Speaker name: Christian Kroun Damgaard, Aarhus University

Title: “Circular RNAs and neuronal differentiation”

Short abstract:
Circular RNAs have emerged as a large class of conserved non-coding RNAs that exquisitely regulate a number of biological processes, including transcription, alternative splicing, translation and mRNA decay. Circular RNAs are enriched in brain tissue and cells subjected to neuronal differentiation markedly change their circular RNA transcriptomes. We have mapped the circular RNA inventory in mouse embryonic stem cells, neuronal progenitor cells and terminally differentiated neurons by deep RNase R-assisted RNA-sequencing and identify hundreds of circular RNAs that become up- or downregulated. A screen for a potential involvement of circular RNAs in neuronal differentiation, revealed that knockdown of two circular RNAs, circZNF827 and circANKIb, enhanced neuronal differentiation, as evidenced by a significant upregulation of key neuronal markers and lowered proliferation rates. Consistent with enhanced neuronal marker expression, we found that, among ~800 genes linked to known neuronal pathways and neuropathological states, several genes become significantly upregulated, including neuronal growth factor receptor and retinoic acid receptors. Although circZNF827 and circANKIb are almost exclusively localized in the cell cytoplasm, their regulation of target genes is elicited at the level of transcription rather than a post-transcriptional modulation of mRNA decay rates. Our results suggest that circZNF827 and circANKIb function by reprogramming transcriptional events to keep neuronal differentiation in check.
Here we used a marker-free approach to computationally reconstruct the blood lineage tree in zebrafish and order cells along their differentiation trajectory, based on their global transcriptional differences. By reconstructing their developmental chronology computationally, we were able to place each cell along a continuum from stem cell to mature cell, refining the traditional lineage tree. Within the population of transcriptionally similar stem and progenitor cells our analysis revealed considerable cell-to-cell differences in their probability to transition to another, committed state. This suggested that although global transcriptional changes before and after the branching point were continuous, the probability of a cell progressing to any of the committed states was determined only by a subset of highly relevant genes. Therefore, cells that were transcriptionally similar overall could have a high probability of differentiation to distinct cell types. Once the cell fate decision was executed, the progression of cells along the continuum is characterised by a highly coordinated transcriptional program, displaying simultaneous suppression of genes involved in cell proliferation and ribosomal biogenesis and increased expression of lineage specific genes. Our comparative analysis between zebrafish, mouse and human across seven different haematopoietic cell types, including innate lymphocytes (ILCs), revealed a high level of conservation of blood cell type specific genes. The lowest conservation was observed for lymphocytes, possibly reflecting their adaptation to fish specific pathogens and virulence factors.

Short bio:

Link lab website: http://mbg.au.dk/forskning/forskningsomraader/genekspression-genmedicin/christian-kroun-damgaard/