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BONE DISEASES

SEMA3A strikes a balance in bone homeostasis

Bone diseases such as osteoporosis result from an imbalance between the natural process of bone resorption (mediated by osteoclasts) and formation (mediated by osteoblasts); however, the precise molecular mechanisms that control this regulation are unclear. Moreover, most current drugs aim to redress this imbalance by targeting osteoclasts to reduce the rate of bone resorption, but it seems that the consequent disruption of the linkage between osteoclast and osteoblast activity also leads to the reduction of new bone formation. Now, Takayanagi and colleagues have identified semaphorin 3A (SEMA3A) as a dual regulator of osteoclasts and osteoblasts, and suggest that this could be a promising new therapeutic target to circumvent this limitation of existing drugs.

SEMA3A is a member of the soluble class III semaphorins that, together with their respective receptors (for SEMA3A, this is neuropilin 1; NRP1), are involved in diverse physiological processes ranging from axonal guidance to mediating immune responses. Previous studies had implicated semaphorins in bone regulation, and in this current study SEMA3A was identified through functional screening as one of the more potent anti-osteoclastogenic factors. Moreover, it was shown that it is expressed in cells from an osteoblast lineage only, and its expression in calvarial cells was the highest compared with other semaphorin family members examined.

Next, the authors used *Sema3a*$^{-/-}$ mice and *Nrp1*$^{\text{Sema}-}$ mice (in which the expressed NRP1 lacks the SEMA-binding site) to examine how SEMA3A exerts its effects. These mice have severe osteopaenia, which is reflected by both an increase in osteoclast numbers and a decrease in osteoblast numbers. Interestingly, the number of adipocytes in these mutant mice was also increased. At the molecular level, it seems that the SEMA3A–NRP1 axis regulates osteoclast differentiation by blocking the downstream immunoreceptor tyrosine-based activation motif (ITAM) and RHOA signalling pathways, whereas it regulates osteoblast and adipocyte differentiation through the canonical WNT–β-catenin signalling pathway.

Finally, the therapeutic potential of SEMA3A was investigated. Intravenous injection of recombinant SEMA3A into normal mice produced a simultaneous decrease in osteoclastic parameters and an increase in osteoblastic parameters, which culminated in a bone-increasing effect. In addition, SEMA3A treatment enhanced bone regeneration in a mouse model of cortical bone defect induced by drill-hole injury and decreased the rate of bone loss in ovariectomized mice.

PHOTOALTO

Overall, the authors suggest that SEMA3A has a pivotal role in the bone formation phase of bone remodelling, and is a plausible target for developing therapeutics that have both antiresorptive and pro-regenerative properties for treating bone disorders.

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FURTHER READING Kawai, M. *et al.* Emerging therapeutic opportunities for skeletal restoration. *Nature Rev. Drug Discov.* **10**, 141–156 (2011)