ELSEVIER

Cellular and molecular mechanisms of bone damage and repair in inflammatory arthritis

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Bone remodelling relies on tightly controlled cycles of bone resorption and formation, mediated by osteoclasts and osteoblasts, respectively. The past two decades have seen a huge increase in our understanding of immune modulation and disruption of bone homeostasis in rheumatic diseases; identification of the molecular pathways responsible for accelerated bone loss in such conditions has given rise to potential novel therapeutic targets. Most recently, the role of microRNAs in inflammatory and noninflammatory bone loss raises the intriguing possibility that modification of cellular protein translation could also be a treatment strategy for bone damage.

Introduction

All inflammatory arthropathies are associated with disruption to bone architecture, but the principle site and patterns of structural change differ between even the prototypical rheumatic diseases. In rheumatoid arthritis (RA) bone loss predominates in the form of peri-articular osteopaenia, systemic osteoporosis and discrete erosions at the synovial–bone interface. Indeed, bone erosions are detectable very early in the clinical course of disease, often being present within a few months of symptoms, and their presence is associated with a poor clinical and functional outcome. Repair of such erosions, even with apparently satisfactory suppression of inflammation, is rare and stands in stark contrast to the spondyloarthropathies (SPA) such as psoriatic arthritis (PsA), in which enhanced bone formation alongside erosion is characteristic, with the development of syndesmophytes and ankylosis and consequently detrimental effects on mobility. Although the synovium is the characteristic site of inflammation in RA, the enthesis complex (i.e. enthesis and neighbouring synovium) is central to disease in SPA [1].

The maintenance of structural integrity in bone is ultimately dependent on the balanced activity of osteoclasts and osteoblasts–cells that resorb and form bone, respectively. New insights into the biology of these cells have progressed our understanding of different patterns of bone disease in inflammatory conditions, and, crucially, have highlighted potential therapeutic targets to ameliorate or even prevent inflammatory bone disruption.

Osteoclasts: osteoimmunology and bone loss

Osteoclasts are the only cells able to degrade bone. They are derived from the monocyte–macrophage lineage and are phenotypically closely related to macrophages and dendritic cells [2]. Mature osteoclasts resorb bone by generating a sealing zone beneath their ruffled border, into which they secrete hydrochloric acid to solubilise calcium from bone and proteolytic enzymes, such as matrix metalloproteinases and cathepsin K, to degrade the remaining matrix. Enhancement of osteoclast numbers and activity is a hallmark of inflammatory bone loss, and the inflammatory milieu within synovitis serves to augment not only precursor recruitment from bone marrow but also their subsequent differentiation into mature osteoclasts. The mutual relationships between inflammatory disease, the immune system and osteoclast biology have given rise to the research field of osteoimmunology, with intense focus particularly on osteoclast-supporting inflammatory cells or cytokines.

The identification of multinucleated giant osteoclasts in the synovium and at areas of bone erosion in RA dates back to the early 1980s [3] but receptor activator of nuclear factor κB ligand (RANKL), the essential signal for osteoclast differentiation, was only identified in 1998 [4]. The receptor for RANKL is RANK, a type I transmembrane protein expressed on osteoclast precursor cells and mature osteoclasts, and the binding of RANKL to RANK is inhibited by the decoy receptor osteoprotegerin (OPG), such that

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 1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.06.025

the RANKL:OPG ratio is central to a balanced process of osteoclastogenesis. In bone, RANKL and OPG are expressed by osteoclast-supporting cells, including osteoblasts and osteocytes, the principle RANKL source in physiological remodelling [5], and their activities are tightly controlled, contributing to balanced cycles of bone resorption and formation. There is abundant evidence for a central role for RANKL in inflammatory bone loss: RANKL-deficient mice are osteopetrotic [6] and resistant to inflammation-induced bone loss [7] and there is high expression of RANKL in RA synovium [8]. Indeed, RA patients with active disease have greater synovial RANKL expression at the protein and mRNA level when compared with those with lesser disease activity, and this increase in RANKL is accompanied by a decrease in OPG expression [9], leading to a microenvironment that favours osteoclastogenesis. In addition, RANKL is expressed by synovial fibroblasts and its expression is upregulated by the inflammatory cytokines such as tumour necrosis factor (TNF)α, interleukin (IL)-1β and IL-6, all of which are abundantly represented in RA synovial tissue. In concert with its effect on RANKL expression, TNFα has also been shown to stimulate expression of the osteoclast co-stimulatory molecule osteoclast-associated immunoglobulin-like receptor (OSCAR) which, along with RANKL, facilitates final osteoclast differentiation [10]. OSCAR expression is in fact not restricted to osteoclasts alone but has been identified on monocytes (including those surrounding synovial microvessels in RA), granulocytes and macrophages. Moreover, the peripheral blood monocytes of patients with RA exhibit elevated expression of OSCAR compared with healthy subjects [11] and this monocytic OSCAR expression appears to be positively associated with disease activity and the serum inflammatory response (CRP and/or ESR).

