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Fat's loss is bone's gain

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Commentary

Osteoporosis, characterized by low bone mass and structural deterioration of bone tissue with an increased susceptibility to fractures, is a major public health threat to the elderly. Bone mass homeostasis in adults is maintained locally by the balance between osteoblastic bone formation and osteoclastic bone resorption. Haploinsufficiency of PPARγ, a key transcription factor implicated previously in adipogenesis, lipid metabolism, and glucose homeostasis, has now been shown to promote osteogenesis through enhanced osteoblast formation. These findings support a reciprocal relationship between the development of bone and fat, and may prompt further exploration of the PPAR pathway as a potential target for intervention in osteoporosis.

Fat's loss is bone's gain

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Osteoporosis, characterized by low bone mass and structural deterioration of bone tissue with an increased susceptibility to fractures, is a major public health threat to the elderly. Bone mass homeostasis in adults is maintained locally by the balance between osteoblastic bone formation and osteoclastic bone resorption. Haploinsufficiency of PPARγ, a key transcription factor implicated previously in adipogenesis, lipid metabolism, and glucose homeostasis, has now been shown to promote osteogenesis through enhanced osteoblast formation (see the related article beginning on page 846). These findings support a reciprocal relationship between the development of bone and fat, and may prompt further exploration of the PPAR pathway as a potential target for intervention in osteoporosis.

Osteoclast and osteoblast: the yin and yang that control skeletal homeostasis

In vertebrates, bones undergo a process of continual renewal throughout life. This process, called bone remodeling, can be viewed as a balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption (1). Osteoclasts are specialized cells derived from the monocyte/macrophage lineage that degrade extracellular bone matrix (2). On the other hand, mesenchyme-derived osteoblasts rebuild the resorbed bone by elaborating matrix that subsequently undergoes mineralization (3). An imbalance between the two arms of bone remodeling is associated with diseases including rheumatoid arthritis and osteoporosis (Figure 1). According to the National Institutes of Health and the National Osteoporosis Foundation, in the US alone, 10 million individuals have osteoporosis, and almost 34 million more have low bone mass, placing them at increased risk for osteoporosis.

PPARγ: adipocyte determinator and osteoblast terminator?

Besides osteoblasts, mesenchymal progenitor cells can also give rise to adipocytes, myocytes, and chondrocytes. The nuclear receptor PPARγ is the dominant regulator of adipogenesis and is required for the expression of many adipocyte genes, including adipocyte-specific fatty acid binding protein, phosphoenolpyruvate carboxykinase, and lipoprotein lipase (4). Multiple studies have suggested that a certain degree of plasticity exists within the mesenchymal lineage. For example, myoblastic cell lines can be converted to adipocytes through expression of PPARγ and CCAAT/enhancer binding protein α (5); bone morphogenetic protein and retinoic acid cooperate to induce osteoblast differentiation of preadipocytes (6); and ligand activation of PPARγ drives the differentiation of multipotent mesenchymal progenitor cells towards adipocytes over osteoblasts (7, 8). Clinically, the decreased bone mass observed in age-related osteoporosis is accompanied by an increase in marrow adipose tissue (9).

In the current issue of the *JCI*, Akune et al. further explore the relationship between osteogenesis and adipogenesis using cells and animals deficient in PPARγ expression (10). They showed that homozygous PPARγ-deficient ES cells failed to differentiate into adipocytes but spontaneously differentiated into osteoblasts (Figure 1). Furthermore, PPARγ haploinsufficiency was shown to enhance osteoblastogenesis in vitro and to increase bone mass in mice in vivo. Indeed, several osteoblast markers and key molecules for osteoblast differentiation, including Runx2 and osterix, were more highly expressed in primary cultured marrow cells lacking expression of one PPARγ allele. In contrast to the effect on osteoblasts, Akune et al. found no change in osteoclast function in cells lacking PPARγ. A number of important issues remain to be addressed, however, including the molecular mechanism whereby loss of PPARγ leads to enhanced osteogenesis. For example,

