LEVELS OF CELL FATE REGULATION (FATELEVELS)

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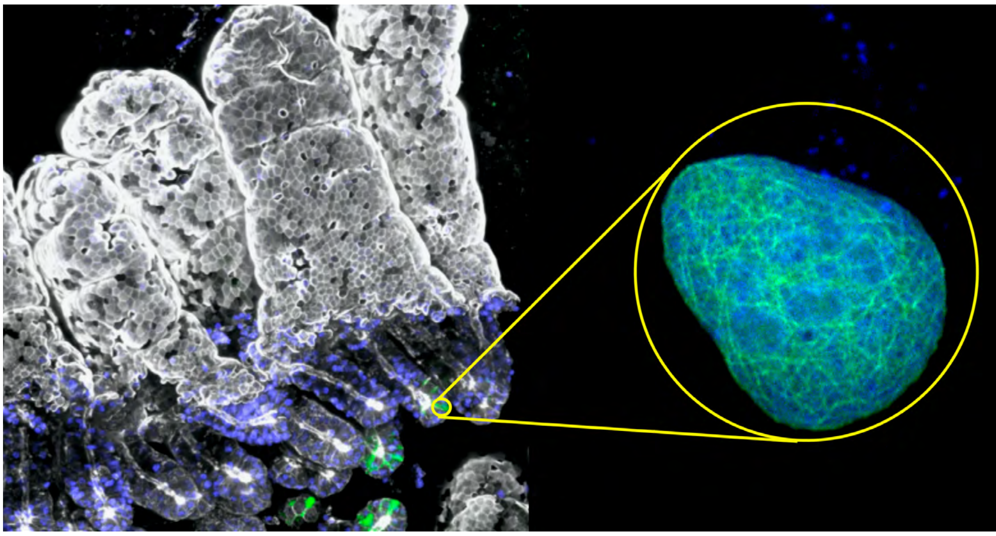

Intestinal epithelium (left) renews constantly and adapts to alterations in food availability. Stem cells (green) receive many cues from their surroundings. Such external cues are transmitted inside the cell via signaling networks that ultimately coalesce on the level of gene regulation including the nuclear organisation (left).

Our tissues must maintain functions despite the challenges posed by continuous changes for example in food availability and composition. Stem cells balance current tissue function and future renewal by producing either more stem cells, or functional cells by differentiation. These cell fate decisions must integrate information from multiple levels spanning from physiology of the entire organism, to events occurring inside individual stem cells. However, currently the hierarchy and temporal coordination of cell fate regulating networks remains unclear. In the FateLevels project, we combine our expertise in cellular transport, nuclear organization, and stem cells to address the interplay of key input signals that regulate cell fate.

First, as the cellular phenotypes ultimately depend on how the genomic information is read, we will map how chromatin is reorganized during stem cell differentiation. We will also analyze the hierarchy between changes in chromatin structure, transcription and metabolism. Second, stem cells function in tissues under continuous input from neighboring cells that guide and support stem cells by secretion of a plethora of physiological factors. We will address whether this secretion is spatially directed and regulated in response to physiological cues including nutrition, and whether directed cell-cell secretion constitutes a novel intercellular regulatory network. Third, extrinsic cues must eventually reach the target cell nucleus. We will take advantage of the well-characterized topology of kinase-mediated signal transduction networks, and aim to identify novel signaling routes mediating signals between the tissue environment and the stem cell nucleus. All these aims depend on cutting-edge technologies, such as the combination of functional genomics, advanced imaging, organoid cultures and chemical biology, but also involve development of new technologies to benefit the research community.

In summary, FateLevels project studies how the many levels controlling stem cell fate decisions jointly form a hierarchy of regulatory networks that keeps us alive today and prepares our tissues for the challenges of tomorrow.

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