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COMMENTARY

Periostin, a major factor in the envelope-specific bone anabolic response to PTH?

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Bone Anabolic Effects of Parathyroid Hormone

Intermittent parathyroid hormone (PTH) is the only approved bone anabolic treatment for postmenopausal osteoporosis, which has been shown to increase bone mineral density in the axial skeleton, leading to significant reduction in vertebral fractures.[1] PTH also improves cortical area and/or thickness of the proximal femur by increasing endocortical apposition, and not as perhaps expected from the perspective of optimizing mechanical properties, by a predominant anabolic effect at the periosteal envelope. Intermittent PTH exerts a complex temporal biphasic response pattern with the most rapid event being the activation of 'osteoclast-independent' modeling-based bone formation, which is mediated by the reactivation of quiescent osteoblasts (lining cells), an effect which can be observed within 6 h after exposure to the peptide.[2,3] PTH also triggers the differentiation of mesenchymal stem cells into the osteoblast lineage, which is undoubtedly important to sustain the bone formation response.[4] In a second phase, the peptide stimulates the development and activation of osteoclasts through the regulation of receptor activator of nuclear factor-κB and osteoprotegerin expression by osteoblasts.[5] In PTH-treated patients, modeling- and remodeling-based bone gain appear to coexist, albeit at different proportions, depending on the duration of treatment and, thus, the time of analysis. At a 1-month time point, treatment of postmenopausal women with osteoporosis with PTH was shown to stimulate the bone formation rate on cancellous, endocortical and periosteal surfaces of the iliac crest by 4.5-, 5- and 4-fold, respectively.[6] Bone gain on cancellous and endocortical surfaces was primarily caused by stimulation of formation in ongoing remodeling units, with only a modest increase in the formation on previously quiescent surfaces (modeling response). Although the activation of osteoclast-independent modeling-based bone gain is likely the principal mechanism during the early bone formation response to PTH (<3 months), the increase in bone remodeling activity with positive bone balance is likely the dominant mechanism, which is responsible for the sustained formation response observed during long-term treatment.[7,8] The shift in the relative importance of the early modeling-based bone gain to the more sustained remodeling-based bone acquisition after 6 months of treatment is also apparent in the bone biomarker response. The rapid increase in bone formation markers, such as PINP and PICP, which is already detectable as early as 7 days after the initiation of treatment,[9] is typically followed by an increase in bone resorption markers NTx and CTx at 3–6 months.[10,11] Thus, PTH stimulates a sequence of events that initially favors processes associated with direct osteoclast-independent bone formation (modeling), which, over time, appear to be increasingly replaced by a slower process of bone remodeling-based bone acquisition. This pattern has led some investigators to coin the term of the 'anabolic window,' with suggestions to add an anti-resorptive therapy to keep the increasing remodeling activity at a certain level, thereby extending the anabolic window.[12] This appears to make sense especially at the level of cortical bone, where the increase in bone mineral density, resulting from the bone apposition at the endocortical- and periosteal surface, is 'counteracted' by the increase in cortical porosity. Sites that are predominantly composed of cortical bone (distal radius and radius shaft) may thus show a decrease in bone mineral density.[1]

New Insight into the Molecular Mechanism of the Envelope-Specific PTH Effects

Over the past few years, substantial information describing the temporal as well as the envelope-specific (periosteal, endocortical and trabecular) response to PTH has been published.[13,14] On the other hand, the information regarding the molecular mechanisms that guide the complex anabolic responses triggered by the peptide is still incomplete. The paper published by Bonnet *et al.*[15] describing an important role of the 90-kDa secreted extracellular matrix protein periostin (Postn) in the bone anabolic response to PTH greatly expands our knowledge. The preferential expression of Postn in the outer cortex (periosteum and osteocytes), as well as its rapid upregulation by mechanical stimuli and PTH raised the intriguing possibility that it may act as a crucial mediator of the bone

