

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## PYK2 inhibition promotes bone formation: anabolic approach for the treatment of osteoporosis

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**P**roline-rich tyrosine kinase 2 (PYK2) is a non-receptor tyrosine kinase, expressed in both bone-forming osteoblasts and bone-resorbing osteoclasts. Up to now, the skeletal phenotype of PYK2<sup>-/-</sup> mice has not been described. In vitro studies pointed to a positive role for PYK2 in osteoclast maturation and bone resorption. PYK2 localizes to the podosomes of osteoclasts. PYK2 might have a positive role in osteoblasts as well. Treatment of osteoblast cells with fluoroaluminate led to increased PYK2 activity and was associated with increased cell attachment and spreading, and PYK2 activity was stimulated in osteoblast-like cells after mechanical strain. In a recent study [1], the function of PYK2 in bone was elucidated using PYK2<sup>-/-</sup> mice and derived bone marrow cultures, as well as molecular and pharmacological inhibitors of this enzyme.

Exploring the phenotype of PYK2<sup>-/-</sup> mice did not reveal evidence supporting an essential function for PYK2 in osteoclasts. PYK2<sup>-/-</sup> mice have high bone mass resulting from an unexpected increase in bone formation. Bone marrow cultures show that PYK2 deficiency enhances differentiation and activity of osteoprogenitor cells, as does expressing a PYK2-specific siRNA or dominantly interfering proteins in human mesenchymal stem cells. Furthermore, the daily administration of a small-molecule PYK2 inhibitor increases bone formation and protects against bone loss in ovariectomized rats, a preclinical model of postmenopausal osteoporosis.

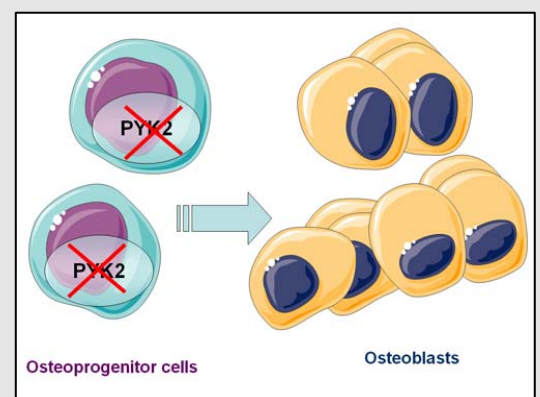
These findings demonstrate that PYK2 regulates the differentiation of early osteoprogenitor cells across species and that inhibiting PYK2 may have potential as a bone anabolic approach for the treatment of osteoporosis.

1. Buckbinder L et al. *Proc Natl Acad Sci USA*. 2007;104:10619-10624.

### PYK2 inhibition promotes bone formation

Proline-rich tyrosine kinase 2 (PYK2) is a non-receptor tyrosine kinase, expressed in both bone-forming osteoblasts and bone-resorbing osteoclasts. Exploring the phenotype of PYK2<sup>-/-</sup> mice revealed that they have high bone mass resulting from an increase in bone formation. PYK2 deficiency enhances differentiation and activity of osteoprogenitor cells, as does expressing a PYK2-specific siRNA or dominantly interfering proteins in human mesenchymal stem cells. Furthermore, the daily administration of a small-molecule PYK2 inhibitor increases bone formation and protects against bone loss in ovariectomized rats.

These findings demonstrate that PYK2 regulates the differentiation of early osteoprogenitor cells and that inhibiting PYK2 may have potential as a bone anabolic approach for the treatment of osteoporosis.



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