The diversity of cell types generated during development needs to be faithfully maintained for normal homeostatic tissue functions. How cells integrate developmental and signalling-dependent instructions to acquire or alter transcriptional states remains a fundamental question in developmental biology. Polycomb and Trithorax group members act as epigenetic regulators to maintain target gene silencing or activation, respectively. Remarkably, tissues are capable of restoring homeostasis upon damage or stress, with inherent chromatin alterations supporting dynamic regulation of cell states. We are investigating how developmental and signalling pathways translate into modulating chromatin states underlying distinct tissue responses.

Signalling pathways modulate developmental and regenerative processes but can also be exploited by cancer cells to promote tissue invasion and growth advantage. Motivated by the parallels between the two processes, we identified context-specific features that can discriminate regenerative from tumorigenic states. We explored the contribution of ectopic signalling pathways to promote tumour development upon impaired Polycomb silencing. We employed quantitative analyses to measure the effect of JNK, JAK/STAT and Notch pathways in a Drosophila epithelial tumour model and found that these pathways support tumour growth. Furthermore, JAK/STAT signalling functions in parallel to JNK, while Notch signalling relies on JNK. We thus defined a signalling hierarchy in tumours that is distinct from the sequential activation determined during tissue regeneration.

Furthermore, we are also developing novel methods for tissue-specific chromatin profiling of rare cell populations. These approaches overcome the current limitations of small tissue amounts, and can be generally applicable to a diverse array of organisms and developmental stages. The combination of emerging technologies with powerful genetics in a real tissue context will support mechanistic insights driving chromatin alterations during development and homeostasis.

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PS5.50
Wnt/B-catenin signalling facilitates cell fate decision making in the early mouse embryo

Elena Corujo-Simon, Joaquin Lilao-Garzon, Silvia Muñoz-Descalzo

University of Bath, United Kingdom

Mouse pre-implantation development is characterized by cell division and differentiation to give rise to three different lineages: trophectoderm (TE), primitive endoderm (PrE) and epiblast (Epi).

The TE, which will differentiate into the placenta, arises at embryonic day E3.5d from cells situated outside of the embryo whilst inside cells form the inner cell mass (ICM). At this stage, ICM cells co-express the transcription factors NANOG and GATA6. Between E3.5d and E4.5d, cells of the ICM differentiate into epiblast (Epi), which will form the embryo proper, or primitive endoderm (PrE), which will form the yolk sac. These two lineages are distinguished by the differential expression of the previously co-expressed transcription factors; Epi cells express NANOG while PrE cells GATA6.

β-catenin is the downstream effector of Wnt signalling, a widespread cell signalling pathway with multiple roles during vertebrate development. β-catenin is also found together with E-cadherin in adhesion complexes in the membrane. In mESCs, which origin is the mouse pre-implantation embryo, there is a dual role for β-catenin: it promotes differentiation when activated as part of the Wnt/β-catenin signalling pathway, and promotes stable pluripotency independently of signalling.

My working hypothesis is that changes in both cellular pools of β-catenin are involved in differentiation of ICM cells into either Epi or PrE. To investigate this hypothesis we use a combination of in vivo studies as well as a mESC model for PrE differentiation together with small molecule inhibitors and quantitative image analysis. Our results indicate that increases in nuclear β-catenin levels allow the cells to move further into the PrE fate, determined by the expression of GATA6, SOX17 and GATA4, while decreasing nuclear β-catenin levels slows the PrE differentiation.

Establishing a role for β-catenin in cell fate choice at this stage will help to understand cellular differentiation and how different lineages arise in mouse development.

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PS5.51
Identification of Ryk binding proteins in Wnt signal transduction

Gun-Hwa Kim, Seung-Hwan Lee, Ju-Hyun Shin

Korea Basic Science Institute (KBSI), Daejeon, South Korea
Chungnam National University, Daejeon, South Korea

Ryk is a member of atypical receptor tyrosine kinase family that consists of an extracellular WIF (Wnt inhibitory factor) domain, an intracellular atypical kinase domain, and a PDZ binding motif at C-terminus. Ryk has previously been shown to regulate canonical Wnt/β-catenin signaling by directly binding to Wnt ligands and Dishevelled. A recent study showed that Ryk also regulates non-canonical Wnt pathway in convergent extension (CE) movements by promoting Wnt11-mediated endocytosis. However, downstream signaling mechanism of Ryk receptor still remain to be resolved in detail. In this study, we tried to identify binding proteins of Ryk by using IP-Mass method. To identify novel binding partners of Ryk receptor, HEK 293T cells were transfected with (1) empty vector, (2) Ryk-myc, (3) Ryk-myc + canonical Wnt 3a and (4) Ryk-myc + non-canonical Wnt11. Then, IP was performed using myc antibody and putative Ryk binding proteins were identified by LC-MS. We found several novel proteins that may interact with Ryk receptor as well as previously known binding partners such as Cdc37 and EphA4.

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PS5.52
Single-cell RNAseq Profiling of Early Heart Developmental Physiology

Antonio Miranda[a], Richard Tyser[a], Paul Riley[a], Antonio Scialdone[b], John Marioni[b], Shankar Srinivas[a]

[a]*DPAG, University of Oxford, United Kingdom*
[b]*EMBL-EBI, Hixton, Cambridge, United Kingdom*

The heart is the first organ to form and function during mammalian development. Recently we established that in the mouse embryo, spontaneous asynchronous calcium oscillations (SACOs) occour in the cardiac crescent prior to the onset of cardiac contractions. Blocking Sodium Calcium Exchanger (NCX1) function inhibits these oscillations and cardiac differentiation.

The genetic control of the physiological dynamics observed in the cardiac mesoderm, and how these are integrated to control cardiac differentiation, remains unknown. By imaging the propagation of calcium transients in the cardiac crescent, we now have evidence of