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IL-17A and pathological new bone formation: The myth of Prometheus revisited.

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Inflammation has been linked with tissue regeneration from mythological times, however despite recent advances the cellular and molecular pathways that govern the regenerative process remain elusive. Herein we discuss the recent findings of the Van Tok study that shed new light in the complex phenomenon of bone regeneration as it pertains to inflammatory arthritis.

In an ancient Greek myth, Prometheus, upset the gods by offering them bones wrapped in fat instead of a proper sacrificial offering and by stealing fire to return it to humankind. As an eternal punishment for his actions the myth has it, that Prometheus was chained on a rock and had to endure an eagle feeding on his liver each day while it regenerated at night. Although Prometheus is a mythical character, modern science has confirmed that within this myth lays the fascinating scientific fact of tissue regeneration. Liver regeneration occurs after injury and to date, many other tissues have also been shown to exhibit regenerative abilities, including bone. Bone repair after injury involves multiple events starting with the formation of a hematoma due to the rupture of blood vessels at the injury site. Injury to the soft tissues and degranulation of platelets results in the release of pro-inflammatory cytokines, which results in the accumulation of an inflammatory infiltrate mainly consisting of neutrophils, macrophages and lymphocytes. The hematoma is gradually replaced by granulation tissue before the repair process continues with the formation of new blood vessels (neovascularization) and the recruitment of specialized cells depending on the nature of regenerative tissue. Despite the local tissue cellular differences, a well-orchestrated immune response regulated by pro-inflammatory mediators precedes the repair process. Indeed the molecular mechanisms are so aligned that Hepatocyte Growth Factor (HGF), which regulates liver regeneration (1) has been shown to act as a coupling factor for osteoclasts and osteoblasts (2). Similarly, tumor necrosis factor (TNF) which also participates in liver regeneration (1) is also critical in bone repair as TNF-deficient mice exhibit impaired fracture healing (3). The link between inflammation and pathologic new bone formation is also demonstrated in spondylarthropathies, a group of chronic inflammatory diseases of the skeleton and associated soft tissues, which include ankylosing

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spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease-associated arthritis, reactive arthritis, juvenile SpA and undifferentiated SpA. The precise cellular and molecular pathways and the role of pro-inflammatory cytokines in regulating inflammatory bone remodeling remain elusive. Undoubtedly, HGF and TNF are not the only factors that contribute to pathologic new bone formation and in this manuscript Van Tok et al, addressed the fundamental question of the Prometheus myth by investigating the role of the pro-inflammatory cytokine IL-17A in the coupling of inflammation and new bone formation.

The role of IL-17A has been extensively studied in inflammatory arthritis and bone remodeling. Multiple groups have shown that cortical and trabecular bone in femurs of IL-17A-deficient and WT mice exhibit similar bone mineral density, establishing an overall agreement that IL-17A does not significantly alter normal skeletal development (4, 5). This is merely due to the fact that IL-17A expression is highly restricted under non-inflammatory conditions. However under inflammatory conditions when IL-17A is expressed at high concentrations multiple observations have confirmed that IL-17A exhibits pro-osteoclastogenic effects *in vitro* and *in vivo* by upregulating RANKL expression in stromal cells and RANK expression in osteoclast precursors, and thereby disturbing the RANKL/RANK/OPG axis (4, 5). The role of IL-17A in inflammatory bone formation is complex. IL-17A deficiency and/or blockade promotes periosteal bone formation in the K/BxN serum transfer model of inflammatory arthritis whereas other groups using the drill-hole injury animal model have demonstrated enhanced bone regeneration to be dependent on IL-17A (6, 7). The observations of the effects of IL-17A on osteoblasts using different animal models are indicative of the differences in experimental parameters and the multiple signaling pathways that orchestrate the outcomes of IL-17A in inflammatory bone remodeling and further research is required.

Herein the authors investigated the osteogenic capacity of IL-17A by performing *in vitro* osteoblast differentiation assays in primary human FLS cultures isolated from synovial biopsies of SpA patients to effectively demonstrate that IL-17A promotes the differentiation of osteoblasts and mineralization in SpA stromal cells. Moreover, the research team led by Prof. Baeten performed a series of *in vivo* experiments using the HLA-B27/Huβ2m transgenic rat experimental animal model of spondyloarthritis in which IL-17A was inhibited by administering a neutralizing antibody to IL-17A either before (prophylactic) or after (therapeutic) the observed clinical onset of disease. In this set of experiments it was convincingly demonstrated that in anti-IL-17A treated rats there was a reduction of inflammation and bone destruction as evidenced by histological examination and micro-CT analysis, which correlated with reduced bone formation in the spine and ankles.

Although IL-17A interference with the RANKL/RANK signaling regulates a number of transcription factors to enhance osteoclastogenesis and bone loss, paradoxically, the same transcriptional regulatory elements also exert dramatic effects on osteoblastogenesis and bone formation. One such transcription factor is NFATc1, that induces osteoclastogenesis and NFATc1 deficient mice are unable to generate osteoclasts, leading to reduced bone resorption. Surprisingly, at least in one report, mice expressing a constitutively nuclear NFATc1 variant (NFATc1nuc) exhibited massive osteoblast overgrowth and enhanced osteoblast proliferation (8). Therefore it seems that although transcriptional activation of

NFATc1 in osteoclasts induces bone loss, in osteoblasts, the same pathways have the potential to induce bone formation. In keeping with these observations, and the fact that TNF superfamily members, (including RANKL and TNF) are known to act as a bidirectional signaling molecules that generate intracellular reverse signaling, the transcriptional regulation under inflammatory conditions in osteoblasts may have dual effects both promoting and inhibiting bone formation. Despite the fact that the precise mechanisms of pathological bone formation remain to be determined, the potential of pro-inflammatory mediators hijacking cellular and molecular processes to activate osteogenesis is nothing short of fascinating.

