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The role of the Ku complex in the DNA damage response

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Keywords:
Ku complex, double-strand breaks, end-tethering, DNA damage response, *S. cerevisiae.*

Abstract:
DNA double-strand breaks (DSBs) are highly cytotoxic lesions that can form accidentally during DNA replication or upon exposure to genotoxic agents. DSBs must be repaired to avoid loss of genetic information or chromosome rearrangements[1]. Eukaryotic cells can repair DSBs by two main mechanisms: non-homologous end-joining (NHEJ) and homologous recombination (HR). The Ku70-80 heterodimer is rapidly recruited to DNA ends and is involved in these two DSB repair mechanisms[2]. To better understand the role of this complex in DSB repair, we searched for *ku70* mutations that suppress the hypersensitivity to DNA damaging agents of cells lacking Sae2, a protein involved in early steps of DSB processing. We identified some *ku70* alleles that restore DNA damage resistance of *sae2Δ* cells. All the 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 these Ku70 mutant variants shows an increase of Ku70 association at DSBs and a suppression of the end-tethering defect of *sae2Δ* cells. The high degree of tethering activity by this *ku70* mutation can explain the suppression of DNA damage sensitivity of *sae2Δ* cells and suggests a role of the Ku complex in maintaining the DSB end closed to each other.

References

1. Liu P., Carvalho C. M., Hastings P. J. and Lupski J. R. (2012). *Curr. Opin. Genet. Dev.*, **22**, 211-220
2. Bonetti D., Colombo C. V., Clerici M. and Longhese M. P. (2018). *Front. Genet.*, 9:390