Histone Deacetylase 8: Metal Dependence and Reaction Mechanism

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Histone deacetylases (HDACs) are enzymes that play an important role in regulating gene expression by removing acetyl groups from acetylated lysine residues found in histone proteins and certain transcription factors. As such, HDACs are promising cancer therapeutic targets, with several inhibitors in phase I and II clinical trials.

Human histone deacetylase 8 (HDAC8) is a member of the class I HDAC family, which are metalloenzymes with a conserved catalytic core. HDAC8 has been recombinantly expressed in *E. coli*, and the metal dependence of the amide bond hydrolysis reaction catalyzed by HDAC8 has been studied. The metal stoichiometry of activation of apo HDAC8 indicates that HDAC8 is a mononuclear hydrolase enzyme, with the addition of more than one equivalent of zinc leading to inhibition. Substitution of HDAC8 with various transition metals showed the following trend in reactivity: Co(II) > Fe(II) > Zn(II) > Ni(II) > Mn(II) ≈ Fe(III). This metal preference suggests that the higher coordination number of Co(II) and Fe(II) may be important for transition state stabilization.

The proposed HDAC mechanism [1] contains aspects from both metalloprotease and serine protease enzymes. The catalytic metal is proposed to activate water for attack on the substrate amide bond, with His 142 serving as a general base to deprotonate the water. Tyr 306 and the metal ion are proposed to stabilize the tetrahedral intermediate, with His 143 then protonating the free amine leaving group. The role of the catalytic metal and the active site residues are being studied by pH dependence studies with metal substitution and mutagenesis.

[1] Finnin, M.S., Donigian, J.R., Cohen, A., Richon, V.M., Rifkind, R.A., Marks, P.A., Breslow, R., Pavletich, N.P., Nature, 401: 188-193 (1999).

(Supported by NIH grant RO1 GM40602 (to CAF) and NSF Predoctoral Fellowship (to SLG)).