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Invited Plenary Abstract
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Pathophysiology and prevention of arthritic bone destruction

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Bone erosions are a prognostic turning point in rheumatoid arthritis (RA) as they correlate with increased disease severity, progressive functional disability and greater mortality. Focal bone erosions are highly associated with systemic osteoporosis, as both phenomena reflect high inflammatory disease activity.
Key molecular discoveries coupled with elegant animal studies have highlighted a pathogenic role of osteoclasts in bone destruction and the concept that osteoclasts (OCLs) drive focal bone erosions is now widely accepted. OCLs are consistently detected at erosion sites in all animal models of destructive arthritis and RA. Targeted removal of osteoclasts either by TNF-blockade or RANKL-antagonism, or genetic manipulation in arthritis models blocks this bone destruction.
The transcriptional program controlling osteoclastogenesis depends both on RANK and immunoreceptor tyrosine-based activation motif (ITAM) signals in osteoclast precursors. The inflamed synovium generates very high levels of TNF-α which fuels osteoclastogenesis in the context of RANKL through multiple mechanisms, as well as cytokines such as IL-6 and IL-17, which increase stromal cell RANKL expression and/ or reduce OPG production.

Although soluble RANKL is produced by T cells, expression of membrane-bound RANKL by fibroblast-like synoviocytes or osteoblasts (induced by IL-6 or IL-17) may be quantitatively more important for osteoclastogenesis in the inflamed joint. Osteoclast formation in animal models is a swift and dynamic process leading to rapid attack on juxta-articular bone, a prerequisite for early onset structural damage. Cell-to-cell contact between stromal cells and osteoclast precursors efficiently presents key molecular signals (ie: RANKL + M-CSF) for osteoclast differentiation and survival. At the pannus-bone interface in arthritis, the main stromal support cells are probably fibroblast-like synoviocytes, whereas the major support cells in subchondral bone are osteoblasts.

The importance of osteoclast-mediated injury in inflammatory arthritis has prompted renewed interest in bisphosphonates for bone protection. Targeting osteoclasts with bisphosphonates such as zoledronic acid confers significant bone protection in autoimmune or TNF-dependent models of RA. Nevertheless, the clinical utility of bisphosphonates for structural joint protection in RA has yet to be shown conclusively.

In summary, down-regulation of osteoclastogenesis has emerged as a powerful strategy for prevention of arthritic bone destruction. Of note, the bone protection afforded by reducing osteoclast numbers is not conditional on reducing synovial inflammation. Osteoclast production in arthritis may be intercepted at several levels. Enthusiasm for bisphosphonates is tempered by their long skeletal half-life and possible association with osteonecrosis of the jaw. The potent effect of Denosumab on osteoclastic bone resorption has been witnessed in osteoporosis trials and human monoclonal antibodies are likely to become the treatment of choice for blocking RANKL in arthritis.