Poster Presentation

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Crystal structures of hFPPS in complex with novel anticancer drug leads

J. Park[1], C. Leung[2], Y. Lin[2], J. De Schutter[2], Y. Tsantrizos[2], A. Berghuis[1]

[1]McGill University, Department of Biochemistry, Montreal, Canada, [2]McGill University, Department of Chemistry, Montreal, Canada

Human farnesyl pyrophosphate synthase (hFPPS) produces farnesyl pyrophosphate, an isoprenoid required for a variety of essential cellular processes. Inhibition of hFPPS has been well established as the mechanism of action of the nitrogen-containing bisphosphonate (N-BP) drugs, currently best known for their anti-bone resorptive effects. Recent investigations indicate that hFPPS inhibition also produces potent anticancer effects both in vitro and vivo: N-BPs inhibit proliferation, motility, and viability of tumor cells, and act in synergy with other anticancer agents [1,2]. However, the physicochemical properties of the current N-BP drugs seriously compromise their full anticancer potential in non-skeletal tissues. They show poor membrane permeability and extreme affinity to bone, due mainly to their highly charged bisphosphonate moiety, which mimics the pyrophosphate of the substrates of hFPPS. Both the substrates and N-BPs bind to hFPPS via Mg ion-mediated interactions between their pyrophosphate/bisphosphonate moiety and two aspartate-rich surfaces of the enzyme's active site cavity. Recently, we took a structure-guided approach to develop bisphosphonates with higher lipophilicity for enhanced uptake into non-skeletal tissues. Surprisingly, some of the new compounds were found to bind to hFPPS even in the absence of Mg ions. Crystal structures of hFPPS in complex with a representative compound revealed that this bisphosphonate binds to the enzyme's active site in the presence of Mg ions, but also to a nearby allosteric inhibitory site in their absence. Furthermore, removal of a phosphonate group from the bisphosphonate moiety of this compound resulted in an inhibitor that binds exclusively to the allosteric site. Based on the crystal structures with these lead compounds, we generated of a novel class of non-bisphosphonate, allosteric inhibitors of hFPPS with superior physicochemical properties than those of the current N-BP drugs for broader tissue distribution.

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