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LGR4: A new receptor for a stronger bone

Yunyun Jin & Yingzi Yang

Department of Developmental Biology, Harvard School of Dental Medicine, Boston, MA 02115, USA

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Bone formation and remodeling involves production of bone matrix by osteoblasts and its resorption by osteoclasts. Increased osteoclast activity or reduced osteoblast function leads to osteopenic disorders (Kong et al., 1999). Therefore, it is crucial to understand mechanisms underlying osteoclast regulation. Such understanding will shed light on identifying potential therapeutic targets of osteoporosis, a disease caused by too much bone resorption or insufficient bone formation. RANKL-RANK signaling is required for osteoclast, activating a variety of downstream signaling pathways. RANK, also known as tumor necrosis factor (TNF) superfamily member 11 (TNFSF11), has long been considered to be the sole receptor for RANKL, also known as TNFRSF11A, (Hanada et al., 2011). In a recent study, Mingyao Liu and Jian Luo, Jianru Xiao, et al., at East China Normal University, have discovered that the leucine-rich repeat-containing G-protein-coupled receptor 4 (LGR4, also called GPR48) is a novel receptor for RANKL, in that it competes with RANK for RANKL binding in osteoclasts, and that it negatively regulates osteoclast differentiation and bone remodeling (Luo et al., 2016). This research, published in *Nature Medicine*, provides the first evidence that a RANKL-LGR4-Gα_q-GSK3-β-NFATC1 signaling pathway regulates osteoclastogenesis and suggests that LGR4 is a candidate for treating osteoporosis and other bone-resorption diseases. This finding provides a molecular mechanism explanation to the low bone density of LGR4-deficiency in humans and mice, as well as to many other potential defects caused by LGR4 mutation.

The *Tnfsf11*$^{-/-}$ mice exhibit the osteopetrosis phenotype caused by reduced bone resorption, and it also showed disrupted immune regulation, and failure of mammary gland lobuloalveolar development. Liu's team noticed that the *Lgr4*$^{-/-}$

email: Yunyun_Jin@hsdm.harvard.edu

clast differentiation. By analyzing bone phenotypes of two mutant mice lines-whole-body (*Lgr4*$^{-/-}$) and monocyte conditional mutant mice of *Lgr4* (*Lgr4* CKO)- the authors found that hyperactivation of osteoclasts, as shown by greater numbers of TRAP-positive osteoclasts and larger osteoclast size in the femoral bones and calvaria bones *in vivo*. Further more, the authors also provided *in vitro* evidences that loss of *Lgr4* in the bone marrow monocytes (BMMs) from *Lgr4* CKO mice enhances the formation of osteoclast and accelerates BMMs differentiation when treated with RANKL. In addition, LGR4 also regulates osteoclast survival by inducing apoptosis. The authors' finding mechanically explained the phenomenon that the mature osteoclasts finally undergo apoptosis even in an environment with RANKL.

In osteoblasts, *Lgr4* appears to have a different function. Liu's team showed that *Lgr4* acts through the cAMP-PKA-CREB pathway to regulate the expression level of Atf4 in osteoblasts, showing that *Lgr4* is involved in the osteoblast differentiation and bone formation (Luo et al., 2009). Compared with its function in the osteoclastogenesis, they do suggest that the osteoclast deficiency is the major cause of low bone mass seen in mice and humans with an LGR4 mutation.

RSPOs and Norrin are the ligands of LGR4. The authors found that RSPOs and Norrin are not involved in *Lgr4*-deficiency-induced osteoclastogenesis. Instead, LGR4 regulates canonical RANKL-RANK signaling through: (i) LGR4-ECD competes with RANK to bind with RANKL, (ii) LGR4 decreases interaction between RANK and a downstream component TRAF6, (iii) LGR4 abrogated RANKL- induced NF-κB signaling.

The transcription factor NFATC1 is a master regulator of RANKL-induced osteoclastogenesis, when NFATC1 is expressed in precursor cells. By overexpression of a constitutively active form of $G\alpha_q$ ($G\alpha_q^{CA}$), the authors showed that $G\alpha_q^{CA}$ blocked *Lgr4*-knock-down-induced osteoclast differentiation via decreasing phosphorylation of glycogen synthase kinase 3-β (GSK3-β). GSK3-β phosphorylation inhibits GSK3-β activity that promotes NFATC1nuclear localization. These observations led to the identification of a new RANKL-LGR4-Gα