3-year PhD position funded by CEA

Novel mechanisms to understand rare diseases: the Mediator complex of transcription regulation in DNA repair

Keywords: *DNA repair, transcriptional regulation, Mediator complex, Mediatorpathies, budding yeast, human cells, Cockayne syndrome, functional genomics, genetics*

Location

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Start date of the thesis: 01/10/2022

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Summary of thesis project

Transcription and DNA repair are fundamental functions of the cell, tightly regulated and coordinated. Dysfunctions of these processes are the basis of severe pathologies. The Mediator of transcriptional regulation is an essential and conserved multisubunit coactivator complex. Mutations in human Mediator subunits lead to neurodevelopmental, cardiovascular, behavioural disorders and cancers. Moreover, we discovered a novel function of Mediator complex connecting transcription and nucleotide-excision DNA repair (NER). However, many questions remain to be answered on the molecular mechanisms of Mediator function and their implication in human pathologies. Mutations in NER genes lead to rare genetic diseases including Xeroderma pigmentosum and Cockayne syndrome. New variants in Mediator subunits including MED20 were recently uncovered in patients with neurological and developmental symptoms closely related to transcription-coupled repair disorders named Mediatorpathies, providing a clinical perspective of our findings.

In this project, we intent to decipher the molecular mechanisms of Mediator function linking transcription and DNA repair and use this fundamental knowledge to provide a molecular basis of newly identified pathological variants, focusing on MED20. We aim to decipher how the physical interactions between Mediator and DNA repair components in yeast and human cells contribute to the functional interplay between transcription and DNA repair and how Mediator dysfunctions lead to genetic disorders, applying functional genomics, molecular biology, biochemistry, yeast genetics, human cell biology and bioinformatics. The project will reinforce the links with clinical research and the NGS data analysis. It should form a fundamental biology basis, supporting innovative research in genome biology and contributing to technologies for the future medicine. Expected results will open new exciting perspectives for the mechanisms connecting transcription and DNA repair and will have a deep impact on our understanding of fundamental chromatin processes and their dysfunctions in human diseases.

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