The final pathogenetic steps in focal bone erosions in rheumatoid arthritis

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The presence of peri-articular osteoporosis and focal bone erosions at the joint margins and within the subchondral bone adjacent to inflamed joints has been considered the radiographic hallmark of rheumatoid arthritis (RA).¹⁻⁴ In addition, in recent years there has been an increased awareness that RA also produces adverse effects on systemic bone remodelling at sites not directly involved with joint inflammation. Numerous reports have documented that people with RA have reduced axial and appendicular bone mass and that this bone loss is associated with an increased risk of fracture.⁵⁻¹¹ Thus, it is possible to identify three distinct patterns of bone loss in RA. These include systemic osteoporosis, juxta-articular osteopenia adjacent to inflamed joints and focal marginal and subchondral bone erosions that are associated directly with inflamed synovial tissues. Each of these disorders represents an example of disturbed skeletal tissue remodelling in which there is a net loss of bone, although the precise mechanisms responsible for the bone loss in each of these conditions may involve differential cellular and regulatory processes. This review will focus on the mechanisms involved in the pathogenesis of focal bone erosions that are directly associated with the inflammatory synovial lesion.

Insights into the processes underlying the development of focal bone erosions in RA have been derived principally from histopathological evaluation of joint tissues from patients with RA and from animal models of inflammatory arthritis. Early studies by Bromley and Woolley demonstrated the presence of multinucleated cells with phenotypic features of osteoclasts in resorption lacunae at the pannus-bone interface.¹²⁻¹⁴ More recently, in our own studies,¹⁵ we have used in situ hybridisation to demonstrate that multinucleate and some mononuclear cells in resorption lacunae at the bone-pannus interface exhibit the entire repertoire of phenotypic markers that are associated with the fully differentiated osteoclast. This includes the expression of cathepsin K, tartrate resistant acid phosphatase and the calcitonin receptor. Observations in animal models of collagen induced and adjuvant arthritis have also indicated that cells with phenotypic features of osteoclasts are present in resorption bays at sites of focal bone resorption.^{16 17} The demonstration that marginal joint and subchondral bone erosions are mediated by osteoclasts has significant implications with respect to the development of strategies to directly and specifically target these cells or the regulatory pathways that control their recruit-

ment and differentiation to prevent focal bone erosions in RA.

Despite the evidence that cells with phenotypic features of osteoclasts can be found at sites of focal bone erosions at the bone-pannus interface, there remains some controversy regarding the capacity of other cell types present within the rheumatoid synovium, such as activated macrophages or synovial fibroblasts, to degrade the mineralised bone matrix.¹⁸ Several lines of evidence, however, suggest that these cells have a limited capacity to resorb bone compared with authentic osteoclasts. For example, Hatterleys and Chambers^{19 20} examined the capacity of osteoclast precursors generated in bone marrow cultures to resorb bone matrix. In this system, marrow derived cells of monocyte-macrophage lineage were induced to differentiate into osteoclasts. They demonstrated that the unique resorbing capacity of the osteoclasts generated in these cultures was expressed very late in the differentiation cascade and that the expression of tartrate resistant acid phosphatase and multinuclearity were poor indicators of the ability of cells to resorb bone. The unique capacity of the osteoclast-like cells to resorb bone coincided with the expression of the calcitonin receptor. We have made similar observations in our own studies of calcitonin receptor regulation.²¹ This receptor binds the peptide hormone calcitonin leading to the inhibition of osteoclast mediated bone resorption.^{22 23} The demonstration of calcitonin receptor expression in osteoclast-like cells at the bone-pannus interface thus provides evidence that these cells are functionally mature osteoclasts with full bone resorbing potential.

Further compelling evidence that osteoclasts are the principal cell types responsible for the erosions at the bone-pannus interface is suggested by the recent observations of Kong *et al.*²⁴ They investigated the effects of a newly identified potent inhibitor of osteoclast differentiation and activity, osteoprotegerin (OPG), on the development of cortical and trabecular bone erosions in the rat model of adjuvant arthritis. OPG is a member of the tumour necrosis factor (TNF) receptor family and acts as a decoy receptor to bind a novel factor that has been shown, based on targeted gene knock out studies, to be an essential factor required for osteoclast differentiation.^{25 26} This osteoclast differentiation factor, which has been variously identified as ODF, RANK ligand (RANKL), and osteoprotegerin ligand (OPGL), is a member of the TNF-ligand family of cytokines, and regulates osteoclast differentiation and activity through binding to its

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receptor, RANK (receptor activator of NF- κ B) on osteoclast precursors.^{27–28} Of interest, it was originally cloned as a product of activated T cells and was identified as TNF related activation induced cytokine (TRANCE).^{29–30} Kong *et al*²⁴ showed that treatment of rats with adjuvant arthritis with OPG almost completely abolished the development of focal bone erosions. Examination of the inflamed synovial tissue demonstrated that the OPG treatment had minimal effect on synovial inflammation but there was a marked reduction in osteoclast number at the interface between the bone and synovium. Thus, despite the presence of activated macrophages and synovial fibroblasts, in the absence of osteoclasts there was almost complete inhibition of bone loss. These findings, although limited to an animal model of arthritis, provide the most convincing evidence that osteoclasts are the principal cell type required for focal bone resorption in inflammatory arthritis.

