Clues for New Therapeutics in Osteoporosis  
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More than 25 million people, most of whom are menopausal or elderly women, have a progressive loss of bone mass, which increases their susceptibility to fracture. The increasing prevalence and tremendous costs of this disorder underscore the importance of developing new treatments. Because the pathogenesis of osteoporosis is multifactorial — bone mass is influenced by physical activity, nutrition, and genetic factors — devising new therapeutics is a challenge. The recent findings of Klein et al. therefore come as welcome news: the authors identified an enzyme, 12/15-lipoxygenase, that contributes to natural variations in bone mass and skeletal development in mice, and showed that compounds that target this enzyme increase bone mass.1

Klein et al. used inbred mouse strains and genetic analyses to identify a region of chromosome 11 that influences bone mineral density. Substituting an 82-megabase stretch of this chromosome in the D2 strain of mice with the corresponding region from the B6 strain increased bone mineral density and femoral strength in the D2 mice. The investigators then narrowed the search to a stretch of about 31 megabases and found that, among the genes in this portion of the genome, only Alox15, which encodes 12/15-lipoxygenase, was differentially expressed in the two mouse strains. They then used engineered mice that completely lacked Alox15 and found that these mice had greater bone mineral density and stronger bones than wild-type mice. Mice carrying a single Alox15 allele had bones of intermediate strength, as compared with the knockout and wild-type mice. These findings demonstrate that the expression of 12/15-lipoxygenase is a key osteogenic regulator. Consistent with this observation are the findings that transient expression of 12/15-lipoxygenase in mouse models of osteoporosis reduces the expression of certain cytokines, such as interleukin-1β and tumor necrosis factor α, and growth factors that maintain osteoclast activity and that these lipoxins may therefore provide protection against cytokine-mediated bone loss. (In bone remodeling during menopausal osteoporosis, osteoblasts secrete higher-than-normal levels of cytokines, such as interleukin-1β, tumor necrosis factor α, and interleukin-6, as well as prostaglandins.) In addition, transgenic rabbits that overexpress human 15-lipoxygenase type 1 are protected against bone loss associated with periodontal disease.2 Thus, it seems possible that 15-lipoxygenase type 1 and type 2 may have antagonistic effects, with type 1 providing protection against bone loss through lipoxin-mediated suppression of specific cytokines, and type 2 aggravating bone loss.

The authors went on to test two inhibitors of 12/15-lipoxygenase in mouse models of osteoporosis and, in so doing, showed that interleukin-4 effects bone loss by increasing the expression of Alox15. Mice in which interleukin-4 is overexpressed typically have lower peak bone mass and bone strength than wild-type mice. After weaning, trans-
genic mice with overexpression of interleukin-4 were given feed containing one of the inhibitors. Twelve weeks later, these mice had greater bone mineral density and stronger bones than littermates that were given feed without an inhibitor. The other model of osteoporosis appropriately involved ovariectomy, which induces premature menopause. Ovariectomized mice that received feed containing an inhibitor lost less bone mass than did controls.

At least one of these inhibitors is not believed to be particularly selective, meaning that it cannot differentiate between 15-lipoxygenase type 1 and type 2. Moreover, one of the inhibitors may simply act as an antioxidant.

These findings underscore the need to determine the types of cells, substrates, and metabolic pathways of lipid mediators that are altered in bone during osteoporosis. A better understanding of the function and expression of 12-lipoxygenase and 15-lipoxygenase isoenzymes type 1 and type 2 may hasten the development of novel antiosteoporotic drugs.

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