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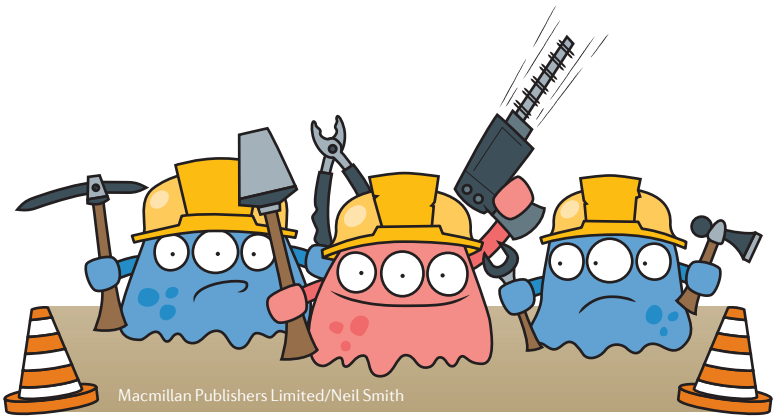
RHEUMATOID ARTHRITIS

Regulating the osteoclast workforce



New findings published in *Immunity* shed light on the mechanisms by which hypoxia augments inflammation and bone destruction in pathologic inflammatory conditions such as rheumatoid arthritis. In this study, Murata *et al.* identify COMM domain-containing protein 1 (COMMD1) as both a negative regulator of osteoclastogenesis and bone resorption, and as a key protein suppressed by hypoxia during osteoclastogenesis, linking these two processes.

> “COMMD1 acts as a negative regulator of inflammatory bone resorption under pathologic conditions”

To investigate how hypoxia influences osteoclastogenesis, the researchers first looked at the pathways differentially regulated under hypoxic and normoxic conditions in human blood-derived macrophages (a source of osteoclast precursors) stimulated with receptor activator of nuclear factor-κB ligand (RANKL; also known as TNFSF11). In these cells, hypoxia augmented RANKL-induced osteoclast differentiation and resorption *in vitro*, but suppressed RANKL-induced pathways downstream of COMMD1. Small interfering RNA-silencing of COMMD1 under normoxic conditions promoted RANKL-induced osteoclast differentiation and resorption; whereas overexpression of COMMD1 almost completely suppressed osteoclastogenesis, even under hypoxic conditions, supporting a role for COMMD1 as a negative regulator of osteoclastogenesis.

Using two mouse models of pathologic bone loss, the researchers investigated the importance of COMMD1 regulation *in vivo*. Myeloid-specific deletion of COMMD1 resulted in increased osteoclastogenesis in the K/B×N serum-induced mouse model of arthritis, and in a mouse model of inflammatory osteolysis. In patients with rheumatoid arthritis, genetic variants of *COMMD1* associated with increased COMMD1 expression were concurrently associated with decreased bone erosion, supporting a model in which COMMD1 acts as a negative regulator of inflammatory bone resorption under pathologic conditions.

Further investigations demonstrated that hypoxia inhibits COMMD1 function in macrophages by suppressing COMMD1 translation and nuclear accumulation, and that hypoxia and COMMD1 reciprocally regulate inflammatory and metabolic pathways during osteoclastogenesis. Murata and colleagues hypothesize that this reciprocal regulation could enable macrophages to meet the metabolic demands of osteoclastogenesis under challenging environmental conditions, while limiting the amount of bone loss that occurs in pathologic conditions. These findings identify key regulators and pathways of osteoclastogenesis, including COMMD1, that could be therapeutically targeted to suppress pathologic bone loss.

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ORIGINAL ARTICLE Murata, K. *et al.* Hypoxia-sensitive COMMD1 integrates signaling and cellular metabolism in human macrophages and suppresses osteoclastogenesis. *Immunity* http://dx.doi.org/10.1016/j.immuni.2017.06.018 (2017)