Two Ubiquitin-conjugating enzymes complexes ubc13-Mms2 and Ubc13-uev1A function in different signaling pathways.

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The ubiquitin--conjugating complexes Ubc13-Mms2 is required for the Lys63-linked poly-ubiquitination of proliferating cell nuclear antigen (PCNA) and is involved in the error-free pathway of DNA post-replication repair in yeast. The high degree of genetic conservation throughout eukaryotes suggests that similar genes in mammalian cells may function in DNA repair as well. However, human cells contain two homologues with over 90% amino acid sequence identity, namely hMms2, whose function is largely unknown, and Uev1 (with two isoforms, Uev1A and Uev1B), which is a candidate proto-oncogene and is implicated in TRAF-mediated activation of IκB kinase complex in the NF-κB signaling pathway. In this study, we demonstrate by the yeast two-hybrid analysis and GST pull-down that Ubc13 forms distinct complexes with Mms2 and Uev1A, but not Uev1B. Immunocytochemical analyses with specific antibodies and myc-tagged constructs indicate that the Ubc13-Mms2 complex forms DNA damage-induced recombinational repair nuclear foci. In contrast, Uev1A is often concentrated to the nucleus and Uev1B is excluded from the nucleus regardless of the DNA damage treatment, and they do not form DNA damaged-induced nuclear foci. Experimental reduction of gene expression using interference RNA technology targeting either Ubc13 or Mms2, but not Uev1A, resulted in a significant increase in the RAD51 nuclear foci formation, indicating the accumulation of spontaneous DNA strand breaks in the absence of functional Ubc13-Mms2 complex. These observations are consistent with a hypothesis that, like its yeast counterpart, the mammalian Ubc13-Mms2 complex is involved in DNA post-replication repair to protect genome integrity, whereas the Ubc13-Uev1A complex promotes stress-induced NF-κB activation and tumorigenesis. Hence, competition between the two distinct ubiquitin-conjugating complexes may govern how cells respond to environmental stresses.