Editorial

Bone development, maintenance of tissue integrity, and response to physiologic requirements involve both regulation of and communication between the two principle skeletal cells, bone forming osteoblasts and bone resorbing osteoclasts. Bone marrow stromal cells and mature osteoblasts contribute to modulating development of osteoclast progenitors. Osteoblasts are responsive to hormones and secrete cytokines that stimulate osteoclast activity in mediating bone resorption. Reciprocally, activation of bone resorption and the products from released bone matrix provide "coupling" cues for recruitment and differentiation of osteoblast progenitors for bone formation. In this issue of *The Journal*, Lajeunesse et al. (1) address fundamental in vivo interrelationships between osteoblasts and osteoclasts, parameters central to understanding the pathogenesis of osteopetrosis.

Osteopetrosis is characterized by impaired bone resorption arising from defective formation and/or activity of the osteoclast (2, 3). The clinical consequences of human osteopetrosis can be severe and fatal. The heterogeneity of inherited osteopetroses in human and animals and resulting from ablation of the c-*src* (4) and c-*fos* (5) genes has contributed new insights into specific molecular mechanisms required for osteoclast differentiation and functional activities. Current understanding of the series of events, regulated by hormones and cytokines, that contributes to formation, maturation, and activation of the multinucleated cell residing in a resorption lacunae has been reviewed (2, 3, 6).

It is believed that osteoclast differentiation is dependent on both hematopoietic stem cell competence and signals derived from the osteoblast or the extracellular bone matrix. Osteopetrosis variants are characterized by either an absence of multinucleated osteoclasts in bone, indicating a potential cell lineage abnormality, or the presence of inactive osteoclasts. When the defect lies in the osteoclast lineage, bone marrow transplantation (BMT) cures the disorder by osteoclast replacement via donor hematopoietic progenitors. In contrast, some mutations, as the *op* mouse and *tl* rat, cannot be improved by BMT, indicating that a defect lies in the bone microenvironment. A series of studies of the *tl* rat (reviewed in reference 2) demonstrated reductions in osteoblast proliferation and precocious expression of bone phenotypic genes. These osteoblasts were also incompetent to direct in vitro bone resorption. Such findings suggest that aberrations in the mutant osteoblast contribute to the *tl* disorder. Although the cause of the osteopetrosis in the patients studied by Lajeunesse et al. is unknown, culturing for the first time osteoblasts from the same patient before and after BMT to correct the osteopetrosis provides evidence for osteoblast abnormalities, and like the *tl* rat, may derive from an aberrant bone microenvironment.

Lajeunesse et al. provide evidence which supports two important concepts: that defective osteoblasts exist in osteopetrotic bone in the human, and that osteoclast activity contributes to osteoblast differentiation. It has become increasingly evident that osteoblast differentiation is a multistep series of events modulated by an integrated cascade of gene expression that initially supports proliferation and the sequential expression of genes that contribute to biosynthesis and formation of bone tissue (7). Organization of the bone extracellular matrix and ordered deposition of mineral are key events in regulating progression of osteoblast differentiation. Abundant alkaline phosphatase activity (APase) is one of the earliest phenotypic markers of the committed post-proliferative osteoblast. Osteocalcin (OC), a bone specific protein, is a late stage marker induced to peak expression in mature osteoblasts producing a mineralizing matrix. Pre-BMT osteoblasts were competent with respect to APase, but the inability to produce OC and M-CSF suggests that they may have been "locked" in an early stage of maturation in the aberrant matrix and cellular environment. After BMT, these parameters were normalized. Genetic analyses clearly show that only recipient osteoblasts are found after BMT and only a small fraction of recipient osteoblast progenitors survived chemotherapy; but, these developed into normal osteoblasts. Thus, an inherent defect in the recipient's osteoblasts was not apparent, but this possibility could not be fully ascertained. As suggested by the authors, osteoblast normalization is the consequence of a corrected bone microenvironment as a result of osteoclastic resorption.

The findings of Lajeunesse et al. illustrate the important interplay between functional osteoclasts and osteoblasts, with the resorbing cells contributing either directly to osteoblast differentiation, perhaps by secretion of a cellular factor, or indirectly by correcting the bone microenvironment. Many variables must be considered in interpreting findings from primary human osteoblast cultures; however, given comparable conditions for cell isolation and culture, the results are striking before and after BMT. Restoring osteoblast parameters of the treated patient to normal values is similar to the response in the *tl* rat upon curing the skeletal sclerosis by administration of CSF-1, indicating that the osteoblast modifications in these osteopetrosis cases was the consequence rather than the cause of the disease. Nonetheless, an important question is raised by the study — could any of the human osteopetroses result from an inherent osteoblast dysfunction? Not all BMTs are successful in correcting osteopetrosis (8) and there are no criteria to predict the outcome for this or any other treatment targeted to normalizing the osteoclast population and activity. Consideration of osteoblast and bone matrix deficiencies may therefore be warranted.

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