Involvment of a ubiquitination complex Ubc13-Mms2 in DNA damage tolerance.

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We previously reported the isolation of the first ubiquitin (Ub) conjugating enzyme variant (Uev), Mms2, from yeast and its involvement in DNA repair. Mms2 forms a stable complex with a ubiquitin conjugating enzyme Ubc13 that is required for the poly-Ub modification of PCNA via a non-canonical Lys63 chain. We subsequently isolated two Uevs, Mms2 and Uev1, from mammalian cells, which share >90% amino acid sequence identity in the core region, and showed that both are able to interact with Ubc13. However, Mms2 and Uev1 have distinct cellular functions and only the Mms-Ubc13 is involved in DNA damage tolerance. Mms2 and Ubc13 co-localize to DNA damage induced nuclear foci containing PCNA and newly synthesized DNA. Cells lacking the Mms2-Ubc13 activity display severe genomic instability and rely on mutagenic polymerases such as polζ to survive in the presence of DNA damage, which also will lead to cancer and other genetic diseases. We also generated mouse embryonic stem cell lines defective Mms2 and found that their phenotypes are reminiscent of the yeast *mms2* mutant. These studies collectively confirm that the Ubc13-Mms2 mediated DNA damage tolerance function is highly conserved, from yeast to human cells.