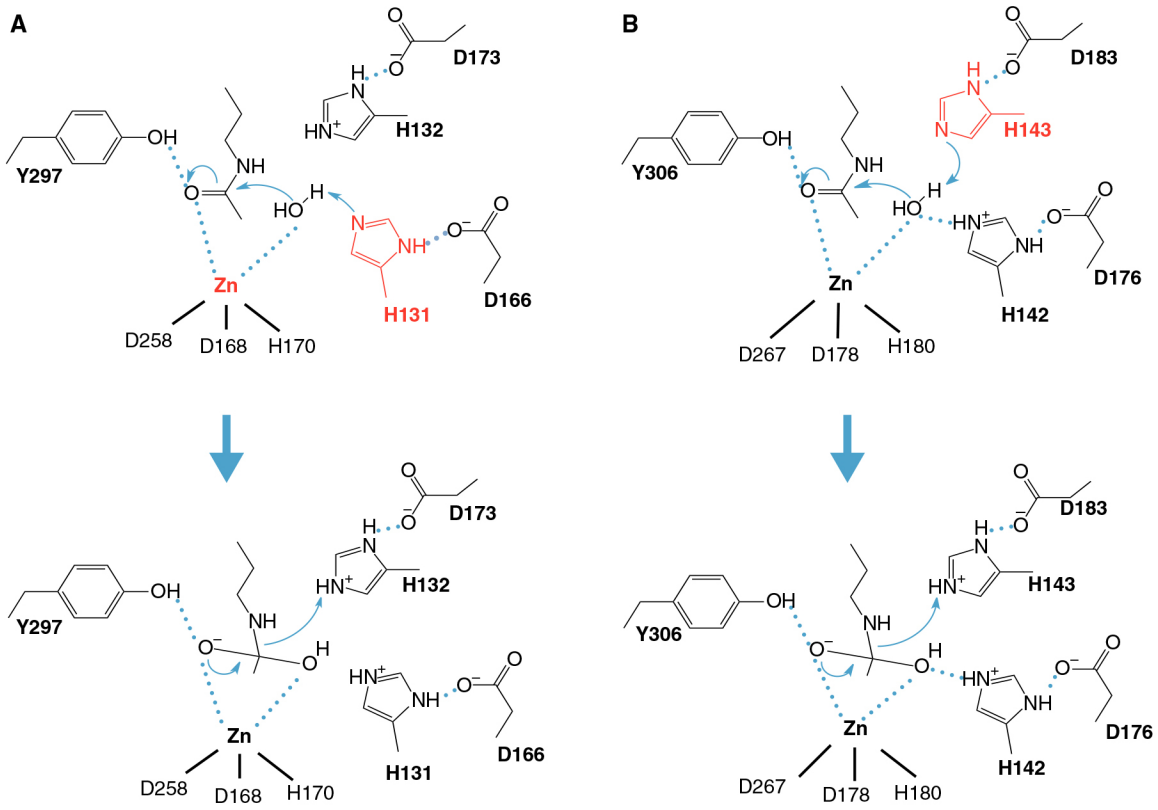

Figure 2. Catalytic mechanism of HDACs. Two models for the catalytic mechanism of the Zn-dependent HDAC reaction have been proposed. (*A*) A model proposed from the HDLP structure. The HDLP catalytic core consists of a tubular pocket, a zinc-binding site, and active-site residues (in bold) of a tyrosine (Y297) and two histidines (H131 and H132) that make hydrogen bonds to two aspartic acids (D166 and D173). One of these catalytic histidines (red) facilitates nucleophilic attack at the substrate carbonyl by activating a water molecule coordinated with the zinc ion. Initially, two tandem histidine residues (H131 and H132) were proposed to function as Asp-His charge relay systems, typical of serine proteases such as chymotrypsin and chymotrypsinogen in the enzyme reaction. The active site zinc ion is coordinated by three residues (two aspartic acids and one histidine). (*B*) A model proposed from the HDAC8 structure, in which the other histidine residue (red) plays an essential role in the electron transfer. Hydrogen bond interactions are drawn in dotted lines.