Role of the Ku complex in the DNA damage response

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Abstract:
DNA double-strand breaks (DSBs) are highly cytotoxic lesions that must be repaired to avoid loss of genetic information or chromosome rearrangements. Eukaryotic cells can repair DSBs by two main mechanisms: non-homologous end-joining (NHEJ) and homologous recombination (HR).

The Ku70-Ku80 heterodimer allows DSB repair by NHEJ and protects the DSB ends from degradation by preventing the access of Exo1. Consequently, deletion of Ku partially suppresses in an Exo1-dependent manner both the sensitivity to camptothecin and methyl methanesulfonate and the resection defect of cells lacking Sae2, a protein involved in early steps of DSB processing. However, the lack of Ku does not rescue the sensitivity to phleomycin of *sae2Δ* cells.

To understand if different Ku functions are involved in the DNA damage response, we searched for *ku70* mutations that restored resistance of cells lacking Sae2 not only on camptothecin but also on phleomycin. We identified some *ku70* alleles, whose mutations are located on an outer face at the N-terminus of Ku70 protein, suggesting that they can alter protein-protein interactions. The characterization of one of them shows that this allele suppresses the end-tethering defect of *sae2Δ* cells in an MRX-independent manner.

This finding, together with the observation that the lack of Ku70 impairs end-tethering, suggests a role for the Ku complex in maintaining the DSB ends tethered to each other. We are currently investigating the role of the Ku complex in this mechanism, as well as possible regulators of this function.