Versatility of Protein Acetylation in Tumorigenesis

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Arrest defective 1 (ARD1) was originally identified to catalyze NH_2-terminal α-acetylation in yeast. Subsequently, we revealed that mammalian ARD1 catalyzed also ε-lysine acetylation of many proteins to regulate their cellular functions related with tumorigenesis. First, we found that ARD1 acetylated lysine residue 532 (K532) of HIF-1α to stimulate its proteosomal degradation, thus played an important role in the inhibition of tumor angiogenesis. After that, we also identified several isoform of ARD1, including mARD1^{225}, mARD1^{235}, and hARD1^{235}, and characterized different cellular functions of isoforms. While mARD1^{225} inhibited tumor angiogenesis by HIF-1α acetylation, mARD1^{235} and hARD1^{235} did not acetylate HIF-1α and had no effect on tumor angiogenesis. Instead, mARD1^{235} and hARD1^{235} stimulated the proliferation of cancer cells by β-catenin acetylation. In addition, we recently identified new function of ARD1 related with chemoresistance. We found that hARD1^{235} acetylated lysine residue 77 (K77) of Hsp70, which is a chaperone protein maintaining cellular homeostasis in response to cellular stress. hARD1^{235}-mediated Hsp70 acetylation regulated the chaperone functions of Hsp70, thus protected cancer cells against cellular stress, such as anti-cancer drug. Interestingly, although ARD1 isoforms differentially regulated tumor angiogenesis, tumor growth and chemoresistnace in an isoform-specific manner, they had a common regulatory mechanism which stimulated their enzymatic activity, called autoacetylation. We found that ARD1 acetylated itself at lysine residue 136 (K136), and this was essential for its acetyltransferase enzyme activity. Thus, when we inhibited K136 autoacetylation of ARD1, diverse roles of ARD1 in angiogenesis, proliferation, and chemoresistance were negatively controlled. Taken together, we suggest that ARD1 is a novel target molecule for cancer therapy and inhibition of ARD1 autoacetylation is a potential way to control diverse functions of ARD1 in tumoirgenesis.