

Sympathetic control of bone mass is regulated by osteopontin

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Activation of the sympathetic nervous system is known to reduce bone mass through mechanisms that remain unclear. Using cell-based studies and murine genetics, the authors [1] showed that osteopontin (OPN) is required for the sympathetic activity on bone metabolism.

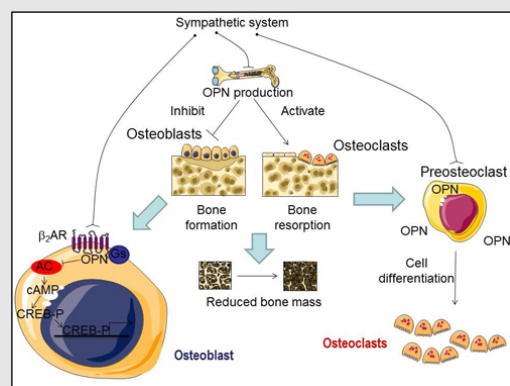
Osteopontin is a cytokine and one of the major members of noncollagenous extracellular matrix proteins of bone. In this work the authors found that the stimulation of sympathetic tone by isoproterenol increased the level of OPN expression in bone, increased osteoclast activity, and reduced osteoblast activity and bone mass. In knockout mice deprived of OPN, isoproterenol had no inhibitory effect on bone mass, suggesting that OPN was directly involved in this pathway. Furthermore, OPN was required to induce the expression of osteoclastic genes and to repress the expression of osteoblastic genes. At the cellular level, this study suggested that osteoblast intracellular OPN modulated the capacity of the β_2 adrenergic receptors to generate cyclic AMP with a corresponding modulation of cyclic AMP responsive element binding (CREB) phosphorylation. This event reduced subsequent transcription, occurring inside the osteoblast.

This study highlights the role of osteopontin and the role of the sympathetic nervous system in the regulation of bone mass through the modulation of the β_2 adrenergic receptor-cyclic AMP signaling system.

1. Nagao M et al. *Proc Natl Acad Sci USA*. 2011;108:17767-17772.

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Stimulation of the sympathetic tone increased osteopontin (OPN) production in bone and thereby plasma concentration. Increased OPN concentration led to the reduction of bone formation by inhibiting osteoblast activity and by increasing the activity of osteoclasts, inducing bone resorption. Extracellular and intracellular OPN were both required to induce bone loss. On one hand, increased OPN concentration was required to promote osteoclast recruitment. On the other hand, OPN regulated Beta2 adrenergic receptor signaling in osteoblasts by interacting with a G protein (Gs) to reduce cyclic AMP production by adenylate cyclase (AC) and the concomitant phosphorylation of cyclic AMP responsive element binding (CREB-P) important for gene transcription. This regulation ultimately reduced bone mass.



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