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Invited Plenary Abstract
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Osteoblast and osteoclasts: local communication through several mechanisms

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Cells of the osteoblast lineage regulate osteoclast formation from hemopoietic precursors through contact dependent mechanisms that are controlled by hormones and by the production of locally generated inhibitors. The key effectors are osteoblast-derived RANKL signalling through its receptor, RANK, on haemopoietic cells, and OPG as the decoy receptor that inhibits the process. Local signalling that results in bone formation during remodelling takes place in several ways. Growth factors released from resorbed bone matrix can contribute to preosteoblast differentiation and bone formation. The preosteoblasts themselves, growing in the resorption space, can communicate through cell contact and paracrine signalling mechanisms to differentiate. Osteocytes can sense the need for bone repair by detecting damage and pressure changes, and signalling to surface cells to respond appropriately. Now that it has been shown through mouse genetics that PTHrP generated locally in bone is a crucial physiological regulator of bone formation, and probably also of resorption, we need to understand how local PTHrP release is controlled in bone in the remodelling process. Finally the observation that concurrent treatment with bisphosphonates impairs the anabolic response to PTH, adds to other clues that osteoclast activity is necessary to complement the direct effect that PTH has in promoting differentiation of committed osteoblast precursors. This might involve the generation of a coupling factor from osteoclasts that are transiently activated by RANKL in response to PTH. Both human and mouse genetics provide evidence supporting the view that osteoclasts, despite in some circumstances being unable to resorb bone, e.g. failure of acidification, can nevertheless be associated with normal, or even increased bone formation. An implication is that it may be possible to design resorption inhibitors that do not block PTH anabolic action when given simultaneously.

It is proposed that transiently activated osteoclasts can contribute to the coupling of bone formation to resorption by producing activity that influences preosteoblast participation in bone formation.

Bone formation results from a complex cascade of events that involves proliferation of primitive mesenchymal cells, differentiation into osteoblast precursor cells (osteoprogenitor, preosteoblast), maturation of osteoblasts, formation of matrix, and finally mineralization. It is highly likely that in some forms of osteoporosis, deficient bone formation results from impaired osteoblast replenishment from precursors, and even from a deficiency of progenitors. Recent studies of control of osteoblast differentiation have provided valuable new insights, including identification of the roles of several key transcription factors in osteoblast differentiation.

The only proven anabolic therapy for bone is PTH. The anabolic effect of PTH is dependent upon intermittent administration, but when an elevated PTH level is maintained even for a few hours it initiates processes leading to new osteoclast formation, and the consequent resorption over-rides the effects of activating genes that direct bone formation.

New approaches to anabolic therapies may come from the discovery that an activating mutation in the LRP5 gene is responsible for an inherited high bone mass syndrome, and the fact that this can be recapitulated in transgenic mice, whereas inactivating mutations result in severe bone loss. This has focused attention on the Wnt/frizzled/βcatenin pathway as an important one in bone formation, and proof of concept has been obtained in experimental models.