M2 Internship: Reconstruction of Gene Regulatory Networks to Predict Cell Trajectories within the Ovarian Follicle

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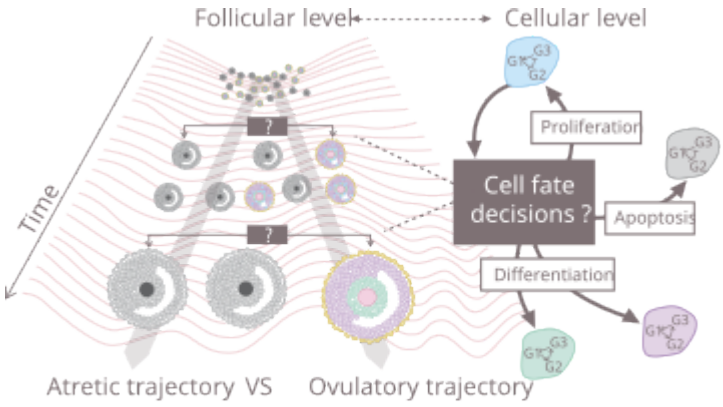
Scientific Background

Ovarian follicles are complex multicellular structures that house mammalian female germ cells. In each ovarian cycle, a cohort of follicles grows; only a limited number reach ovulation, while the majority degenerate through a process known as atresia. The molecular and cellular mechanisms dictating these divergent trajectories remain largely unknown [1].

In mice, the ovarian follicle displays notable variations in size and cellular dynamics, with somatic cell populations ranging from a few hundred (secondary stage) to hundreds of thousands (ovulatory stage), and diameters increasing from $\sim$150 μm to $\sim$500 μm. Two main fates are observed: selection for ovulation or atresia. These can be distinguished by different cellular states, which are often identified only at late stages by morphological cues (size, cell number, nuclear pyknosis).

Recent advances in single-cell and spatial omics approaches have enabled fine molecular characterization of the follicle at different stages, revealing intermediate states and differentiation trajectories. Nonetheless, early identification of dominant follicles remains out of reach, and the mechanisms regulating somatic cell populations are still unclear.



GRN and cell fate decision explains follicle trajectories

Internship Objectives

This internship aims to reconstruct gene regulatory networks (GRN) explaining the different trajectories of ovarian follicles, using scRNA-seq and spatial transcriptomic data from recent studies [2, 3, 4, 5, 9]. The molecular states of ovarian follicles will be analyzed at multiple stages of ovulatory or atretic trajectories, enabling the inference of bifurcation points and early predictive markers.

A previous internship have already reviewed and integrated several datasets [2, 4, 3, 5] and performed preprocessing and fine annotation of cell states (marker identification, cell classification). Inference of GRN will use generative models such as CardamomOT [6], leveraging expression variability and transcription dynamics. We will use as main data size-dependant follicle trajectories that can be reconstructed from spatial transcriptomics using image segmentation to obtain single-follicle scRNAseq snapshots data. The GRN inference will proceed with a careful choice of gene and follicle panel, and will involve several biologically informed validation steps. If time allows it, we will consider spatial extension of GRN inference methods to enforce cell trajectories within follicle trajectories.

Highly motivated students are required, with skills in mathematical modeling, scientific computing, statistics and/or bioinformatic, to use several tools from the scverse ecosystem (Python) and dedicated software for gene regulatory networks (GRN) inference [6, 7, 8].

References

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