Lopes Lab

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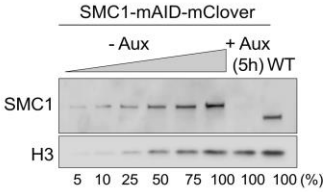
IMCR INSTITUTE OF MOLECULAR CANCER RESEARCH

MSc Thesis

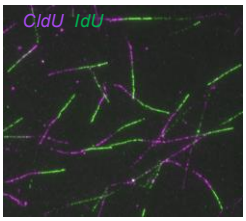
Understanding the role of genome organization in the replication stress response

Background: Approximately 3 billion base pairs are accurately duplicated in the human genome during the S phase. Cells in the body are exposed to tens of thousands of DNA lesions per day, and they often interfere with replication forks triggering their slowdown or eventually stopping DNA synthesis. This leads to a situation called replication stress (RS), which is commonly induced by cancer chemotherapeutic agents. Cells have evolved a response to RS that ensures proper stabilization and re-initiation of replication forks preventing genomic instability. Although there has been a significant progress in our understanding of the RS response in recent years, very little is known about how it is influenced by 3D chromatin folding.

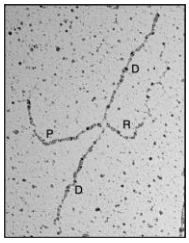
The genome is organized in the nuclei in a tightly-regulated manner, where linearly distant genomic regions are brought together to regulate for instance gene expression. The cohesin complex, which organizes 3D chromatin folding, has been shown to participate in the RS response through yet-elusive mechanisms. Importantly, the cohesin complex is one of the 12 most mutated complexes in cancer. The aim of this project is to characterize the role of cohesin complex subunits and their cancer associated mutations in the RS response in cancer-relevant contexts.



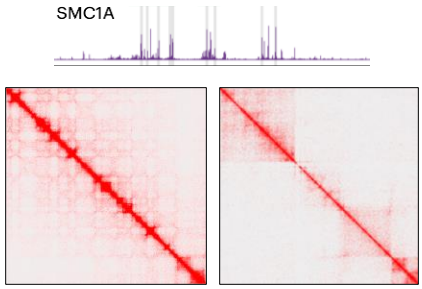
1. Auxin inducible degron of SMC1 cohesin subunit where SMC1 can be depleted by a short 5h treatment with Auxin. (Lopes lab)



2. Replication forks observed by DNA fiber assays (Lopes lab)



3. Architecture of a reversed replication fork. P, parental strand; D, daughter strands; R, reversed arm (Schmid et al. Mol Cell, 2018)



4. CUT&TAG profile of genomic occupation of SMC1 subunit (top) and Micro-C 3D genome maps of different regions (bottom)

Techniques: The student will generate and make use of state-of-the-art technology to induce protein degradation in human cell lines containing Auxin-inducible degrons (AID) for cohesin subunits and their replacement with cancer-mutated versions (**1**). In this project, the student will use flow cytometry, immunofluorescence - including proximity-ligation assay - biochemical techniques (chromatin fractionation and WB), single-molecule analysis of DNA replication fork progression (DNA fibers; **2**) and architecture (electron microscopy; **3**). Moreover, the student will have the opportunity to perform and learn genome-wide profiling techniques such as CUT&TAG and 3D genome contact maps by Micro-C (**4**)

Team: We are looking for a highly-motivated student to join a group of enthusiastic researchers, working on diverse aspects of RS. The student will be supervised by Daniel González Acosta, Postdoc in the lab.

Starting date: End 2025 – Beginning 2026 (Negotiable).

Interested candidates should send their CV and a brief motivational letter to lopes@imcr.uzh.ch and gonzalez@imcr.uzh.ch