



Leucine-rich repeat-containing G-protein-coupled receptor 4: a new receptor of RANKL for osteoclast regulation

Jin Liu, Ge Zhang

Institute for Advancing Translational Medicine in Bone & Joint Diseases, Hong Kong Baptist University, Hong Kong SAR, China

Correspondence to: Ge Zhang. Institute for Advancing Translational Medicine in Bone & Joint Diseases, Hong Kong Baptist University, Hong Kong SAR, China. Email: zhangge@hkbu.edu.hk.

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Bones are constantly remodelled through the coordinate work by the bone-forming osteoblasts and bone-resorbing osteoclasts. Physiologically, the osteoblast-mediated bone formation and osteoclast-mediated bone resorption are coupled for maintaining bone homeostasis. However, such coupling is disrupted in pathological conditions such as osteoporosis that is caused by the hyperactivated bone resorption or insufficient bone formation (1). The RANKL-RANK signalling, including the receptor activator of NF- κ B (RANK) expressed by osteoclast lineage cells, its ligand RANKL expressed by osteoblastic cells, and the decoy receptor osteoprotegerin (OPG) secreted by osteogenic cells, are essential for osteoclast development and osteoclast function (2). The upregulation of RANKL and the imbalance of RANKL/OPG ratio will lead to osteoclast hyperactivation and rapid bone resorption. However, the mature osteoclasts finally undergo apoptosis even in an RANKL-enriched environment (3), suggesting that RANKL-RANK signalling may not be exclusively regulated by the OPG-mediated inhibitory mechanism. In a recent study published in *Nature Medicine*, Luo *et al.* uncovered a novel receptor of RANKL, i.e., leucine-rich repeat-containing G-protein-coupled receptor 4 (LGR4), for regulating osteoclastogenesis and osteoclast-mediated bone resorption through the RANKL-LGR4-G α_q -GSK3- β -NFATc1 signalling (4).

Given that the RANK^{-/-} mice and LGR4^{-/-} mice shared some similar phenotypes with disrupted immunity regulation, mammary gland development, body-temperature modulation, and energy expenditure (5,6), the

authors suspected that there might be potential crosstalk between the LGR4 and the RANKL-RANK signalling. As expected, they performed a series of biochemical assays to document that RANKL could compete with the other LGR ligands, i.e., R-spondins (RSPOs), to bind with LGR4. They further identified the extracellular domain (ECD) of LGR4 that could mediate the physical interaction between RANKL and LGR4.

In addition, the authors rigorously demonstrated that the RANKL-RANK-NFATc1 signalling during osteoclast differentiation could directly induce the expression of LGR4, which in turn competes with RANK for RANKL binding on osteoclast lineage cells. More importantly, they showed that the binding of RANKL but not the other LGR ligands, i.e., RSPOs or norrin, to LGR4 activated the G α_q -GSK3- β signalling pathway to suppress the expression and activity of NFATc1 during osteoclastogenesis. It provides the first evidence to indicate RANKL-LGR4 as the negative feedback loop underlying the RANKL-RANK signalling during osteoclast differentiation.

By genetic approach, they further found that both the systemic LGR4 knockout mice and osteoclast precursor (monocyte)-specific LGR4 knockout (CKO) mice exhibited the enhanced osteoclast activity and decreased bone mass *in vivo*. In addition, they demonstrated that loss of LGR4 in osteoclast precursors from the LGR4 CKO mice not only enhanced the formation but also blocked the apoptosis of osteoclasts, suggesting that LGR4 could induce apoptosis to inhibit osteoclast survival. This finding also provides a mechanistic explanation on the RANKL-induced osteoclast

apoptosis.

Finally, the authors showed that soluble LGR4 ECD could inhibit the RANKL-induced osteoclast activity and ameliorate the bone loss in the ovariectomized mice, RANKL-injected mice and *Tnfrsf11b*-deficient mice, respectively. Thus, it might provide an alternative approach, to a certain extent, mirroring that of the human RANKL antibody denosumab in neutralizing the detrimental effect of RANKL-induced osteoclast hyperactivation in osteoporosis (7). However, the bone formation and osteoblast-related parameters were not reported in this study. Thus, it remains unclear whether the LGR4 ECD treatment could also affect the LGR4-mediated osteogenic signalling in osteoblast, since the authors have previously reported a proosteogenic effect of LGR4 for activating the expression level of *Atf4* in osteoblasts through the LGR4-cAMP-PKA-CREB signalling pathway (8).

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Footnote

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