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## MECHANISMS OF OSTEOCLASTIC BONE RESORPTION

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Chronic renal failure is typically attended by hyperparathyroidism, and as such accelerated bone remodeling initiated by increased osteoclast recruitment and activity. Thus, understanding the mechanisms by which osteoclasts differentiate and resorb bone provides potential therapeutic targets.

Human and murine osteopetrosis represent excellent tools by which to study the osteoclast. Using such models, we have established that the osteoclast is of hematopoietic origin and a member of the monocyte/macrophage family. The precursor cell arises in the marrow and binds to bone prompting multinucleation via fusion with sister macrophages. At the same time, stromal cells and osteoblasts produce M-CSF and RANK ligand which are necessary and sufficient for the polykaryon to assume the osteoclast phenotype. The specifics of the differentiated osteoclast include expression of the  $\alpha_v\beta_3$  integrin and the c-Src tyrosine kinase which, in conjunction with matrix-derived signals organize the osteoclast actin cytoskeleton to polarize its resorptive machinery to the bone-apposed plasma membrane. Degradation of bone matrix involves formation of an isolated extracellular microenvironment between the cell and bone which the osteoclast acidifies to a pH approximating 4.5. This acidification process is mediated by an electrogenic  $H^+$ ATPase, similar to that expressed by the intercalated cell of the renal tubule. Electroneutrality is maintained by a  $Cl^-$  channel charge coupled to the proton pump and intracellular pH by a  $Cl^-/HCO_3^-$  exchanger, again similar to that of the renal tubule. The acidified milieu of the resorptive microenvironment serves to mobilize bone mineral exposing organic matrix which is subsequently degraded by the lysosomal enzyme, cathepsin K. These insights into the mechanisms of osteoclastic bone resorption have yielded anti-resorptive drugs targeting c-Src, the  $\alpha_v\beta_3$  integrin, cathepsin K, RANK ligand and the  $H^+$ ATPase, which are presently in clinical trial.