DOCTORAL THESIS

The role of osteocyte Kindlin-2 in the anabolic actions of PTH in bone

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Abstract

In vertebrates, PTH receptor 1 (PTH1R) plays a pivotal role in control of bone development and homeostasis; however, how it is regulated is poorly defined. Here we report that Kindlin-2 binds to and modulates PTH1R to regulate bone mass and PTH actions. Deleting Kindlin-2 expression using the 10-kb mouse *Dmp1-Cre* severely impairs the anabolic effects of intermittent PTH on bone in adult mice with or without ovariectomy. Of particular interest, *Kindlin-2* and *Pth1r* double heterozygous mice (*Dmp1-Cre; Kindlin-2*$^{f/+}$*; Pth1r*$^{f/+}$), but not either singly heterozygous mice (*Dmp1-Cre; Kindlin-2*$^{f/+}$ or *Dmp1-Cre; Pth1r*$^{f/+}$), display severe osteopenia and fail to increase bone mass in response to administration of intermittent PTH. Mechanistically, Kindlin-2 interacts with the C-terminal cytoplasmic region of PTH1R. When overexpressed, this region efficiently inhibits the endogenous PTH/PTH1R signaling in osteoblasts, which is reversed by introduction of a point mutation that abolishes the Kindlin-2 interaction. Furthermore, Kindlin-2 loss inhibits PTH-induced CREB phosphorylation and cAMP production *in vitro* and in bone. PTH upregulates, while estrogen deficiency downregulates, expression of Kindlin-2 *in vitro* and in bone. Collectively, we demonstrate that interplay between Kindlin-2 and PTH1R regulates bone mass by modulating PTH1R and provide a potential therapeutic target for metabolic bone diseases.

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