Pluripotent stem cell biology (Ian Chambers)

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Transcription Factor Control of Pluripotent Cell Identity

Our work on pluripotent stem cells focuses on three strands: (i) how transcription factors (TFs) interact with partner proteins and chromatin to direct efficient self-renewal, (ii) how changes in TF interactions drive commitment to differentiate, (iii) how the pluripotency TF network is reconfigured to enable entry to the germline. (i) To understand how TFs control cell identity we use mass spectrometry to identify partner proteins (Gagliardi et al., ***The EMBO J., 2013***). Repeating this with mutant proteins focussed attention on 6 NANOG interacting proteins. We are using biochemical and advanced microscopic approaches to determine how these partners deliver NANOG function. (ii) To assess how TFs act on chromatin we analyse RNA-seq and ChIP-seq data. Coupling ChIP with FACS to dissect distinct sub-populations of pluripotent cells tells us about TF interdependencies at individual loci before, and at the earliest stages of commitment to differentiation (Festuccia et al. ***The EMBO J., 2018***). Coupling ChIP with a technique for genome-wide analysis of enhancer activity (ChIP-STARR-seq) enables us to find novel active enhancers, genome-wide in distinct pluripotent populations (Barakat et al. ***Cell Stem Cell, 2018***). (iii) We have recently shown that OTX2 restricts entry of cells into the germline and that in the absence of OTX2, germline differentiation exhibits aspects of a default differentiation (Zhang et al, ***Nature, 2018***). These results suggest that OTX2 acts like a traffic warden, to restrict access to the germline and to usher cells towards the soma.