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Identification of anti-apoptotic AREL1 E3 ubiquitin ligase as a novel oncogene that promotes tumor angiogenesis via HIF-1

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We previously reported the anti-apoptosis functions of a novel anti-apoptotic E3 ubiquitin ligase, AREL1, which ubiquitinates and promotes the proteasome-dependent degradation of cytosolic forms of IAP antagonists. In the present study, we identified AREL1 as an oncogene that targets PHD2. Elevated expression of AREL1 was detected in 65% of randomly selected human lung and colon cancer cell lines and also found in 42% of 424 human tumor tissues. Furthermore, AREL1-trangenic mice enhanced chemical-induced carcinogenesis as compared to wild-type ones. The oncogenic function of AREL1 led us to screen AREL1 target proteins involving in oncogenesis. PHD2, which regulates angiogenesis and tumor development, was identified as an AREL1-interacting protein from a yeast two-hybrid screen. PHD2 was down-regulated by AREL1. This down-regulation was blocked by either a potent proteasome inhibitor, MG132 or expression of an E3 activity-deficient mutant form of AREL1, AREL1-A790A. Taken together with that ubiquitination of endogenous PHD2 was enhanced by AREL1, these results indicate that AREL1 ubiquitinates and promotes a proteasome-dependent degradation of PHD2. Tumor angiogenesis of xenograft of AREL1-expressing cells was enhanced in association with down-regulation of PHD2 and up-regulation of HIF-1. Furthermore, endothelial cell tube formation assay revealed enhanced release of pro-angiogenic factors from AREL1-expressing cells. Therefore, these results suggest that elevated expression of AREL1 contributes to tumorigenesis through targeting PHD2 as well as IAP antagonists, thus blocking apoptosis and enhancing angiogenesis.

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