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Commentary

Bone homeostasis

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The functions of bone(s) are (*i*) mechanical support of soft tissues, (*ii*) levers for muscle action, (*iii*) protection of the central nervous system, (*iv*) release of calcium and other ions for the maintenance of a constant ionic environment in the extracellular fluid, and (*v*) housing and support of hemopoiesis. The structure and amount of bone, both at the macroscopic and microscopic level, are determined by the genetic blueprint and by regulatory factors that help carry out bone functions. Genetic information is responsible for the highly conserved anatomical shape of bones and most likely for restoring that shape after fracture.

To accomplish its functions, bone undergoes continuous destruction, called resorption, carried out by osteoclasts, and formation by osteoblasts. In the adult skeleton, the two processes are in balance, maintaining a constant, homeostatically controlled amount of bone. This fact, as well as the histological observation that osteoclastic bone resorption is followed by osteoblastic bone formation (1), led to the concept that the two processes are mechanistically ''coupled'' and to the search for ''coupling factors.''

No single factor has been proven to link the two processes. Existing evidence suggests that multiple factors probably are involved in the maintenance of bone homeostasis. Growth factors found in bone (2), such as IGFs or TGFβs, were proposed to be released during resorption and initiate local bone formation (3, 4). Factors deposited on the bone surface by osteoclasts at the end of the resorption phase were proposed to initiate the bone formation that follows (5). Humoral factors, such as parathyroid hormone and prostaglandin E, that stimulate both bone resorption and bone formation, could increase the two processes in tandem. The action of these factors and other hormones and cytokines on osteoclasts was proposed to be mediated by osteoblast-lineage cells, which possess the cognant receptors (6, 7), intimately linking osteoblast–osteoclast interaction to bone turnover.

Last, but not least, the ability of bone to change its structure and adapt to mechanical loads implies that mechanical forces can regulate bone resorption and formation: increased loads should increase formation and decrease resorption whereas unloading should have the opposite effect. Indeed, immobilization stimulates resorption and suppresses formation (for review, see ref. 8), providing a clear example of ''uncoupling'' between the two processes. The mechanism for these effects has not been elucidated fully, but, here again, osteoblast lineage cells, osteocytes, and lining cells were proposed to mediate the mechanical signals because their location is best suited to perceive them (9).

The link between bone formation and bone resorption was examined in an elegant study by Corral *et al.* (10), reported in this issue of the *Proceedings*, who used a transgenic model to demonstrate clear separation between the two processes in 6- to 14-week-old mice. Using the osteocalcin promoter, responsible for selective expression of this gene in mature osteoblasts, the authors destroyed these cells by expressing thymidylate kinase (tk) and by treating the animals with gancyclovir, a toxin activated by tk. This study shows that the elimination of bone-forming osteoblasts and arrest of bone formation does not affect osteoclastic activity. The imbalance between the two processes resulted in significant bone loss, mimicking an osteoporosis phenotype, which could be completely prevented by treatment with the osteoclast inhibitory bisphosphonate alendronate. Furthermore, osteoclasts generated in culture from bone marrow and calvaria bone cells, obtained from the transgenic animals, resorb bone normally *in vitro* in the presence or absence of gancyclovir, indicating that osteocalcin-expressing cells are not required for differentiation or activity of the murine osteoclasts *in vitro*. At first sight, these findings seem to challenge the current dogma and prevailing concepts on bone turnover and osteoblast/osteoclast interaction, but do they?

The findings raise two important and related questions: (*i*) What is the nature of the coupling of bone resorption to bone formation, and (*ii*) which osteoblastic cells, if any, affect osteoclast activity? The authors were cautious in interpreting the findings and stated only that active bone formation and living osteoblasts, at least those expressing osteocalcin, are not required for osteoclast activity in these mice. These conclusions are justified fully by the data.

Regarding the broader questions raised by this study, the integration of these findings into the existing literature should take into account the following. At the age of 6 weeks, mice are still growing. During growth, bone shape and structure are maintained in part by active resorption in the subepiphyseal (bone growth) region, the primary site of observation and analysis in this study. There should thus be a strong genetic influence on bone formation and resorption at that site during this stage, more closely related to shaping bone structure (modeling) than to maintaining bone mass during adult bone ''remodeling,'' where local coupling between the two processes should occur (11).

The second point relates to the duration of the study, which was 4–8 weeks long. Of note, the bone loss caused during the first 4 weeks of osteoblast shut-off was vastly larger than that occurring during the following 4 weeks (Fig. 4 in ref. 10). The lack of bone formation between the ages of 14 and 18 weeks does not appear to markedly reduce bone volume further (Fig. 4 in ref. 10), suggesting that osteoclastic activity has abated substantially during that period in comparison to the previous 4 weeks. It would be of interest to measure the osteoclastic surface at the end of the second 4-week gancyclovir treatment period. If osteoclastic activity was reduced it could suggest the influence of age (genetic?) or feedback provided by bone mass, rather than bone formation. The molecular basis for changes in osteoclast activity, if present, could be investigated further in this model.

In the same context, complete cessation of osteoblastic bone formation does not seem to lead, at least within 8 weeks, to continuous wasting of the skeleton, which may be leveling off at ≈50% of the initial bone volume, at the sites examined.

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Further study of this phenomenon, including longer duration of treatment and the mechanisms involved, also could be explored in this model.

An unequivocal finding of this study is that osteocalcin-expressing osteoblasts are not required for osteoclast generation and osteoclast activity. This does not contradict a large number of previous studies, showing that osteoclast formation and activity, at least in culture, require interaction with stromal cells or osteoblast lineage cells but not necessarily mature osteoblasts (12). This interaction was recently shown to be mediated, at least in part, by the TNF-related molecule RANK ligand (13, 14).

Another interesting point made in this study is the fact that, when bone turnover was virtually turned off by combined treatment with gancyclovir and alendronate for 8 weeks, there were no apparent deleterious effects on the skeleton. It has been assumed, primarily on theoretical grounds, that mechanical usage causes fatigue damage in bone, which is repaired by bone remodeling, the absence of which may increase the risk of fracture (15). Eight weeks may be too short a period to detect such effects in relatively young mice; longer studies would be necessary to evaluate this point.

In summary, this is an interesting study that applies the tools of genetic engineering to a long term quest for unraveling the basis of bone homeostasis. The novel observation is that (in mice) bone formation and mature osteoblasts *per se* are not required for osteoclast activity, which nonetheless may be influenced by cells that do not express osteocalcin and by age or the amount of bone. This model could help further elucidate the links between the processes of bone formation and bone resorption, which ought to be present to maintain bone homeostasis.

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