

PARATHYROID FUNCTION

Action of parathyroid hormone in osteocytes

Teriparatide, a recombinant form of parathyroid hormone, is the only anabolic agent approved by the FDA for use in patients with osteoporosis. However, the mechanisms by which teriparatide increases bone formation are poorly understood. Now, new research reveals how parathyroid hormone acts on osteocytes to increase bone formation and mass.

Marc Wein and collaborators showed that, *in vitro*, parathyroid hormone activates protein kinase A, which then phosphorylates salt-inducible kinase 2 (SIK2) leading to inhibition of the action of this kinase. Unphosphorylated SIK2 phosphorylates the histone deacetylases HDAC4 and HDAC5; when SIK2 is inhibited, the phosphorylation levels

of HDAC4 and HDAC5 fall, which allows them to enter the nucleus. Once in the nucleus, HDAC4 and HDAC5 block the action of the transcription factor MEF2C, which leads to reduced expression of *SOST* (encoding sclerostin, an inhibitor of bone formation).

Next, the team used RNA sequencing to show that small molecule SIK inhibitors mimic the action of parathyroid hormone on many of the genes known to be regulated by parathyroid hormone in osteocytes. Furthermore, when mice were given a small molecule SIK inhibitor for 2 weeks, their bone mass and formation increased. “Inhibition of SIK2 could lead to a new generation of osteoporosis therapies,” says author Henry Kronenberg.

Future work will elucidate the other important targets of SIKs in osteocytes to further improve our understanding of parathyroid hormone action. “As kinases such as SIK2 can be targeted by small, orally active inhibitors, we are hopeful that this target might prove useful in the clinical setting,” concludes Kronenberg. “The challenge will be to find strategies that minimize potential toxicity of these agents and optimize their effectiveness.”

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ORIGINAL ARTICLE Wein, M. N. *et al.* SIKs control osteocyte response to parathyroid hormone. *Nat. Commun.* <http://dx.doi.org/10.1038/ncomms13176> (2016)