bone remodelling is mediated by the action of cytokines and hormones on the bone-lining cells. Among the factors that act on bone-lining cells are parathyroid hormone (PTH), PTH-related peptide (PTHrP; the humoral factor associated with hypercalcaemia of malignancy), 1,25-OH2-vitamin D3, prostaglandin E2 and several cytokines, including IL-1, TNFα, IL-11 and IL-17. Binding of these factors to receptors on the bone-lining cells results in the release of products that act directly on osteoclast precursors to induce their differentiation into osteoclasts. These factors include macrophage-colony-stimulating factor (M-CSF), RANKL, IL-1, TNFα, IL-6, IL-11 and IL-15 [15, 16, 24, 25].

Finally, there are several factors that can act directly on osteoclasts to enhance their resorbing activity, including IL-1, TNFα and RANKL. Among these regulatory factors, there has been considerable interest in RANKL because of its potent regulatory activity in controlling osteoclastogenesis. A member of the TNF family of ligands, RANKL has been identified by several different laboratories, which have designated it as osteoclast-differentiating factor, TNF-related activation-induced cytokine, or OPG ligand [26]. RANKL exerts its actions by binding to its cognate receptor, the receptor activator of NF-κB (RANK). RANK is a member of the TNF family of receptors and is expressed on osteoclast precursors, osteoclasts, dendritic cells and certain non-immune cells, notably chondrocytes. As shown in Fig. 2, RANKL activity is regulated by a naturally occurring inhibitor, OPG. OPG is a member of the TNF-receptor family and a soluble protein that acts as a decoy receptor by binding to RANKL, preventing the normal RANKL–RANK interaction and, thereby, disrupting osteoclastogenesis [27].

Several lines of evidence indicate a role for RANKL in the pathogenesis of focal bone loss in RA. Our group and others have shown that RANKL messenger RNA (mRNA) and protein are expressed in synovial tissue from patients with RA [28–32]. Expression is localized to both synovial fibroblasts and T-cells, both of which have been shown to have the capacity to induce osteoclastogenesis in vitro [29, 31, 33]. In studies reported by Weitzmann et al. [33], treatment of cell cultures with OPG did not completely block osteoclastogenesis, indicating that, in addition to RANKL, other products derived from synovial cells may have osteoclast-inducing activity.

Results in animal models of arthritis provide additional evidence implicating RANKL in the pathogenesis of osteoclast-mediated focal bone loss in inflammatory arthritis. Using a rat adjuvant arthritis model, Kong et al. [22] demonstrated that RANKL was expressed by activated T-cells in synovial tissues. Treatment with OPG at the onset of the arthritis markedly suppressed bone destruction, even though inflammation was unaffected. Similar results with OPG blockade of bone erosions have been reported with the TNFα transgenic model of inflammatory arthritis [20]. RANKL mRNA expression has also been demonstrated in cells in the inflamed synovium and in osteoclasts at sites of bone erosion in collagen-induced arthritis [34].

Although data from human RA studies and animal models of inflammatory arthritis indicate that RANKL plays a role in the pathogenesis of focal bone loss, inflamed synovial tissues produce a variety of other factors with osteoclastogenic activity (Table 1). These include IL-1α, IL-1β, TNFα, IL-6, M-CSF, IL-17 and PTHrP [24, 25].

IL-1 and TNFα have dual effects on osteoclasto-
Mechanisms of cartilage loss in RA

In contrast to bone remodelling, in which nonresident cells of haematopoietic and mesenchymal origin are recruited to the bone surfaces to remodel the bone matrix, the cartilage remodelling process is conducted entirely by a single cell type, the chondrocyte. This cell is responsible not only for the synthesis of the complex extracellular matrix of the articular cartilage, but is also the source of proteinases and other mediators that degrade the damaged matrix to permit repair. Unlike bone, which is continuously remodelled throughout life, cartilage turnover is relatively limited and this tissue appears to have restricted capacity to repair its matrix once it is damaged.

Many of the same factors produced by the inflamed RA synovium and involved in regulating bone remodelling also affect chondrocyte function. These include effects on up-regulating products that enhance matrix degradation but also suppress matrix synthesis and repair (Table 2). Among the synovial products implicated in cartilage loss, IL-1 and TNFα appear to play particularly important roles, although IL-1 has more potent effects than TNFα on a molar basis. Numerous studies have demonstrated that IL-1 stimulates chondrocytes to increase production of MMPs and other degradative products such as nitric oxide [38–43]. Other in vitro and in vivo studies have shown that the effects of TNFα are similar to, or synergistic with IL-1, thus indicating a role for this cytokine in cartilage destruction as well [43, 44]. In addition to up-regulation of degradative products, these cytokines further contribute to the depletion of the cartilage matrix by decreasing the synthesis of cartilage-specific collagens and proteoglycans [45–48].

There are two principal mechanisms by which the RA synovial tissues contribute to cartilage loss (Table 2). The first is indirect and involves the effects of cytokines and other mediators released from the synovium that produce dysregulation of chondrocyte function. IL-1 and TNFα are two of the synovial factors that function in this manner. The second mechanism by which RA synovial tissues adversely affect cartilage remodelling is direct and involves products—in addition to cytokines—produced by the RA synovium that have the capacity to degrade the articular cartilage matrix.

Conclusions

It is now well established that treatment with DMARDs, such as methotrexate and leflunomide, can attenuate the progression of cartilage and bone loss in patients with RA. The recent development and introduction of biological therapies that target IL-1 or TNFα has expanded the therapeutic options for RA management. These cytokines play a significant role in the initiation and perpetuation of the synovial inflammation and also act directly on bone and cartilage cells to adversely affect their function. Inhibition of their activity can therefore target the destructive and inflammatory processes that characterize RA. Characterization of the cellular events associated with bone and cartilage loss has further revealed additional potential therapeutic targets such as RANKL that act in tandem with IL-1 and TNFα to produce joint destruction. Therapies that specifically target these cytokines and their signal pathways represent
rational objectives for enhanced treatment of patients with RA.

References


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