DEVELOPMENTAL BIOLOGY MODULE

INSTITUTO DE MEDICINA MOLECULAR, FAC. MEDICINA UNIV. LISBOA

Coordinator: Domingos Henrique (henrique@fm.ul.pt)

Faculty:

23RD APRIL, 10AM, ROOM 8, LEVEL 0 EEM

Fernando Giraldez (Univ. Pompeu Fabra, Barcelona, Spain)
"Signals and Factors in Ear Development"

http://www.upf.edu/devbiol/projectes/progenitors.html

24TH APRIL, 10AM, ROOM 8, LEVEL 0 EEM

Catarina Ramos, Cláudia Gaspar (UBD, IMM)
"Notch Signalling and Neurogenesis"

Elsa Abranches (UBD, IMM)
"Into the heart of stemness"

26TH APRIL, 9.30AM, ROOM 8, LEVEL 0 EEM

Ana Pombo (MRC Clinical Sciences Center, London, UK)
Inês de Santiago (MRC Clinical Sciences Center, London, UK)
"Chromatin mechanims in the regulation of pluripotency"

http://www.csc.mrc.ac.uk/research/groups/edc/genomefunction/

27TH APRIL, 9.30AM , ROOM P3-32

José Silva (Center for Stem Cell Research, Cambridge, UK)
"Biology of induced pluripotency"

http://www.cscr.cam.ac.uk/research/principal-investigators/dr-jos-silva

Josh Brinkman (Danish Stem Cell Center, University of Copenhagen, Denmark and Center for Regenrative Medicine, University of Edinburgh, UK)
"Mechanisms of Lineage Specification in Embryos and Embryonic Stem Cells"

http://danstem.ku.dk/people/brickman/
http://www.crm.ed.ac.uk/research/group/embryonic-patterning

ABSTRACT FOR FERNANDO GIRALDEZ
Signals and Factors in Ear Development

The function of the brain relies on the activity of an enormous number of different neurones that establish stereotyped connections. The generation of such diversity arises during embryonic development and depends on a precise allocation of competence states to cell progenitors and their development into precise cellular fates. The diversification of neuronal subtypes results from the combination of autonomous and cell-to-cell communication factors that act on neural progenitors. The developing inner ear is an interesting models system to address these questions. The basic functional unit of the ear consists of three elements of neural origin: the mechano-transducing hair-cells (HCs), the supporting cells (SCs), and the primary afferent neurons that connect hair cells to central neurones. All three elements derive from the otic vesicle, which in turn is the result of the proliferation, growth and invagination of the ***otic placode***. The generation of hair cells, and otic neurons follows a stereotyped spatial and temporal pattern by which otic neurons become specified prior to hair cells and supporting cells.

How sensory patches develop? Sensory patches arise from a common neurosensory competent field that split into prosensory domains. Notch signalling is required for the specification of sensory organs and for the determination of hair cells. The latter function results from lateral inhibition, whereby Notch ligands are expressed in hair cells and signal to neighboring cells to prevent their differentiation. However, the prosensory function of Notch seems to operate through a different mechanism that is called lateral induction in which Notch signaling is propagated into a coherent field. By this mechanism, Notch activity restricts *Sox2* function and sensory competence to the sensory patches, providing an example of coupling between patterning and cell fate in development. But, how the same Notch signaling pathway operates both for lateral induction and lateral inhibition? We shall discuss some theoretical possibilities and experimental evidence that may shed some light on how this occurs.

How otic progenitors commit to hair cell fate? The commitment to the sensory fate is associated with the expression of *Atoh1*, a bHLH transcription factor that behaves as a master gene for hair cell fate specification. Therefore, the understanding of hair cell development is very much that of the onset and regulation of Atoh1 expression. Sox2 is a High Mobility Group (HMG) box domain transcription factor, belonging to the B1 subfamily of Sox proteins that are crucial for neural development. Sox2 shows two seemingly contradictory functions: to promote neural competence of progenitors and at the same time to prevent their differentiation. In the inner ear, Sox2 directly activates *Atoh1* through a transcriptional activator function. But besides, Sox2 also promotes de expression of *Atoh1* inhibitors through an incoherent feed-forward loop that transiently silences *Atoh1* expression. The indication is that sensory competence is established very early in otic development by the activation of *Atoh1*. However, the incoherence in the Sox2 response results in the procrastination of hair cell differentiation until later stages of development.

Reading:

Sarah Bray (2006) Notch signalling: a simple pathway becomes complex http://www.nature.com/nrm/journal/v7/n9/full/nrm2009.html

Neves et al., (2012) The Prosensory Function of Sox2 in the Chicken Inner Ear Relies on the Direct Regulation of *Atoh1*
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0030871

Topics and Question to be addressed on Friday:

- What is induced pluripotency?
- What is an induced pluripotent stem (iPS) cell?
- What are the key players for successful induced pluripotency?
- What does Oct4 do?
- What are the different pluripotent cell states? What defines these? Are these specific to species or representative of a different pluripotent developmental stage? Are all or some of in vitro pluripotent cells an artefact?
- Is transdifferentiation an alternative to pluripotent cells?
- What next for induced pluripotency?

- What is an Embryonic Stem (ES) Cell?
- Are the functional properties of ES cells defined based on the population or single cells?
- Does lineage priming in ES cells provide insights into the nature regulative nature of mammalian development?
- What are mechanisms of lineage priming?
- Is chromatin necessary to suppress differentiation in ES cells?
- Can ES cells be used to decipher developmental mechanism?
- How does Fgf signaling promote endoderm differentiation - lesions learned from ES cell differentiation to endoderm.