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Abstract

Expression of the UBE4B ubiquitin ligase is associated with neuroblastoma patient outcomes, but the functional roles of UBE4B in neuroblastoma pathogenesis are not known. We evaluated interactions of UBE4B with the E3 ubiquitin ligase ITCH/AIP4 and the effects of UBE4B expression on Ku70, c-FLIPL, and p53 ubiquitination and proteasomal degradation by co-immunoprecipitation and Western blots. We also evaluated the role of UBE4B in apoptosis induced by HDAC inhibition in our neuroblastoma cell lines model using Western blots. UBE4B was found in a complex with ITCH, with binding mediated by WW domains in the ITCH protein. ITCH activation led to ITCH-UBE4B E3-E4 ubiquitin ligase complex formation and recruitment of Ku70 and c-FLIPL via ITCH WW domains, followed by Ku70 and c-FLIPL Lys48/Lys63 branched polyubiquitination and proteasomal degradation. Histone deacetylase (HDAC) inhibition induced Ku70 and c-FLIPL acetylation, leading to release of c-FLIPL and Bax from Ku70, increased Ku70 and c-FLIPL Lys48/Lys63 branched polyubiquitination via the ITCH-UBE4B complex, and induction of apoptosis. UBE4B depletion in our neuroblastoma cell lines model led to reduced polyubiquitination and increased levels of Ku70 and c-FLIPL proteins leading to the massive reduction of apoptosis induced by HDAC inhibition via stabilization of Ku70 and c-FLIPL proteins allowing the inhibition of the full caspase 8 activation. Our results have identified novel

interactions and novel targets for UBE4B ubiquitin ligase activity and a direct role of the ITCH-UBE4B complex in responses of neuroblastoma cells to HDAC inhibition, suggesting that the ITCH-UBE4B complex plays a critical role in responses of neuroblastoma to therapy and suggesting a potential mechanism underlying the association of UBE4B expression with neuroblastoma patient outcomes.

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