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EDITORIAL

T cells as key players for bone destruction in gouty arthritis?

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Abstract

The deposition of monosodium urate (MSU) crystals in synovial fluid and tissue leads to gouty arthritis frequently associated with synovial inflammation and bone erosions. The cellular mechanism that links MSU crystals to an increased number of osteoclasts has not yet been fully understood. In a recent issue of *Arthritis Research & Therapy* Lee and colleagues proposed that bone destruction in chronic gouty arthritis is at least in part dependent on expression by T cells of receptor activator of NF-κB ligand (RANKL). The authors showed that pro-resorptive cytokines such as IL-1β, IL-6, and TNFα are expressed within tophi and stromal infiltrates. *In vitro* stimulation with MSU crystals revealed monocytes as a source for these cytokines, whereas T cells produce RANKL, the major trigger of osteoclastogenesis.

Gouty arthritis is a chronic disease, characterized by hyperuricemia, precipitating the deposition of inflammatory monosodium urate (MSU) crystals in various tissues. Phagocytic uptake by monocytes and granulocytes of these crystals causes tissue inflammation such as synovitis and often results in bone destruction. Under physiological conditions, the integrity of bone is maintained by the balanced activity of osteoclasts and osteoblasts, which are responsible for bone resorption and bone formation, respectively. The differentiation of monocytes into osteoclasts depends on the presence of the receptor activator of NF-κB ligand (RANKL) and is antagonized by osteoprotegerin. In chronic inflammatory diseases, such as arthritis, a preponderance of RANKL leads to bone loss by enhanced osteoclastogenesis. In the case of gout there has been evidence for an association between the occurrence of gouty tophi and bone destruction. Yet so far the mechanisms are still elusive.

In samples of gouty tissue Lee and colleagues observed osteolytic lesions close to the tophi [1]. Stromal tissue was infiltrated with inflammatory T cells, B cells, and mast cells, whereas the tophi themselves were surrounded by tartrate-resistant acid phosphatase-positive multinucleated osteoclasts. The occurrence of the latter may be explained by the presence of the pro-resorptive cytokines IL-1β, IL-6, and TNFα in the infiltrated stromal tissue. These cytokines reportedly enhance generation and activation of osteoclasts directly or indirectly via the induction of RANKL [2]. Analyzing CD3-expressing cells, the authors further claim a key role for T cells in bone destruction, since activated T cells in the tissue upregulate the expression of RANKL, considered the master regulator of osteoclastogenesis.

Twelve years ago Kong and colleagues first reported that activated T cells promote osteoclastogenesis by the expression of RANKL [3]. Meanwhile several groups investigated the relationship between T cells and osteoclasts. In many osteolytic conditions (for example, rheumatoid arthritis or periodontal disease), RANKL-expressing T cells are located at the sites of increased bone resorption [4]. Lee and colleagues added gouty arthritis to this list [1]. Interestingly, we recently reported that, in contrast to effector T cells, regulatory T cells suppress osteoclastogenesis [5]. In this context, the exact subpopulation(s) of T cells and the pathways responsible for the expression of RANKL within the inflamed gouty tissue are of major interest.

Lee and colleagues and others reported that MSU crystals induce the expression and the release of the pro-resorptive cytokines IL-1α, IL-1β, IL-6, and TNFα in monocytes in a dose-dependent manner [6,7]. The up-regulation and downregulation of RANKL and osteoprotegerin by MSU-stimulated T cells was observed 24 hours and, even stronger, 72 hours after co-incubation, respectively. The authors employed negatively selected highly enriched T cells (>95%) for their experiments, and

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therefore claim a direct effect on the T cells of MSU crystals. However, there are other options as well: negatively selected T cells often contain huge numbers of platelets, which are not addressed by the depleting antibody cocktail; and minor contaminations with other leukocytes may influence the outcome.

Nevertheless, the expression of RANKL by T cells after stimulation with MSU is a new and interesting finding and has not yet been described. The authors' hypothesis of T cells promoting osteoclasts is strengthened by *in vitro* assays employing peripheral blood mononuclear cells or synovial fluid mononuclear cells (SFMCs) of patients suffering from gout. After stimulation with RANKL, SFMCs formed more osteoclasts than the peripheral blood mononuclear cells. This is consistent with the data of Dalbeth and colleagues [8]. Lee and colleagues further showed that T-cell depletion from SFMCs almost abrogated osteoclastogenesis. This finding is consistent with the hypothesis that T cells are a main source of RANKL under inflammatory conditions. A recent publication, however, reported that B cells outrange T cells in the transcription of mRNA for RANKL in patients with RA [9]. In this regard, it would be interesting to perform osteoclast assays with B-cell-depleted SFMCs.

In summary, bone destruction in gouty arthritis seems to be the result of an imbalance in bone remodeling. The overexpression of RANKL, presumably by infiltrating T cells in a proinflammatory environment, promotes osteoclastogenesis. Concomitantly, the RANKL antagonist osteoprotegerin is downregulated. Tophus-associated monocytes contribute IL-1β, IL-6, and TNFα, which act as additional promoters for osteoclast differentiation.

Abbreviations

IL, interleukin; MSU, monosodium urate; NF, nuclear factor; RANKL, receptor activator of NF-κB ligand; SFMC, synovial fluid mononuclear cell; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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