Structural Biology and Chemistry of Histone Deacetylases in Human Disease and Drug Discovery

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Metal-dependent histone deacetylases (HDACs) catalyze the hydrolysis of acetyllysine side chains in histone and non-histone proteins to yield unmodified lysine side chains and acetate ions. Reversible lysine acetylation rivals phosphorylation in the regulation of protein structure and function, and the interruption of acetylation-deacetylation cycles through the administration of HDAC inhibitors is a validated approach for cancer chemotherapy.

HDAC6 is the cytosolic tubulin deacetylase that regulates microtubule dynamics; inhibition of HDAC6 results in hyperacetylation of α-tubulin, which suppresses microtubule dynamics and leads to cell cycle arrest and apoptosis. Isozyme-specific inhibitors of HDAC6 are therefore a high priority in the search for new therapies for cancer and other diseases. Our recently-determined HDAC6 structures reveal new insight on the mechanism of catalysis and inhibitor binding modes, including the binding of novel macrocyclic peptide inhibitors as well as chemically-reactive oxadiazole inhibitors. Notably, HDAC6 contains two catalytic domains, CD1 and CD2. Crystal structures interpreted in light of enzyme activity measurements reveal the identity of a "gatekeeper" responsible for the strict substrate specificity of CD1 and broad substrate specificity of CD2. Analysis of other isozymes indicates that the related class IIb enzyme HDAC10 contains an alternative gatekeeper residue that suppresses lysine deacetylase activity altogether. Instead, HDAC10 is the cytosolic polyamine deacetylase that functions in eukaryotic polyamine metabolism.