

OSTEOSCOOP

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Molecular bases of leptin control of bone formation

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Fortunately only one adrenergic receptor, the β_2 adrenergic receptor ($Adr\beta_2$), is expressed in osteoblasts and mice lacking this receptor have already been generated. These animals are not obese, are fertile, and have none of the metabolic abnormalities seen in *ob/ob* and *db/db* mice. Yet, they display an increase in bone formation and in bone mass that cannot be rescued by leptin ICV infusion. This experiment established genetically that the sympathetic nervous system, via $Adr\beta_2$, mediates leptin regulation of bone mass [1].

Since most homeostatic functions are regulated in a circadian manner, the hypothesis that bone remodeling is also subject to circadian regulation, and therefore regulated by the molecular clock, was tested. Consistent with this, the secretion of the two most abundant proteins made by osteoblasts, type I collagen and osteocalcin, cycles during a 24-h period.

The circadian clock includes a central component located in the suprachiasmatic nucleus of the hypothalamus and subordinate components in peripheral tissues. Molecularly, "the engine" of the clock is composed of *Bmal1* and *Clock*, two transcription factors that regulate the expression of other core circadian genes such as the *Period (Per)* genes and the *Cryptochrome (Cry)* genes. Mutant mice lacking molecular clock components have been generated and analyzed; they all display a similar increase in bone formation parameters [2].

Most components of the molecular clock are expressed in osteoblasts, where their expression cycles during a 24-h period and is regulated by the sympathetic tone. Furthermore, osteoblast-specific deletion of the *Per* genes results in high bone mass due to an increase in bone formation. Altogether these observations support the hypothesis that components of the molecular clock mediate, in osteoblasts, the leptin-dependent sympathetic regulation of bone formation.

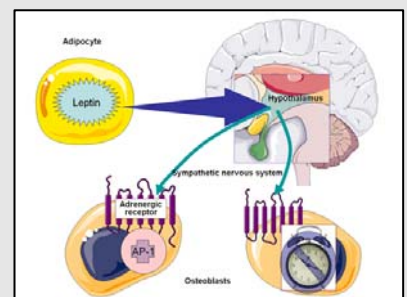
In summary, following binding to its receptor on VMH neurons, leptin uses sympathetic signaling as its only identifiable mediator to act negatively on osteoblasts. In these cells, sympathetic signaling exerts two actions: a minor one through a transcription complex, AP-1, favors osteoblast proliferation, while a major one, through the molecular clock, inhibits osteoblast proliferation [3].

1. Elefteriou F. et al. *Nature*. 2005;434:514-520.
2. Fu L. et al. *Cell*. 122: 2005;803-815.
3. Karsenty G. *Cell Metabolism*. 2006;4:341-349.

Molecular basis of leptin control of bone formation

Leptin secreted by adipocytes activates hypothalamic neurons. From there, the sympathetic nervous system mediates the leptin signal to osteoblasts, which express β -adrenergic receptors.

Two antagonistic signaling pathways are then activated in osteoblasts. AP-1, a minor pathway, promotes bone formation. Genes involved in the circadian clock are expressed in osteoblasts and are activated by catecholamines. Through them, leptin inhibits bone formation.



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