Fig. 1. PYK2 signaling in osteoclasts (Left) and osteoblasts (Right). PYK2 is a negative regulator of osteoblast differentiation and activity. The unknown mechanism may involve inhibition of regulators of osteoblast function, Runx2, osteir, or Wnt signaling factors or stimulation of the inhibitor Dkk1. The role of PYK2 differs in osteoclasts: PYK2 null mice had normal osteoclast differentiation and activity, possibly caused by the compensatory activity of FAK. The PYK2 kinase inhibitor, PF-431386, may represent a novel treatment for osteoporosis in addition to other anabolic agents under development, such as sclerostin- and Dkk1-neutralizing antibodies, statins, strontium, and selective estrogen receptor modulators (SERMs).

Buckbinder et al. (3) characterized the bones of PYK2−/− mice. Microcomputed tomography and bone histomorphometric analysis showed a high bone mass phenotype, suggesting that PYK2 negatively regulates bone mass. However, the high bone mass was caused by increased bone formation, rather than reduced bone resorption in PYK2−/− mice, where osteoclast function appeared normal. Analyses in vivo and in vitro showed no differences in osteoclast number, activity, or degree of differentiation between PYK2−/− and wild-type mice, in direct contrast to previous work supporting a role for PYK2 in osteoclast activation. Osteoblast differentiation and mineralization were increased in bone marrow cultures from PYK2−/− mice compared with control. Knockdown of PYK2 with shRNA increased osteoblast differentiation of human mesenchymal stem cells, supporting a role for PYK2 as a negative regulator of the osteoblastic lineage.

A recent study by Kim et al. (10) provides insight into the role of PYK2 in osteoblasts. In a bone injury repair model of transgenic mice deleted for FAK expression in osteoblasts, osteoprogenitor cells migrated to sites of skeletal injury but displayed delayed osteoblast maturation and bone repair. Osteoblast activity also was delayed. The delays were temporary, and new bone deposition was equal to control by 21 days postinjury. PYK2 relocalized from the perinuclear region of FAK null osteoblasts to focal adhesions and may compensate for the absence of FAK. The results of these two studies (3, 10) suggest a model in which relocation and increased activity of PYK2 at focal adhesions prevents osteoblast maturation and delays bone healing (Fig. 1).

These studies raise numerous mechanistic questions. How does PYK2 affect osteoprogenitor maturation? Where does PYK2 act in the osteoblastic lineage? Does PYK2 suppress known regulators of osteoblast differentiation and function, such as Runx2 or osteir, or stimulate the Wnt inhibitor Dkk1? How can the finding that deletion of PYK2 had no effect on osteoclast function be reconciled with previous data that PYK2 stimulates osteoclast activity? The role of c-Src and FAK in this process is unclear.

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unclear and will be important to reconcile because c-Src inhibitors are under development as antiresorptive agents. Crossing PYK2 null mice with targeted FAK null mice would test how these related kinases contribute to the bone phenotype of the mice. FAK null transgenic mice could be treated with a PYK2 inhibitor to determine whether PYK2 activity delays osteoblast maturation at sites of bone injury. Lastly, Buckbinder et al. (3) tested PYK2 as a target for osteoporosis therapy in an ovariec-tomized rat model of postmenopausal osteoporosis. Animals were treated with vehicle, estrogen replacement, or a PF-431396, potent small molecule inhibitor of PYK2 kinase activity, for 28 days. The drug significantly increased bone formation and mineralization and rescued ovariec-tomy-induced bone loss. Estrogen replacement suppressed bone turnover and prevented bone loss compared with vehicle but, unlike PF-431396, did not increase bone formation.

There is a great need for osteoblast-stimulatory, bone-building osteoporosis therapy. Bisphosphonates are currently the first-line therapy for osteoporosis, but the long half-life in bone, chronic suppression of bone turnover, and association with osteonecrosis of the jaw (2) raise concerns about the long-term use of these agents. Alternative Food and Drug Administration (FDA)-approved antiresorptive therapy, selective estrogen receptor modulators, do not share these issues but are less commonly prescribed. Promising new antiresorptive agents, such as RANK ligand-neutralizing antibody, are under development.

Teriparatide is the only FDA-approved anabolic agent. It reduces vertebral fractures by >65% and stimulates significant increases in lumbar spine bone mineral density (11). It effectively restores bone microarchitecture and stimulates new bone formation more than antiresorptive therapies (12–14). Teriparatide is especially useful for patients who fail or cannot tolerate bisphosphonate therapy. However, its use is restricted to 2 years because of a black box warning applied when rat studies indicated an increased risk of osteosarcoma. Other animal studies indicate that parathyroid hormone may increase tumor growth in bone (15, 16). Patients with cancers in bone or who have received radiation to the skeleton are not candidates for teriparatide therapy (13, 16). Thus, therapeutic alternatives, such as PF-431396, could be useful for these patients.

Novel anabolic approaches for treating osteoporosis are welcome but also viewed with caution.

Another target for anabolic therapy is sclerostin, whose gene is mutated in sclerosteosis, a rare genetic disorder characterized by a generalized increase in bone mass (17). Patients homozygous for sclerostin mutation have very thick bones, particularly the skull, which cause nerve entrapment and increased intracranial pressure. Sclerostin is expressed by osteocytes, terminally differentiated osteoblastic cells embedded within bone that may secrete the factor to regulate bone homeostasis. Mechanical stress leads to osteocyte apoptosis and decreased levels of sclerostin, which permits new bone formation (18). Sclerostin acts downstream of bone morphogenetic protein signaling (17) and is a negative regulator of the Wnt pathway (18). The factor is expressed only in bone, and antibodies to sclerostin increase bone formation rate and density in mice, suggesting that such antibodies could provide a future anabolic therapy (18). Antibodies to another Wnt inhibitor, Dkk1, are also under development.

Statins represent a third anabolic osteoporosis therapy. They are lipid-lowering agents that inhibit 3-hydroxy-3-methylglutaryl-CoA reductase. In animal models, statins increase bone mass by a bone morphogenetic protein-2-mediated effect on osteoblasts (19). A limited number of studies have been reported in which statin therapy increased bone mass in patients. Effect of statins on bone mass have been difficult to demonstrate because of high drug uptake by the liver and limited systemic bioavailability (20). Randomized, controlled clinical trials in which statins are delivered efficiently to bone would test their value as an anabolic osteoporosis therapy. Strontium is in common use outside of the United States to treat osteoporosis. The mechanisms by which strontium alters bone resorption and formation are unclear, and the compound itself may confound measurement of bone mineral density.

Agents that stimulate bone formation, such as PF-431396, modulators of the Wnt pathway (sclerostin and Dkk1 antibodies), and statins could be useful ad-ditions to the limited armamentarium to treat osteoporosis. Novel anabolic ap-proaches for treating osteoporosis are welcome but also viewed with caution. Future studies will determine whether the new anabolic agents increase risk for osteosarcoma, as seen with teriparatide in rats, and will likely be required before FDA approval is granted. Also crucial to approval will be clinical data on whether these anabolic agents improve bone quality, reduce fracture risk, and improve fracture healing, because bone mineral density represents only one parameter of bone quality. These new agents could have a significant impact on the future of osteoporosis treatment.