Osteoporosis

New Target for Treatment of Osteoporosis

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Technology

This technology offers a completely new approach to specifically fight osteoporosis by the possibility of the well-defined modulation of osteoblast activity. Contrary to the known therapies (inhibition of osteoclast activity; that is stop of bone resorption and continuing damage) this invention offers the possibility to develop methods and substances that could lead to the reconstruction of bone substance resembling normal bone mineral density. In this context we provide means and methods for regulating the activity of osteoblasts. This invention further relates to methods for identifying compounds that are useful in the treatment of osteoporosis.

Innovation

Novel strategy to prevent bone loss by increasing the anabolic activity of osteoblasts only:
- Fhl2 is a major regulator of osteoblast function
- Fhl2 functionally interacts with Runx2, a regulator of osteoblast activity
- Enforced Fhl2 expression in mature osteoblasts display increased bone mass
- Enforced expression of Fhl2 increases bone formation rate by modulation of osteoblast activity in vivo

Application

- Prevention / treatment of osteopenia and osteoporosis
- Fhl2 as diagnostic marker for osteopenia
- Fhl2 knock-out mice as model of osteopenia / osteoporosis

Market Potential

Osteoporosis is of outstanding individual and economic significance. It is the most prominent degenerative disease in the western world. About 10 million people in the United States have osteoporosis and additional 18 million individuals in this country already have low bone mass, placing them at increased risk for this disease.

Responsible Scientist

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NEW TARGET FOR TREATMENT OF OSTEOPOROSIS

Fhl2 regulates bone formation by increasing osteoblast activity

Bone is an organ of crucial importance because it confers resistance to mechanical stress and protects internal organs from trauma. In addition it contains the body's main reservoir of calcium and phosphate ions. Bone is produced by only three major cell types. During embryogenesis chondrocytes form a blueprint of cartilage for most bones. Chondrocytes are required for growth in length. The cartilage is successively replaced by bone substance secreted by osteoblasts. This extracellular matrix calcifies under their control. Therefore, osteoblasts are the bone forming cells. However, bone is not a static organ. It is regenerated through continuous formation by osteoblasts and resorption by osteoclasts throughout life. This bone remodeling process maintains a constant bone mass. In pathological conditions, the tight balance between bone formation and resorption is not preserved. The most common bone disease is osteoporosis, which results from a relative gain of osteoclast activity. A reduction in bone mass leads to an increased susceptibility to fractures. Osteoporosis is of outstanding individual and economical significance. It is the most common degenerative disease in the industrialized world.

The most prominent cause of osteoporosis is the raise in osteoclast activity in postmenopausal women due to reduced estrogen synthesis. Most pharmacological treatments for osteoporosis are directed against osteoclasts, thereby only slowing down the process of bone loss. Just a few years ago, intermittent treatment with parathyroid hormone was approved by the FDA as the only anabolic treatment for osteoporosis. Although this effect has been analyzed for decades now, the molecular mechanism remains to be understood. This coincides with little knowledge about loss of bone substance (osteopenia) due to decreased osteoblast activity (Karsenty and Wagner 2002).

Our data reveal Fhl2 as a tissue specific bona fide coactivator localized in the nucleus. In addition, Fhl2 also associates with the cell membrane. We demonstrated nuclear translocation upon stimulation of Rho GTPases unraveling how extracellular stimuli lead to a change in gene expression pattern via the Rho signaling cascade (Müller et al., 2002).

We detected Fhl2 expression in osteoblasts using a detailed in situ analysis. Our histomorphometric analysis of Fhl2-deficient mice uncovered a progressive loss of bone substance up to 32% (Fig.1 C). The osteopenia is solely caused by the reduced activity of osteoblasts while the activity of osteoclasts is not affected. In a proof of principle experiment we further validated in vivo that over-expression of Fhl2 exclusively in osteoblasts of transgenic mice leads to a gain of bone substance due to enhanced osteoblast activity. Transgenic mice with ectopic expression of Fhl2 in osteoblasts on the other hand show no difference to wild-type mice (Fig. 2 A-B). A comparison of ex-vivo cultures of osteoblasts from wild-type and Fhl2-deficient mice corroborate our implication of Fhl2 as a regulator of osteoblast activity (Fig. 2 C-D).

We obtained similar results with an osteoblastic cell line by ectopic expression of Fhl2 and by reducing the endogenous amount Fhl2 by RNAi, respectively (Fig. 3 E). Our data demonstrate that Fhl2 directs osteoblast activity in a cell autonomous manner, in part by interaction with the master regulatory gene of bone formation Runx2. Both proteins interact on the osteoblast-specific osteocalcin promoter where Fhl2 serves as a transcriptional coactivator of Runx2. In summary, our data characterize Fhl2 as an important regulator of bone formation (Günther et al., 2005).

RESULTS

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REFERENCES

