【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy)

Title of Project： Elucidation of Wnt signaling network controlling bone metabolism

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Research Area： Basic Dental Science, Biochemistry, Bone Cell Biology
Keyword： Coupling factor, Osteoclast, Osteoblast, Osteocyte, Wnt signaling, Sclerostin

【Purpose and Background of the Research】

Bone is remodeled throughout the life. Osteoclasts (OCs) resorb bone, while osteoblasts (OBs) form bone. OCs are believed to produce a coupling factor which activates OB function. Characteristics of the factor are not known (Fig. 1). Wnt activates canonical and noncanonical pathways. Activation of the canonical in OBs induces OB function. Osteocytes (OCys) in bone secrete sclerostin which inhibits the Wnt pathway in OBs. Activation of the noncanonical in OC precursors stimulates their differentiation into OCs. We have also observed that OCs secrete some Wnt which activate OB function, and OCs also secrete an unknown factor (Factor X) which suppresses sclerostin secretion of OCys. In this study, we will uncover the Wnt signaling network that controls bone metabolism.

【Research Methods】

Ryk and Ror2 signals: Ryk is a Wnt receptor, but its function is not known. Analysis of Ryk-KO mice showed that Ryk signals in OBs stimulate OB function. OCs secrete new Wnt which binds to Ryk. Wnt produced by OCs will be identified. Ryk signals in OBs will be clarified. Wnt5a secreted from OBs activates OCs through the receptor Ror2. The activation mechanism will be clarified (Fig. 2).

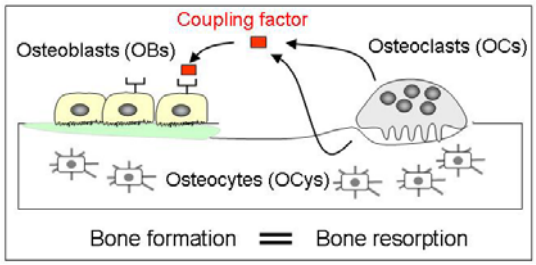

Figure 1 Coupling in bone metabolism

Elucidation of the coupling mechanism: Factor x will be identified. Osteoprotegerin (OPG) is a decoy receptor for OC differentiation factor. Both bone resorption and formation are activated in OPG-KO mice. Ovariectomized (OVX) mice exhibit high turnover of bone resorption and formation. OVX-mice are the model of postmenopausal osteoporosis. Using OPG-KO and OVX-mice, the coupling mechanism will be elucidated (Fig. 2).

Development of new treatments: Most of the drugs for osteoporosis are inhibitors of bone resorption. New treatments which stimulate bone formation are expected. Drugs which stimulate bone formation will be developed (Fig. 2).

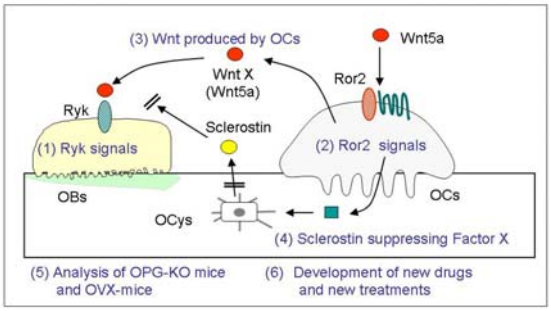

Figure 2 Six research plans in this project

【Expected Research Achievements and Scientific Significance】

We will elucidate the Wnt signaling network in bone and clarify the mechanism of coupling between bone resorption and bone formation. These lines of experiments will bring the great benefit for patients with osteoporosis.

【Publications Relevant to the Project】

・Takahashi N, Kobayashi Y et al.: Regulatory mechanism of osteoclastogenesis by RANKL and Wnt signals. Front Biosci 16:21-30, 2011.
・Maeda K, Kobayashi Y, Takahashi N et al.: Wnt5a-Ror2 signaling between osteoblast-lineage cells and osteoclast precursors enhances osteoclastogenesis. Nature Med 18:405-412. 2012.

【Term of Project】 FY2013-2015

【Budget Allocation】 101,400 Thousand Yen

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