anabolic response to PTH at the periosteal envelope, where modeling-based bone gain appears to represent the dominant mechanism leading to bone gain. In a series of elegant experiments, the authors were able to demonstrate that unlike in *Postn*$^{+/+}$ mice, PTH was unable to significantly increase femoral cortical thickness, strength and stiffness in *Postn*$^{-/-}$ mice. Dynamic histomorphometric indices of bone formation determined at the femoral periosteal and endocortical envelope suggest that in *Postn*$^{-/-}$ mice, PTH failed to induce the 'normal' increase in periosteal mineral apposition rate and that the increase in the mineralizing surface was also reduced. Similar, but clearly less pronounced, effects were observed at the endocortical surface. This is in strong contrast to the normal anabolic response to PTH treatment of *Postn*$^{-/-}$ mice, which was observed in cancellous bone at the distal femur metaphysis and in vertebral bodies when analyzed by micro-computed tomography (Supplementary Table S1 in Bonnet *et al.*[15]). Dynamic histomorphometric parameters confirm the near-normal response in trabecular mineral apposition rate and the mineralizing surface in *Postn*$^{-/-}$ mice as compared with wild-type animals (Supplementary Table S2 in Bonnet *et al.*[15]). Taken together, these data suggest that Postn is a crucially important mediator of the bone anabolic response to PTH at the periosteal envelope and a significant mediator at the endocortical envelope, while not having a major role in the response to PTH in cancellous bone.

Anti-Sost antibodies partially rescued PTH anabolism in *Postn*$^{-/-}$ mice, suggesting that a substantial proportion, but not all of the anabolic effect of PTH, may be mediated via the inhibition of Sost. This finding appears to be in line with the work from Kramer *et al.*[16] who reported that the cortical bone formation response to PTH was reduced (but not abolished) in *Sost*$^{-/-}$ mice. In contrast, Robling[17] reported normal or enhanced cortical bone formation rates in *Sost*$^{-/-}$ mice when treated with PTH, but interestingly also increased cortical porosity. Because of this increase in cortical porosity, *Sost*$^{-/-}$ mice showed reduction or even absence of anabolic effects in cortical bone in response to PTH, as based on dual-energy X-ray absorptiometry-derived bone mineral density measurements. Bonnet *et al.*[15] demonstrated that PTH treatment increased Postn expression at 24 h at the periosteum (the site of the modeling response to PTH), but not the endocortical surface of the proximal tibia. Furthermore, in a series of elegant experiments the authors showed that osteoblast proliferation, differentiation, migration and response to PTH were altered in the absence of Postn. Their results identify Postn as a regulator of Wnt-β-catenin signaling, a crucial mediator of bone anabolism.

Conclusions and Open Questions

Taken together, the data presented by Bonnet *et al.*[15] suggests that Postn may have an important role in the periosteal anabolic response to PTH. Mechanistically, this response appears to be mediated by both a direct suppression of MEF2C and *Sost* gene expression in osteocytes, a and direct stimulatory effect of Postn on Wnt signaling and osteoblast functions. In addition, Postn expression in osteocytes near the endocortical ridge could be involved in remodeling processes at this surface. In the absence of Postn, bone formation appears to be impaired and PTH is unable to effectively improve cortical structure and strength.

Although highly informative, we still have substantial knowledge gaps that need to be addressed in future studies. We only have limited information regarding the effect of different doses of PTH on the molecular mechanisms identified by Bonnet *et al.* for the individual bone envelopes (periosteal-, endocortical- and cancellous bone surface). From clinical studies it appears that the periosteal bone formation response is less robust and may require higher doses of PTH as compared with the endocortical- and cancellous bone envelopes. Moreover, the molecular response pattern identified by Bonnet *et al.* may be particularly relevant for the early response to PTH, where the significance of modeling-based bone gain appears to dominate over remodeling-based bone acquisition. Our current level of mechanistic understanding does not allow us to resolve the complex, temporal biphasic response pattern, which is observed clinically with a shift in the relative contribution of modeling- and remodeling-based bone gain observed with increasing treatment duration. The polarized preferential expression of Postn in the outer third of the cortex near the periosteum, where the anabolic response to PTH is almost exclusively based on modeling, may suggest that Postn is directly linked to the modeling response, and that it may have less (or no) direct relevance for remodeling-based bone gain. This is of course highly speculative, but it may be worth of investigation. From the clinical point of view, modeling-based bone gain is no doubt the most desirable, rapid and most effective way of improving bone mechanical properties, as it does not require activation of the rather 'lengthy' bone remodeling process, and does not temporarily weaken bone structures due to the introduction of surface-based stress raisers.[18,19] Understanding the molecular mechanism of how PTH induces modeling-based bone gain may thus lead to highly effective novel anabolic treatment options for bone metabolic disorders associated with bone fragility and fractures.

Conflict of Interest

JAG is an employee at the Novartis Institutes for BioMedical Research, Basel, Switzerland.

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