BONE DISEASES

Leptin bares our bones, sympathetically

The hormone leptin, which is well known for regulation of body weight as an anorexigenic factor, also plays a central role in the regulation of bone formation. In the 1 November issue of *Cell*, new work has identified the mediator of this action of leptin and points toward a therapeutically useful way of manipulating this pathway to increase bone mass. Osteoporosis is a degenerative bone disease that affects many millions of women, especially after menopause, causing bones to lose mass, so that they become brittle and prone to fracture. Drugs are available that can arrest the bone destruction caused by osteoporosis, but none can increase bone formation or reverse the effects of bone damage.

Leptin is known to be an anti-osteogenic factor — a powerful inhibitor of bone formation. Previous studies have shown that mice lacking leptin are not only extremely obese, but also have a greater bone mass than normal mice. However, that it is leptin signalling rather than body weight that controls bone mass is seen from the analysis of fat-free mice that have no adipocytes, the cell type that produces leptin. Fat-free mice that are lean have the same high-bone-mass phenotype as mice deficient in leptin.

In this study, Karsenty and colleagues have characterized the mechanism by which leptin regulates bone mass, and they show that the sympathetic nervous system is the intermediate between leptin and osteoblasts, and that this mode of action does not affect body weight. The sympathetic nervous system regulates stress responses, such as increasing heart rate, blood pressure and respiratory rate; it also stimulates endocrine glands such as the adrenal and the thyroid to produce the hormones adrenaline and cortisol, respectively. Studies in mice show that neuropeptides that mediate anorexigenic functions and regulate body weight do not affect bone formation. In addition, it was found that anti-osteogenic signals are transmitted through G-protein-coupled β-adrenoceptors on osteoblasts. In wild-type and leptin-deficient mice, β-adrenoceptor agonists decreased bone mass, whereas in wild-type and ovarectomized 'menopausal' mice β-adrenoceptor antagonists increased bone mass.

This research suggests that β-blockers, drugs that are used routinely to treat high blood pressure, could also help reverse osteoporosis. But does this regulatory pathway operate in humans as well as mice? There is evidence indicating that the sympathetic nervous system has a role in the regulation of human bone mass, but further studies in rats and with humans will be needed for confirmation.

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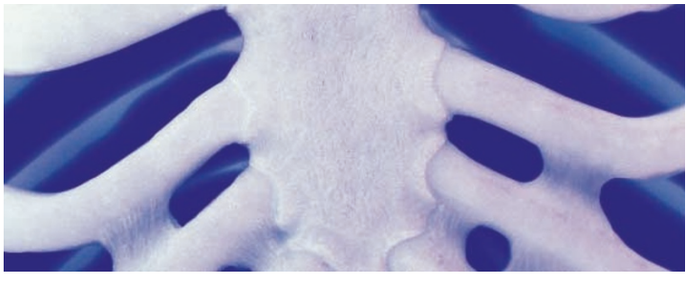
References and links

ORIGINAL RESEARCH PAPER Takeda, S. *et al.* Leptin regulates bone formation via the sympathetic nervous system. *Cell* **111**, 305–317 (2002)
FURTHER READING Goltzman, D. Discoveries, drugs and skeletal disorders. *Nature Rev. Drug Disc.* **1**, 784–796 (2002)
WEB SITE Gerard Karsenty's lab: www.bcm.tmc.edu/cnrc/faculty/karsenty.htm
Encyclopedia of Life Sciences: http://www.els.net adrenaline



IN BRIEF

GENE THERAPY

Synthetic small inhibiting RNAs: Efficient tools to inactivate oncogenic mutations and restore p53 pathways.

Martinez, L. A. *et al. Proc. Natl Acad. Sci. USA* **99**, 14849–14854 (2002)

RNA interference — a highly selective gene-silencing mechanism involving small inhibiting RNAs (siRNAs) that bind to and degrade specific messenger RNAs — is causing much excitement in drug discovery at present. One potential application is with the tumour-suppressor gene *p53*, as this is inactivated by single-base-pair mutations in more than 50% of all cases of cancer. The authors found that a single base difference in siRNAs distinguished between mutant and wild-type *p53* that were co-expressed in cells, and restored wild-type p53 function. The findings show that siRNA could be used to selectively inhibit oncogenes, and could therefore potentially form the basis of a customized gene-targeted cancer treatment.

LEAD IDENTIFICATION

Identification of potent and selective small-molecule inhibitors of caspase-3 through the use of extended tethering and structure-based drug design.

Choong, I. C. *et al. J. Med. Chem.* **45**, 5005–5022 (2002)

Caspases are important in inflammation and apoptosis, and potent and selective caspase inhibitors would be useful in the delineation of the roles of individual caspases, and as leads for drug discovery. However, most inhibitors discovered so far are not completely specific, and are often peptidic, limiting their potential as drug leads. By using an initial hit discovered from a novel 'extended tethering' strategy, in which a fragment that is known to bind to the target is covalently attached to the active site and then allowed to react reversibly with a library of compounds to probe the characteristics of the binding site, Choong and colleagues designed several potent and selective non-peptidic inhibitors of caspase-3.

STRUCTURE-BASED DRUG DESIGN

NMR-based modification of matrix metalloproteinase inhibitors with improved bioavailability.

Hadjuk, P. J. *et al. J. Med. Chem.* 2002 Nov 20 (doi: 10.1021/jm020160g)

Automated analysis of large sets of heteronuclear correlation spectra in NMR-based drug discovery.

Damberg, C. S. *et al. J. Med. Chem.* 2002 Nov 14 (doi: 10.1021/jm020866a)

NMR (nuclear magnetic resonance) spectroscopy has evolved into an important technique in support of structure-based drug design (see Wüthrich *et al. Nature Rev. Drug Disc.* **1**, 211–219 (2002)). Hadjuk *et al.* show that NMR-based screening of fragments can be effectively applied to improve the physiochemical or pharmacokinetic profile of lead compounds, and Damberg *et al.* describe an automated procedure for the analysis of the many spectra that such strategies typically require.