Cellular stress responses regulated by two ubiquitin-conjugating enzyme variants.

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When cells face environmental stresses such as bacterial and viral infections, they activate pro-survival and anti-apoptotic pathways to enhance proliferation of defending cells. On the other hand, stresses that cause DNA damage activate cell-cycle checkpoints and induce apoptosis when the damage cannot be repaired. A central question is how cells detect different types of environmental stresses and make the correct response.

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 Lys-63 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. The Mms2-Ubc13 complex plays a central role in an error-free DNA post-replication repair (PRR) characteristic of its yeast counterpart. Cells lacking the Mms2-Ubc13 activity display severe genomic instability and rely on mutagenic polymerases to survive in the presence of DNA damage, which will lead to cancer and other genetic diseases. On the other hand, the Uev1-Ubc13 complex is not required for DNA repair, but is essential for bacterim and virus induced activation of the NF-κB signal transduction pathway. More specifically, Uev1-Ubc13 is required for the Lys63-linked pol-ubiquitination of NEMO/IKKγ. In contrast, Mms2 is not involved in the NF-κB activation. Based on the above observations, we propose that mammalian Uevs are the regulatory subunits of Ubc13-mediated Lys63-linked poly-ubiquitination of target proteins and play critical roles in directing the Uev-Ubc13 complex to two distinct cellular pathways, namely the DNA repair pathway (by targeting PCNA) to deal with genotoxic stress and the NF-κB pathway (by targeting NEMO) in response to non-genomic stresses such as bacterial or viral infection.