Calcium signaling during osteoclastogenesis

S. Sims[1], S.J. Dixon[1], K. Tiedemann[2], S.V. Komarova[2]

[1]University of Western Ontario, London, Ontario; [2]McGill University, Montreal, Quebec

Osteoclasts are cells responsible for destruction of mineralized tissues. They are important for both physiological growth and turnover of bone, and pathological destruction of bone in rheumatoid arthritis, periodontitis, and cancer metastasis to bone. To form osteoclasts the specific intracellular signaling program is induced by a key pro-resorptive cytokine RANKL. Calcium signaling is one of the critical components of this program. In undifferentiated osteoclast precursors, calcium levels are stable over time and maintained at a level of ~0.1-1 μM, which is markedly lower than extracellular levels of 1-2 mM. After 24 to 48 hours of exposure to RANKL, calcium levels in a sub-population of precursors start exhibiting large fluctuations (sometimes referred to as oscillations due to their repetitive nature). By 4 to 5 days of RANKL treatment mature multinucleated osteoclasts have formed, and the calcium levels in mature osteoclasts are again stable over time. The regulation of intracellular calcium depends on the action of membrane channels that allow calcium entry from extracellular space, and intracellular signaling pathways resulting in activation of phospholipase C (PLC)γ, formation of short-leaved messenger inositol trisphosphate (IP3), and release of calcium from intracellular stores. We have collected experimental measurements of changes in calcium over differentiation time and the effects of different inhibitors on calcium signaling and the osteoclastogenic outcome. We envision the development of a mathematical model that would take into account the function of different regulators of calcium levels in differentiating osteoclast precursors and would suggest the potential mechanism underlying the development of the observed fluctuations.

Background literature

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