In the studies by Kong and more recently by our group and others, human synovial fibroblasts, as well as CD4+ and CD8+ T lymphocytes, from RA synovium and synovial fluids have been shown to express RANKL/ODF.^{24,31–32} Direct evidence that synovial fibroblasts can support osteoclast formation that is at least in part dependent on RANKL/ODF is provided by the studies of Takayanagi *et al*³³ who showed that RA synovial fibroblasts could induce osteoclast-like cells when cocultured with peripheral blood mononuclear cells. A direct role for T cell regulation of osteoclastogenesis is provided by studies demonstrating that activated T cells support osteoclast formation from haematopoietic precursors in the absence of osteoblast/stromal cells.^{24,32} Despite these compelling data indicating a role for RANKL/ODF in the pathogenesis of focal bone erosions in RA, further studies are necessary to prove that this factor plays a primary part in this process. The data thus far indicate that RANKL/ODF activity is essential for osteoclast mediated bone resorption, but this does not prove that RANKL/ODF is the factor directly responsible for the increased osteoclast formation and activity in inflammatory forms of arthritis.

In addition to RANKL/ODF, RA synovium produces a wide variety of cytokines and other products involved in the regulation of osteoclast differentiation and activity. These include interleukin 1 α and β (IL1 α and IL1 β), interleukin 6, interleukin 11, monocyte colony stimulating factor, TNF α and parathyroid related protein, which is the factor responsible for humoral hypercalcaemia of malignancy.^{34–38} The results from recent clinical trials in patients with RA treated with agents that specifically target IL1 or TNF α provide the most compelling evidence that these cytokines play a part in the pathogenesis of focal bone erosions.^{39–40} These studies indicate that interference with the activity of these cytokine can retard or even prevent the progression of focal bone erosions in RA subjects. However, it is difficult to differentiate the effects of these treatments on reduction in synovial inflamma-

tion from possible direct effects on osteoclast differentiation or activity. Additional insights are provided by analysis of the effects of anticytokine treatment in animal models of arthritis. Of interest, these studies indicate that although inhibition of TNF or IL1 activity reduce the synovial inflammation in the murine collagen induced arthritis model, only IL1 blockade prevents the development of bone erosions.^{41–42}

In considering the optimal treatment regimen for RA, the ultimate goal would be the development of a therapeutic approach that could halt or prevent the progression of the inflammatory synovial lesion. Until recently, although it has been possible to demonstrate amelioration in clinical symptoms and improvement in certain laboratory parameters of inflammation, there has been limited evidence that the treatments prevented progressive cartilage and focal articular bone loss. However, several recent studies have shown that certain treatment regimens, including those that specifically block the activities of IL1 and TNF, can retard or in some cases prevent the development of focal bone erosions.^{39–43–46} In addition to these approaches that target the proliferative synovial lesion, it is reasonable to consider treatments that are directed specifically at the pathological processes associated with the pathogenesis of focal bone and cartilage destruction. The demonstration that osteoclasts mediate a component of the focal bone destruction at the bone-pannus interface suggests that treatments directed at blocking osteoclast differentiation or activity could prevent or retard the progression of bone erosions. The best support for the efficacy of this approach is derived from the demonstrated in an rat model of adjuvant arthritis the capacity of OPG, the decoy receptor for the potent osteoclast differentiation factor, RANKL/ODF, to block osteoclast mediated bone erosions.²⁴ In patients with RA, trials with bisphosphonates or calcitonin, which have been shown to inhibit osteoclast mediated bone resorption, did not prevent the progression of focal bone erosions, although they did have a beneficial effect on systemic osteoporosis.^{47–49} In contrast, there is evidence from studies in animal models of inflammatory arthritis that certain regimens with bisphosphonates may retard or prevent the development of focal bone erosions. Until uniformly effective treatments are available that can successfully prevent or halt the progression of both the synovial inflammation and focal bone destruction in RA, it is reasonable to further explore the possibility of parallel treatment approaches that specifically target osteoclast mediated bone resorption in people with RA.

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