SY-III-1 RUNX3 AS A TARGET OF CANCER RESEARCH

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Genetic analyses of animals and humans have revealed that insufficient expression of RUNX3 gene expression is closely linked to the pathogenesis of various human diseases. Targeted deletion of Runx3 in mice was shown to induce hyperplasia of the gastric epithelium. In human, lower levels of RUNX3 expression due to a combination of hemizygous deletion of the gene and hypermethylation of the RUNX3 promoter region have been shown to be associated with development of cancers of the lung, colon, pancreas, liver, prostate, bile duct, breast, larynx, esophagus, endometrium, uterine cervix and testicular yolk sac. Here we report that acetylation and ubiquitination are important post-translational modifications of RUNX3 that affect its stability and activity. RUNX3 is a direct target of the acetyl transferase activity of p300. The p300-dependent acetylation protects RUNX3 from ubiquitin ligase Smurf-mediated degradation. The extent of acetylation is positively regulated by the TGF-b signaling pathway and decreased by HDAC activity. Our findings demonstrate that RUNX3 protein levels can be regulated by the acetylation and deacetylation of RUNX3, since these processes competitively control the ubiquitination-dependent degradation of these proteins. These observations reveal a new mechanism by which the RUNX3 proteins are regulated.

Key Words: P300, HDAC, Cancer, Acetylation, Ubiquitination