

Controlling bone formation and resorption.

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INTRODUCTION: At present, the majority of efforts to control bone metabolism still focus on the inhibition of osteoclast recruitment (osteoprotegerin, RANKL antagonists, cytokine inhibitors), osteoclast attachment (integrin antagonists), osteoclast function (calcitonin, bisphosphonates, V-type ATPase inhibitors, chloride channel inhibitors, c-Src, p38, NFκB, Pyk2 kinase inhibitors) or osteoclast mediated collagen degradation (Cathepsin K or MMP-inhibitors). Likewise, the search for bone anabolic treatments is usually restricted to efforts aiming at influencing osteoblast proliferation or differentiation.

The obvious disadvantage of these approaches is that they act by blocking 'effector' cells like osteoclasts or osteoblasts, instead of trying to influence the cell in bone which controls bone mass and architecture, namely the osteocyte. Experience shows that very often, feed-back mechanisms are 'neutralising' and ultimately defeating these attempts, so that the impressive effects that were seen in cell culture do not translate into the complex in vivo environment where such feed-back mechanisms are operating.

Mechanical Sensing: Osteocytes appear to represent the cells responsible for adaptive processes which lead to either bone formation, in case of skeletal overload, or bone loss in disuse¹. It is presumably through these 'strain sensors', that mechanical usage above the habitual level will trigger an adaptive response in the form of a bone modeling drift, i.e. direct bone formation without prior resorption by osteoclasts. The advantages of triggering such a modeling event to gain bone, as opposed to gaining it through a positive bone balance in the remodeling cycle are intriguing, since resorption in the latter process will result in temporal weakening of the structure, a problem not associated with modeling. Unfortunately with aging, the skeleton and its strain sensor appear to become relatively insensitive to exercise induced bone gain, and elderly patients can no longer endure the vigorous level of exercise that would be required to trigger such an event. This raises the question whether it is possible to find agents capable of lowering the modeling threshold? Lowering the modeling threshold would sensitize osteocytes so that they would perceive low strains caused by low intensity exercise as an overload. This in turn would make them signal to the bone

surface to initiate bone formation through modeling.

PTH a modulator of strain sensing?

Interestingly, animal studies show that bone gain with PTH appears to slow down in both rats² and humans³ even in the presence of continuous treatment, and that the increase in bone mass is related to the dose that is administered. In addition, parathyroidectomised rats do no longer respond to mechanical loading, but the bone formation response can be recovered if PTH is injected to the rats prior to loading⁴. In UMR-106.01 osteosarcoma cells, PTH is able to reduce the threshold level of suction required to activate a stretch activated cation channel⁵. A sensitizing effect of 50 nM PTH on sub-threshold loading induced COX-2 expression in MC3T3-E1 cells was also demonstrated⁶. These experiments suggest that PTH may be able to adjust the sensitivity of the osteocyte to strain.

Patients suffering from sclerosteosis experience life-long bone overgrowth resulting in increased bone mass and strength despite having perfectly functional osteoclasts⁷. The lack of SOST expression in osteocytes appears to result in complete dysfunction of the feed-back mechanism which should counterbalance this abnormal accumulation of bone.

If we understand how mechanical strain is turned into molecular signals in osteocytes, and how these signals are amplified and processed to elicit the bone modeling response on the surface, we may be able to identify a number of novel targets capable of manipulating the process. It is expected that the resulting treatment should no longer elicit a feed-back response which will act against our intervention.

REFERENCES: ¹H Frost (1987) *Anat Rec* 219:1-9. ²JA Gasser (1997) *J Jap Soc Bone Morphom* 7:107-14. ³Orwoll et al. (2003) *J Bone Miner Res* 18:9. ⁴J Chow et al. (1998) *Am J Physiol*, 274:E146-54. ⁵R Duncan et al. (1992) *FEBS letters*, 307:219-23. ⁶Ryder et al. (2000) *Calcif Tiss Int*, 67:241-6. ⁷Gardner et al.(2005) *J Clin Endo Metab* 90