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Reciprocal regulation of bone and energy metabolism

N.K. Lee and G. Karsenty

Department of Genetics and Development, Columbia University College of Physicians and Surgeons, New York, NY, USA

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Bone remodeling, the process whereby bones renew themselves, is regulated by multiple hormones. The clinical observation that obesity protects from osteoporosis led us to propose that bone remodeling and energy metabolism could be regulated by the same hormone(s)[1]. We showed that leptin, an adipocyte-derived hormone, is a major regulator of bone remodeling by acting on osteoblasts through two different neural pathways[2]. On the one hand, sympathetic signaling in osteoblasts favors osteoclast differentiation by inducing *RANKL* expression; on the other hand, through CART (Cocaine amphetamine regulated transcript) leptin inhibits *RANKL* expression. The notion that the brain regulate bone mass has now been verified experimentally in multiple laboratories. These studies immediately raised a second question: if fat and brain regulates bone remodeling by acting on osteoblasts, are osteoblasts in turn regulating any aspect of energy metabolism? In other words is the skeleton, in addition to its well-known functions, an endocrine organ?

In the search for a bone-derived hormone regulating energy metabolism we generated *Osteocalcin*-/- mice display a high bone mass phenotype[3]. While analyzing these mutant mice we also noticed that they had an abnormal amount of visceral fat (P. Ducy and G. Karsenty, unpublished observation). This was the first evidence suggesting that the skeleton regulates energy metabolism and it prompted us to study this question.

To identify osteoblast-enriched genes affecting energy metabolism, we generated mutant mouse strains lacking genes expressed only or preferentially in osteoblasts. Through this effort we inactivated, via classical means and in an osteoblast-specific manner, *Esp*, a gene expressed in osteoblasts and sertoli cells that encodes a receptor-like protein tyrosine phosphatase termed OST-PTP4. *Esp* -/- mice are hypoglycemic, protected from obesity and glucose intolerance because of an increase in -cell proliferation, insulin secretion and sensitivity whereas mice lacking *Osteocalcin* display glucose intolerance and decreased β-cell proliferation[5]. Genetic, cell-based and biochemical analyses show that osteoblasts via osteocalcin stimulate β-cell proliferation and expression of *Insulin* and *Adiponectin*, an insulin-sensitizing adipokine, that *Esp*-deficient mice metabolic phenotype is caused by a gain of osteocalcin bioactivity and that OST-PTP regulates indirectly osteocalcin post-translational modification. By revealing that the skeleton exerts an endocrine regulation of sugar homeostasis this study expands our understanding of energy metabolism and its disorders.

The authors have no conflict of interest.

Corresponding author: Na Kyung Lee, Department of Genetics and Development, 701W 168 St HHSC 1620, New York, NY 10032, USA
E-mail: nkl2104@columbia.edu

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References

1. Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, Shen J, Vinson C, Rueger JM, Karsenty G. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell 2000;100:197-207.
2. Karsenty G. Convergence between bone and energy homeostases: leptin regulation of bone mass. Cell Metab 2006;4:341-8.
3. Ducy P, Desbois C, Boyce B, Pinero G, Story B, Dunstan C, Smith E, Bonadio J, Goldstein S, Gundberg C, Bradley A, Karsenty G. Increased bone formation in osteocalcin-deficient mice. Nature 1996;382:448-52.
4. Mauro LJ, Olmsted EA, Skrobacz BM, Mourey RJ, Davis AR, Dixon JE. Identification of a hormonally regulated protein tyrosine phosphatase associated with bone and testicular differentiation. J Biol Chem 1994; 269:30659-67.
5. Lee N, Sowa H, Hinoi E, Ferron M, Ahn J, Dacquin R, Mee PJ, Mauvais-Jarvis F, Ducy P, Karsenty G. Endocrine regulation of energy metabolism by the skeleton. Cell 2007;130:456-69.