

Bone Resorption by Osteoclasts: Molecular Mechanism of Pyk2 dephosphorylation by Dynamin

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Osteoporosis is a bone disease that affects hundreds of millions of people worldwide and is characterized by low bone mass and structural deterioration of bone tissue which increases the risk of bone fracture, frailty, morbidity and mortality. Excessive bone loss is caused by osteoclasts which degrade the organic and inorganic components of bone. The specific aim of this study is to identify and characterize the signaling proteins in osteoclasts that are responsible for the bone resorbing activity of these cells.

The non-receptor tyrosine kinase, Pyk2, is highly expressed in osteoclasts. Mice lacking Pyk2 have an increase in bone mass due to impairment in osteoclast function. It has been demonstrated that phosphorylation of Pyk2 at Y402 is very important for osteoclast spreading and bone resorption. Our group also reported that the GTPase dynamin controls osteoclast bone resorption in part by leading to the dephosphorylation of Pyk2, thus decreasing Pyk2's kinase activity. In the current study we examined the intracellular mechanism by which dynamin regulates Pyk2 dephosphorylation. Our findings demonstrated that Pyk2 dephosphorylation is predominately due to GTPase activity of dynamin since expression of dynamin mutants that have reduced affinity for GTP or exhibit defective GTPase activity resulted in an increase in Pyk2 Y402 phosphorylation. We also found that that Pyk2 phosphorylation was rescued in the presence of phenyl arsine oxide (PAO), a chemical inhibitor of tyrosine phosphatases and our preliminary results indicate that the tyrosine phosphatase PTP-PEST is involved in the dynamin-mediated dephosphorylation of Pyk2.

Understanding the intracellular mechanism that regulates osteoclast function may lead to the identification of novel proteins that can be targeted by anti-resorptive therapies to treat bone related diseases. Over the past few decades, bisphosphonates have played a significant role in the treatment of osteoporosis. Unfortunately, osteonecrosis of the jaw has been recently described as a harmful side effect of bisphosphonate therapy, emphasizing the need to develop alternative approaches to treat osteoporosis. Novel therapeutic approaches may one day involve inhibitors to tyrosine kinases such as Pyk2 or involve combination therapies where inhibitors are paired with bisphosphonates as a way to boost the efficacy of anti-resorptive therapies with fewer side-effects.