More recently, Takayanagi's work, reviewed in [12], has also highlighted a close and crucial link between T cell activation and bone destruction in inflammatory arthritis. The specific CD4+ T cell subset T_H17 cells are induced in the presence of IL-6, transforming growth factor (TGF)β and IL-23 and are characterised by their production of, among others, IL-17. *In vitro* osteoclast formation systems have indicated a central role for these cells in osteoclastogenesis [13,14]: although T_H17 cells express higher levels of RANKL than either T_H1 or T_H2 cells, they are not able to induce osteoclastogenesis in the absence of osteoclast-supporting cells, suggesting that T_H17-bound RANKL is less important than their cytokine products, most prominently IL-17A. IL-17A is thought to exert its effect by stimulating RANKL expression on osteoclast-supporting mesenchymal cells such as osteoblasts and fibroblasts, while concurrently activating and supporting local inflammation. The perpetuation of a local inflammatory response supports local IL-1β, IL-6 and TNFα production, which additionally serve to increase RANKL expression (Fig. 1).

Although T_H17 cells have arguably featured most prominently in the literature, alternative T cell subsets also facilitate the

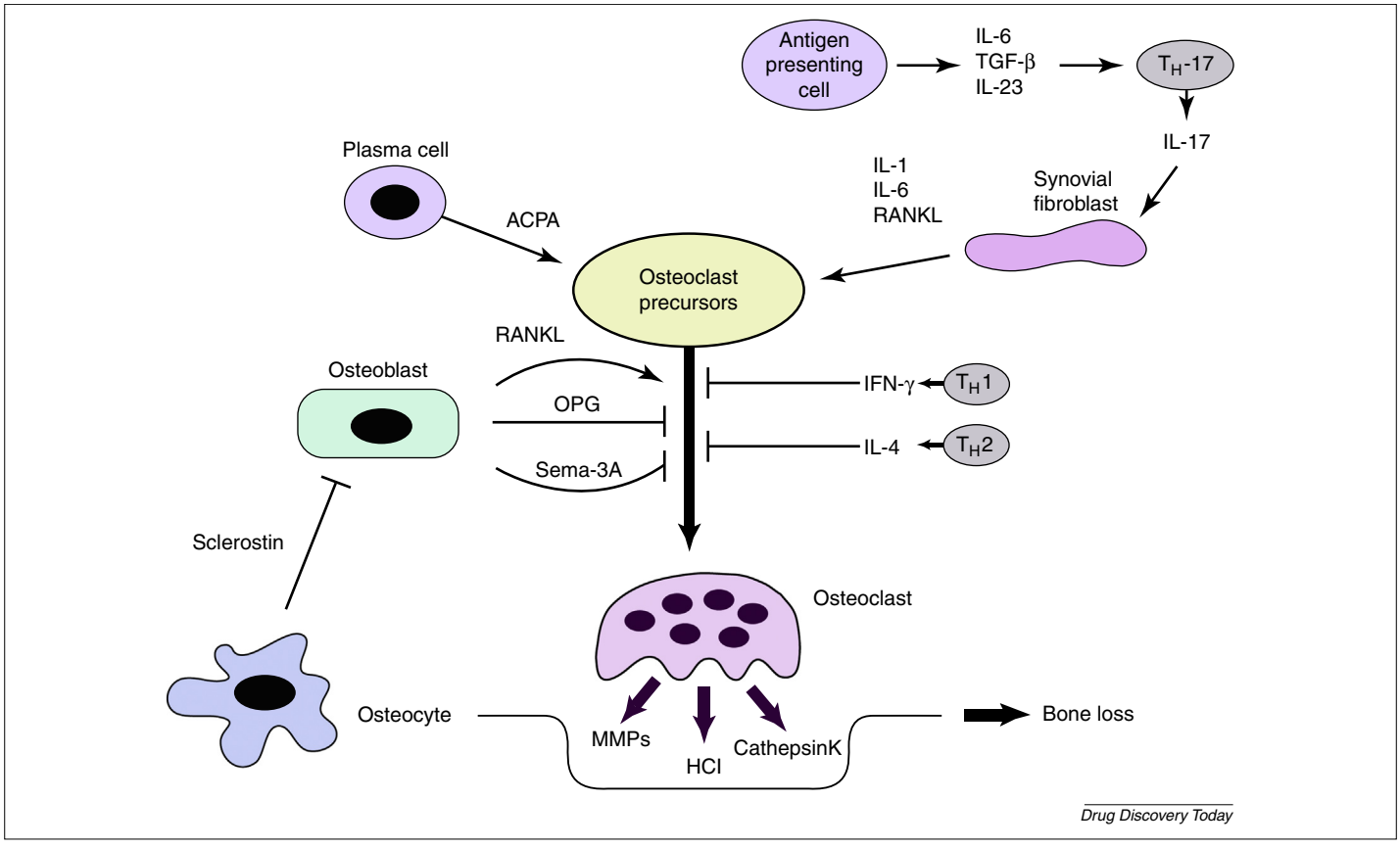

FIGURE 1

Immune modification of osteoclastogenesis. Osteoclastic bone resorption is promoted in rheumatoid arthritis owing to an increased receptor activator of nuclear factor κB ligand:osteoprotegerin (RANKL:OPG) ratio. The inflammatory cytokines interleukin (IL)-1, IL-6, IL-17 and tumour necrosis factor (TNF)α all increase RANKL expression on stromal cells such as fibroblasts and osteoblasts, whereas transforming growth factor (TGF)β and IL-13 also support the osteoclastogenic T cell subset T_H17 cells. Osteoclast maturation is inhibited by OPG, Sema3A, interferon (IFN)γ and IL-4. Mature osteoclasts degrade bone through the secretion of matrix metalloproteinases (MMPs), hydrochloric acid (HCl) and cathepsin K.