Drosophila midgut morphogenesis: Understanding how cells transition to distinct states

Biosketch

I carried out my PhD in the lab of Helen Skaer, University of Cambridge, studying how epithelial polarity is regulated during renal tubule morphogenesis in Drosophila melanogaster. From there I moved to sunny Barcelona to do a postdoc in the lab of Jordi Casanova, and it is during this period that I established the embryonic midgut as a model system for studying epithelial-mesenchymal plasticity. I also started collaborating with Andreu Casali and together we have developed adult *Drosophila* models for studying metastatic-colorectal cancer. I started my own lab in the University of Sheffield in 2017, where we continue to use *Drosophila* to investigate epithelia-mesenchymal plasticity during development and cancer metastasis.

Abstract

The *Drosophila* adult midgut progenitor cells (AMPs) give rise to all cells of the adult midgut epithelium, including the intestinal stem cells. Despite intense focus over the last 15+ years on the origin and molecular mechanisms underlying intestinal stem cell behaviour, it remained unknown precisely how and when their precursor cells, the AMPs, arise in the embryo.

We recently used a combination of single cell RNA sequencing (scRNAseq), imaging and genetic approaches to follow the emergence of distinct midgut cell types during early embryogenesis. We found that the AMPs, together with other cell types required to support gut function during developmental stages, arise from a transient population of endoderm cells which exhibit multiple similarities with *Drosophila* neuroblasts. These cells, which we have termed endoblasts, are patterned by the homeodomain protein Homothorax and undergo asymmetric divisions using the same molecular machinery as neuroblasts, leading to the unequal inheritance of cell fate determinants including Prospero (Pros) and Brain tumor (Brat). When asymmetric division is perturbed in endoblasts, specification of distinct midgut cell types, including the AMPs, does not occur properly and we found that the conservation of this molecular machinery extends through to the generation of the enteroendocrine lineages.

In this talk I will discuss this work, including the logic behind our scRNAseq experiments and how they have (massively) advanced to our understanding of the molecular mechanisms underlying midgut cell transitions. I will discuss where we are going with future work, and some of the challenges we have been having – ideas on how to resolve these and move forward would be very welcome!