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Structure and inhibitor design in integral membrane pyrophosphatases

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Pyrophosphatases (PPases), found in all organisms, are essential enzymes, providing the thermodynamic "pull" such as DNA synthesis by hydrolysing pyrophosphate. A key question in these – as in all enzymes – is their exact structural mechanism. This requires fleshing out static structures into a dynamic picture of enzyme motion. Membrane-bound pyrophosphatases(mPPases), which couple H+/Na+ transport to pyrophosphate synthesis/hydrolysis, are important in the infectivity of protozoan parasites. M-PPases have a unique structure with an alternate-access ion pumping mechanism (1). In this present research the work will be described that led to a thorough model for the mechanism of mPPases and how it differs from other inorganic pyrophosphatases. How three new mPPase structures in different catalytic states indicate that closure of the substrate-binding pocket by helices 5-6 affects helix 13 in the dimer interface, which suggests a possible allosteric mechanism shall be discussed. The closure also leads to a downward motion of helix 12, which springs a "molecular mousetrap", repositioning a conserved aspartate and activating the nucleophilic water (3). Corkscrew motion at helices 6 and 16 rearranges the key ionic gate residues and leads to ion pumping. The structures, the implied position of the pumped ions in those structures, as well as electrometric data, allow us to propose a full catalytic "binding-change" model, where binding causes pumping, which in turn causes hydrolysis. This model has recently been validated and extended by molecular dynamics (4). Finally, our efforts towards developing novel mPPase inhibitors that can kill protozoan parasites (unpubl) shall be discussed.

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