From Genes to Drug: Osteoporesis

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RUNX2/Cbfa1/PEBP2aA is a global regulator of osteogenesis and is crucial for regulating the expression of bone-specific genes. Runx2 is regulated by a number of signaling pathways, including the bone morphogenetic protein (BMPs) pathway. Genetic analysis revealed that Runx2 is degraded through Smurf-mediated ubiquitination and its activity is inhibited by HDAC4. However, the underlying molecular mechanisms are unknown. In this study, we show that BMP-2 signaling results in Runx2 acetylation, which inhibits Smurf1-mediated degradation of the protein. Runx2 acetylation is a dynamic process of acetylation and deacetylation mediated by p300 and HDACs, respectively. HDAC inhibition increased Runx2 acetylation, potentiated BMP-2-stimulated osteoblast differentiation. These results suggest that the level of Runx2 protein is controlled by dynamic equilibrium of acetylation, deacetylation and ubiquitination and thus identifies a new mechanism for Runx2 regulation by BMP-2. Because BMPs are of tremendous interest as therapeutic agents against bone diseases, our finding that enhancement of osteogenic activity of BMP-2 can be achieved by the pharmacological inhibition of HDAC has important therapeutic implications.