Regulation of stem cell biology by RNA-binding proteins during fly development

Supervisory team:
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Project description:
Although transcription is the first step in eukaryotic gene expression, many post-transcriptional events determine the final fate of RNA molecules and impose additional complexity to gene expression. Current models suggest that mRNAs that encode functionally related proteins are co-ordinately regulated as post-transcriptional RNA operons (or regulons) through the formation of highly regulated RNA-protein complexes. Indeed, RNA-binding proteins (RBPs) can act as master regulators of gene expression by binding groups of functionally related mRNAs. Importantly, defects in RBP function cause a variety of pathologies ranging from cancer to muscular, neurological, metabolic, haematologic or immunological diseases.

The aim of this project is to investigate in vivo the mechanisms used by conserved RBPs in the regulation of stem cell identity and cell differentiation. You will use the Drosophila adult mid-gut – a sophisticated model for the regulation of intestinal homeostasis – to investigate how conserved RNA-binding proteins regulate the balance between self-renewal and differentiation, and the appropriate proportions of the different mature cell types that populate and maintain the functionality of the gut. First, you will perform a genetic and functional screen to identify RBPs involved in the regulation of adult stem cell identity and differentiation, both under physiological conditions as well as under stress. Then, you will use state-of the art genomic approaches to identify the RNA molecules associated with the relevant RBPs. Finally, you will combine genetic in vivo approaches (e.g. loss-of-function, gain-of-function or epistasis studies) and biochemical/molecular approaches (e.g. characterisation of the RNA-RBP interactions) to characterize in vivo the molecular mechanisms used by RBP to regulate stem cell function.

The originality of this project is to focus on the potential of RNA regulation, rather than signalling and transcription, as a determinant of cell behaviour. It has the potential to define new and exciting research questions and will offer an excellent training opportunity to the student in stem cell and developmental biology, microscopy and histology, molecular biology and NGS methods.