The role of ACRC/GCNA in the repair of DNA-protein crosslinks.

P-02.3-23

C. Supina[I], I. Anticevic[I], J. Loncar[I], M. Popovic[I]

[I]Ruder Boškovic Institute, Division for Marine and Environmental Research, Laboratory for molecular ecotoxicology, Zagreb, Croatia

DNA-protein crosslinks (DPCs) are DNA lesions which occur when a protein becomes irreversibly covalently linked to DNA. DPC formation is very common in cells, as it can arise from both endogenous (aldehydes and reactive oxygen species) and exogenous sources (ionizing radiation, UV, chemotherapeutics). Due to their bulky nature, DPCs impair all DNA transactions (replication, transcription, and repair). They have adverse effects on the organismal level including cancer, premature aging, and neurodegenerative diseases. Several groups have identified a novel proteases, Wss1 in yeast and SPRTN in higher eukaryotes, which initiate the removal of DPCs through the proteolytic digestion of crosslinked proteins. Considering that they are a common type of DNA damage, a second potential DPC protease in higher eukaryotes might exist. Phylogenetic analysis of the SPRT family in metazoans identified a SPRT-like protein family, ACRC (acidic repeat containing). In line with the phylogenetic proximity, the 3D structure of the protease core within the Sprt domain of ACRC is very similar to that of SPRTN. The goal of our study is to determine if ACRC is proteolytically active and what is its relation to SPRTN, using zebrafish model and CRISPR/Cas9 gene manipulation. To address the role of ACRC in vivo we introduced mutation in the ACRC putative protease active site (E451 deletion) with the aim of creating an enzymatic dead version of ACRC. We also compared both proteases using phylogenetic and syntenic analysis and in regard to mRNA and protein expression across different tissues in zebrafish. Our study will reveal actual contribution of ACRC to the DPC removal on the organismal level.