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Single-Molecule Electronic Measurements of the Dynamic Flexibility of Histone Deacetylases JAMES FROBERG, SEUNGYONG YOU, Dept. Physics, North Dakota State Univ., USA, JUNRU YU, Dept. Chemistry, North Dakota State Univ., USA, MANAS HALDAR, Dept. Pharm. Sci, North Dakota State Univ., USA, ABBAS SEDIGH, Dept. Chemistry, North Dakota State Univ., USA, SANKU MALLIK, Dept. Pharm. Sci., North Dakota State Univ., USA, D.K. SRIVASTAVA, Dept. Chemistry, North Dakota State Univ., USA, YONGKI CHOI, Dept. Physics, North Dakota State Univ., USA — Due to their involvement in epigenetic regulation, histone deacetylases (HDACs) have gained considerable interest in designing drugs for treatment of a variety of human diseases including cancers. Recently, we applied a label-free, electronic single-molecule nano-circuit technique to gain insight into the contribution of the dynamic flexibility in HDACs structure during the course of substrates/ ligands binding and catalysis. We observed that HDAC8 has two major (dynamically interconvertible) conformational states, "ground (catalytically unfavorable)" and "transition (catalytically favorable)". In addition, we found that its cognate substrates/ligands reciprocally catalyze the transition of the ground to the transition state conformation of HDAC8. Thus, we propose that both enzymes and their substrates/ligands serve as "catalysts" in facilitating the structural changes of each other and promoting the overall chemical transformation reaction. Such new information provides the potential for designing a new class of mechanism-based inhibitors and activators of HDAC8 for treating human diseases.

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