In support of reverse RANKL signaling, a recent study highlights that RANKL reverse signaling couples bone resorption and bone formation. Specifically, the study details how vesicular RANK, secreted from terminally differentiated osteoclasts activates the expression of *Col1a1*, *Runx2* and *Osx* to promote osteoblast differentiation, leading to mineralization and new bone formation both *in vitro* and *in vivo* (9). Since IL-17A can induce RANK expression in osteoclast precursors and expand the RANK+ osteoclast precursor population(5), it is plausible that the excess RANK availability in terminally differentiated osteoclasts may be at least one of the mechanisms whereby IL-17A can induce bone formation (Figure 1).

One of the most important findings in the Van Tok study is that mechanistically the inhibition of IL-17A and the observed changes in new bone formation correlated with a reduction of myeloid related genes such as defensins, myeloperoxidase and neutrophil elastase. Although as discussed by Van Tok et al., certain studies failed to reveal a prominent role of IL-17A using the IL-17A minicircle overexpression model, others have repeatedly demonstrated, using the same model, that IL-17A expands distinct myeloid populations including neutrophils as observed in the Van Tok et al., study(10). This is of primary importance as an expansion of neutrophils and in particular neutrophil elastase which plays a significant role in NETosis is critical in the development IL-17A mediated epidermal hyperplasia and skin inflammation (10). Similarly other groups have observed that neutrophils are important effector cells in entheseal inflammation by augmenting the inflammatory response, through the release of proteases and reactive oxygen species and the activation state of neutrophils is critical in determining the development of enthesitis (11). Collectively these new data, illustrate not only the effects of IL-17A on new bone formation, but also the contribution of neutrophils with the potential to deepen our understanding of the pathogenesis of enthesitis and skin inflammation, hallmark pathologic features of SpA.

By demonstrating that at least in the HLA-B27/Huβ2m transgenic rat experimental animal model of spondyloarthritis new bone formation is not observed without inflammation, we conclude that in this animal model, tissue remodeling of bone recapitulates in part, the myth of Prometheus where tissue regeneration is tightly linked with inflammation. In the absence of concrete experimental evidence that detail the exact mechanisms that govern IL-17A mediated bone formation we can only speculate that the answer may still lay deep within the Greek myth and the regenerating liver of Prometheus. Interestingly, previous studies using a reversible model of liver injury in which the injury and recovery phases are distinct, combined with CD11b+ depletion strategies using a CD11b-DTR transgenic mice, provided

us with the first clear evidence that functionally distinct myeloid subpopulations exist in the same tissue and play critical roles in both liver injury and repair (12). Based on the common features observed in liver and bone, it is certainly plausible that heterogeneity in innate immune pathways may underlie the sequential interplay of inflammation and repair (13). The new evidence provided in the manuscript of Van Tok et al., not only elegantly demonstrate and confirm the role of the pro-inflammatory mediator IL-17A in bone formation, but also simultaneously highlight the importance of myeloid cells and neutrophils in SpA, which merits further investigation.

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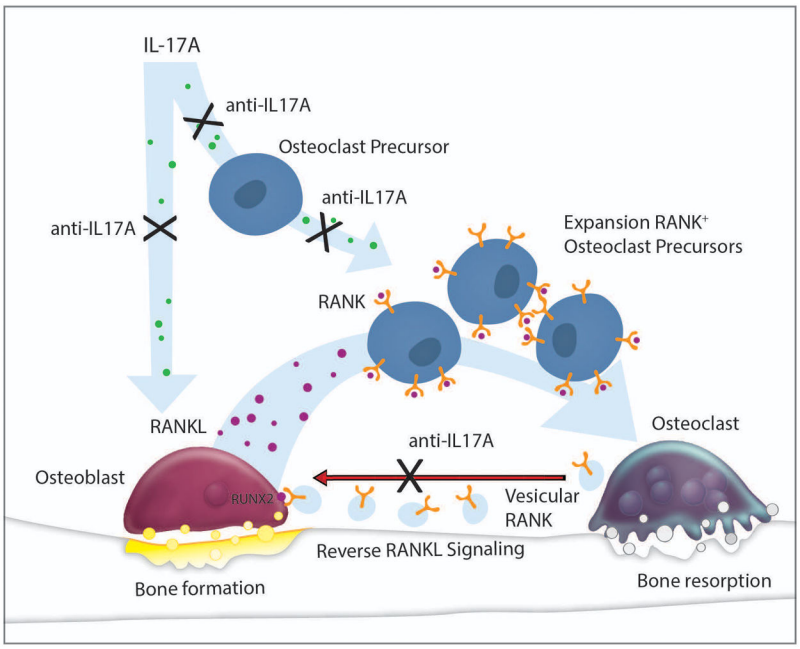

Figure 1: IL-17A in pathological bone formation.

Schematic representation showing the pro-osteoclastogenic roles of IL-17A (green circles) and the induction of RANKL (purple circles) secretion by stromal cells as well as the expansion of $RANK^+$ osteoclast precursors, leading to an increase in vesicular RANK (yellow) that can also potentiate RANKL reverse signaling leading to RUNX2 activation and bone formation. IL-17 induced RANKL and RANK expression is neutralized during IL-17A inhibition (black cross) and therefore may arrest pathological bone remodeling.