RESEARCH

Department of Life Sciences, University of Trieste
Laboratory for non-coding RNA and Genome Stability – Prof. Schoeftner
https://dsv.units. it/it/research/researchareas/researchgroups/20382
Contract type: CoCoCo
Minimum requirement for applicants: Master of Science (Laurea Magistrale)

Title of project: Targeting R-loop resolution machineries as novel therapeutic strategy in human cancer

Background:
R-loops are atypical, three-stranded nucleic acid structures that contain a 60-2000 nucleotide stretch of RNA:DNA hybrid sequences and an unpaired, single stranded DNA. R-loops are reported to encompass up to 5% of the human genome and control physiologically relevant processes. However, un-programmed or persistent R-loops represent a high risk for genome stability by mediating conflicts between transcription and replication, interfering with DNA repair mechanism and become target for mutagenesis. Consequently, multiple mechanisms exist that prevent the formation of R-loops or resolve R-loops.
R-loop mediated genome instability is reported to drive tumor formation and progression and acquisition of therapy resistance is paralleled by an improvement of R-loop management to compensate the genotoxic effect of chemotherapeutic agents.
We found that the RNA-binding protein SFPQ specifically binds R-loop structures in repetitive DNA and recruits an enzymatic complex that resolves R-loops to suppress genome instability and aberrant activation of the cGAS/STING pathway that is reported to modify the tumor-microenvironment (submitted to Molecular Cell).
Consequently, targeting this protein-protein interaction is expected to result in the induction of exacerbated genome instability leading to cancer cell death and/or the production of a tumor-suppressive TME.

Project activity:
We successfully mapped the protein domain of SFPQ responsible for the recruitment of DAXX. Future experiments will focus on the structural analysis of relevant protein domains and the design of small peptides that are able to act as competitors of the SFPQ-DAXX interaction. Potentially functional peptides will be tested for their capacity to induce R-loop formation, alterations in chromatin structure of repetitive elements and activation of the cGAS/STING pathways using preclinical model systems. The impact of these peptides or SFPQ depletion on the sensitivity to therapeutic treatment will be evaluated

Methods:
Structural analysis (collaboration), immunoprecipitation (protein, chromatin), R-loop methodology, binding competition assays, recombinant protein production, protein pull-down experiments, immunofluorescence, DNA-FISH, RNA-FISH, cell culture

Applicant requirements:
Applicants should hold a Master degree or PhD degree in the field of molecular or cell biology or related scientific fields. Experience in the listed methods represents and advantage. Contract type: CoCoCo, up to 12 months; Start date: July/August/September
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