Decoding signal computation in pluripotent stem cells

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Project description:
Understanding how cells change identities in response to signalling cues is one of the fundamental challenges in modern biosciences. This question is most prescient for pluripotent cells that can form all the cell lineages in the mammalian embryo. Pluripotency is transient in the embryo, but it is possible to maintain pluripotent stem cells (PSCs) long term in the laboratory (PMID:39180242). PSCs decide compute biochemical and biophysical signals from other cells in the embryo or provided in the culture environment to decide between self-renewal or differentiation. Our laboratory has established signalling environments for culturing three different types of human PSC. They correspond to sequential stages that pluripotent cells pass through in the early embryo: the pre-lineage inner cell mass (ICM); the naïve epiblast; and the primed epiblast. The three PSC states have distinct cell biological and molecular properties and exhibit different capabilities for differentiation into extraembryonic or embryonic cell lineages. Each type of PSC requires different signalling inputs to maintain self-renewal or switch to differentiation.

This project will focus on a signalling module known as YAP/TEAD that is instrumental for cell fate decisions in the early embryo (PMID:19289085). YAP shuttles between cytoplasm and nucleus in response to changes in the microenvironment. When in the nucleus YAP can interact with TEAD transcription factors to activate expression of target genes. We have found that increased YAP/TEAD signalling is required for differentiation (PMID:36398796). In addition, however, low level YAP/TEAD appears to be necessary for PSC maintenance. How does a single pathway regulate such different responses?

The aim of this project is to investigate the hypothesis that dynamic nucleocytoplasmic shutting of YAP conveys information that is richer than concentration alone and is computed into specific transcriptional outcomes (and thence cell decisions). Testing this hypothesis requires quantitative analysis of YAP localisation dynamics together with transcriptomic assays of gene expression. You will create YAP fusions with fluorescent reporters to visualise nucleocytoplasmic shuttling in live cells (PMID:32917893). Applying advanced image analysis techniques you will measure parameters such as amplitude, frequency and residency time. In parallel you will generate single cell RNA-seq and chromatin accessibility profiles. These analyses will be performed during self-renewal, transitions between PSC states, and differentiation induction. Chemical and genetic perturbations will probe robustness and causation. The overall goal is to produce an explanatory and predictive mathematical network model for how YAP/TEAD gates transcription to guide alternative fate decisions in pluripotent cells.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.