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 osteerin, 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,

Nonstandard abbreviation used: parathyroid hormone (PTH).

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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 anatomical 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).

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 surgery with selective PPARγ agonists. The finding that an antagonist to PPARγ 2 ligands on adipocyte versus osteoblast differentiation.