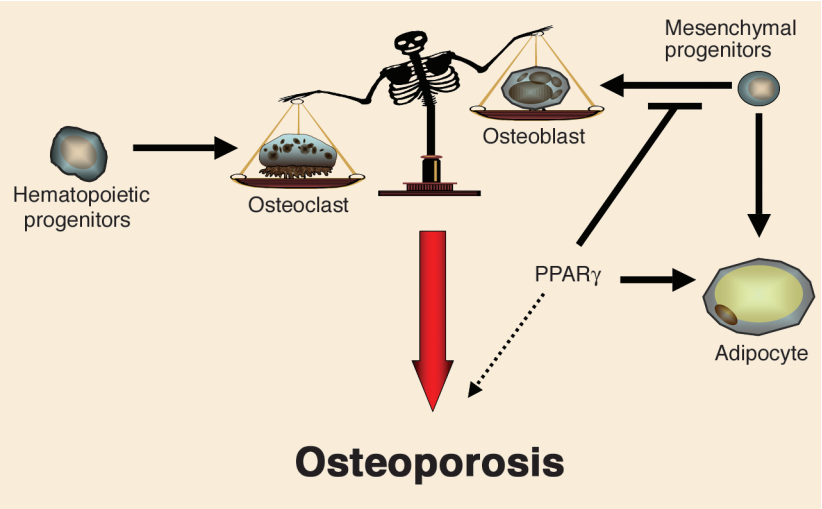

Figure 1
Model for the influence of the PPARγ pathway on osteogenesis. Bone homeostasis is maintained by the balance between osteoblastic bone formation and osteoclastic bone resorption. An imbalance between the two is associated with osteoporosis. The PPARγ pathway not only determines adipocyte differentiation from mesenchymal progenitors, but also inhibits osteoblast differentiation, as revealed by Akune et al. (10). This new finding raises the possibility of interrupting the PPARγ pathway for the treatment of osteoporosis.

Nonstandard abbreviation used: parathyroid hormone (PTH).

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what genes regulated by PPARγ are antagonistic to osteoblast differentiation?

PPARγ and osteoporosis: from bench to clinic

Agents currently approved for treatment of osteoporosis act largely by inhibiting bone resorption. These include hormone replacement therapy, calcium and vitamin D supplementation, and bisphosphonate-based drugs (alendronate sodium/Fosamax and risedronate/Actonel) (11). The only exception is the recently approved parathyroid hormone (PTH)-derived peptide Forteo, which can stimulate bone formation. However, significant disadvantages exist for PTH treatment. For example, sustained exposure to elevated PTH levels results in net bone loss, so intermittent exposure by daily injection is necessary (12). New medicines that promote bone formation/osteoblastogenesis with fewer side effects could have great utility in the treatment of osteoporosis.

The findings of Akune et al. suggest that aspects of the PPARγ pathway might be amenable to pharmacologic intervention in osteoporosis (10). One possibility raised by the authors is the use of PPARγ modulators or antagonists. Some support for this idea comes from a recent study that identified 12/15-lipoxygenase as a susceptibility gene for bone mineral density in mice (13). The authors of this study hypothesized that PPARγ may be involved in these effects, since 12/15-lipoxygenase is capable of generating PPARγ ligands from linoleic/arachidonic acids and oxidized LDL (14, 15). However, the use of PPARγ modulators/antagonists for osteoporosis needs to be approached with caution given the critical role of PPARγ in mammalian physiology. Thiazolidinediones, a class of synthetic PPARγ agonists, are currently used to treat type 2 diabetes. The possibility that an antagonist to PPARγ might exacerbate insulin resistance, particularly in susceptible individuals, needs to be carefully considered. In the case of the estrogen receptor, it has been possible to identify compounds that have tissue-specific actions on a nuclear receptor. A bone-selective PPARγ modulator, in this case an antagonist, may be required to exploit PPARγ as a target in osteoporosis.

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Predicting the clinical course of prostate cancer

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Risk stratification in prostate cancer remains a significant clinical challenge. A study in this issue of the *JCI* describes an exciting application of high-throughput functional genomic technology to further refine our understanding of treatment failure risk in prostate cancer patients (see the related article beginning on page 913).

Since Walsh and Donker first described the pelvic anatomy that allowed for the development of the nerve-sparing anatomic radical prostatectomy in 1982, the morbidity associated with the surgical treatment of clinically localized prostate cancer has decreased substantially (1). The subsequent advent of prostate-specific antigen (PSA) screening has led to a substantial stage migration in newly diagnosed adenocarcinoma of the prostate, and this has resulted in a higher likelihood of surgical cure. Despite these therapeutic advances, our ability to accurately predict the risk of treatment failure for an individual patient with prostate cancer remains limited. The current tools we utilize to guide critical decisions, such as whether or how aggressively to treat prostate cancer, are based on serum PSA levels, biopsy Gleason score, and clinical stage. Despite the incorporation of powerful multifactorial nomograms into our decision process, the ability to predict individual patient outcome remains limited (2, 3).

Nonstandard abbreviations used: prostate-specific antigen (PSA).

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Novel prognostic indicators

In this issue of the *JCI*, a report by Glinsky et al. attempts to advance our understanding and ability to stratify the risk of treatment failure for patients with localized prostate cancer undergoing radical