Farnesyl Pyrophosphate Synthase: Clinical Target for Bone Diseases

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Osteoporosis affects one in three women and one in five men over the age of 50. Bisphosphonate therapy, which inhibits bone resorption, reduces the risk of fracture by 50% within one year.

Nitrogen-containing bisphosphonates are known inhibitors of farnesyl pyrophosphate synthase (FPPS) and are currently used to treat osteoporosis, Paget's disease of the bone, and malignant bone tumors. FPPS resides at a branchpoint of the isoprenoid pathway due to the fact that the farnesyl pyrophosphate product can undergo either chain-elongation or cyclization, or may be utilized for protein prenylation. Since the post-translational addition of a farnesyl moiety is essential to activate many intracellular signaling proteins, inhibition of FPPS leads to apoptosis. Why some nitrogen-containing bisphosphonates are more potent inhibitors, and hence more effective drugs, is poorly understood.

The structure of human pyrophosphate synthase in complex with magnesium and the bisphosphonate risedronate shows the binding mode for this important class of inhibitors. Risedronate occupies the chain-elongation site but not the isopentenyl pyrophosphate site. Two aspartate clusters chelate the magnesiums that mediate ligand binding and are involved in catalysis. Although predictions suggested two inhibitors binding to each protein chain, isothermal titration calorimetry and the crystal structure clearly indicate a one-to-one stoichiometry.

Since this is the first example of a mammalian FPPS, it will provide the basis for more accurate structure-assisted drug design.

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