A Ubiquitin conjugation enzyme variant, Uev1A, activates NK-κB and prevents stress-induced apoptosis in mammalian cells.

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Post-translational modification via Gly76-Lys63 poly-ubiquitination allows target proteins to participate in diverse cellular functions. Poly-ubiquitinchains linked to proteins via Lys63 of ubiquitin requires a unique ubiquitin-conjugating enzyme composed of Ubc13 and a Ubc enzyme variant (UEV). Mammalian cells contain at least two such enzyme proteins, namely Mms2 and Uev1. While Mms2 is known to play a role in DNA post-replication repair, the precise function of Uev1 is currently unclear. *Uev1* was isolated by its ability to trans-activate the c-fos promoter and by two independent mRNA differential display screens. *UEV1* transcript level has been shown to be down-regulated in HT-29-M colon cells undergoing chemical-induced differentiation. We have previously shown that Uev1 is up-regulated in all tumor cell lines examined and when SV40-transformed human embryonic kidney cells undergo immortalization. *Uev1* is mapped to chromosome 20q13.2, a region where DNA amplification is frequently reported in cancer pathogenesis. The above evidence implicates *UEV1* as a putative proto-oncogene. The Ubc13-Uev1 heterodimer was also isolated during the study of the TRAF6 signalling pathway and is indeed required for the TRAF6-mediated activation of the IκB kinase complex by poly-ubiquitination of NEMO/IKKγ, a regulatory subunit of IκB kinase in the NF-κB signalling pathway. Here we show that constitutive high-level expression of UEV1A alone in cultured human cells was sufficient to cause an increase in NF-κB activity and that this effect was reversible upon suppression of UEV1. Over-expression of UEV1A conferred prolonged cell survival upon serum-deprived conditions, and protected cells against stress-induced apoptosis. Taken together, these observations present convincing evidence thatUev1A is a critical regulatory component in the NF-κB signalling pathway in response to environmental stresses and identifies *Uev1A* as a potential proto-oncogene. Further studies will be undertaken to elucidate the precise biochemical function of Uev1 in the above processes.