S27-5 A Novel Ratchet Mechanism of Gastric H^+,K^+-ATPase Revealed by Cryo-Electron Microscopy

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Acid secretion by the stomach results in a pH of about 1. This highly acidic environment is essential for digestion and also acts as a first barrier against bacterial and viral infections. Conversely, too much acid secretion causes gastric ulcer. The mechanism by which this massive proton gradient is generated is of considerable biomedical interest. Here, we propose the first molecular model for this remarkable biological phenomenon, based on the 3D structure of the gastric H^+,K^+-ATPase (proton pump).

The structure of H^+,K^+-ATPase at 6.5 Å resolution was determined by electron crystallography of two-dimensional crystals. The structure shows the catalytic α-subunit and the non-catalytic β-subunit in a pseudo-E_2P conformation. Different from other P-type ATPases, the N-terminal tail of the β-subunit is in direct contact with the phosphorylation domain of the α-subunit. This interaction may hold the phosphorylation domain in place, thus stabilizing the enzyme conformation and preventing the reverse reaction of the transport cycle. Indeed, truncation of the β-subunit N-terminus allowed the reverse reaction to occur. These results suggest that the β-subunit N-terminus functions as a “ratchet”, preventing inefficient ion transport or reverse-flow of protons and thereby enabling the H^+,K^+-ATPase to generate a large H^+ gradient.