Stem cells are essential for development and continued maintenance of tissues and organs. They are characterized by their ability to self-renew as well as to produce differentiated progeny.

Figure 1: Stem cells (green) renew the intestine, giving rise to enteroendocrine cells (red) and enterocytes (large nuclei in blue).

Understanding the dual capacity of self-renewal and differentiation is an important aim of regenerative medicine and also has implications for cancer biology. The aim of work in our group is to identify mechanisms important for these processes and ultimately to understand how they function collectively to promote homeostasis of a tissue. To do so, we are using a simplified model system, the Drosophila intestine, which contains around 1000 multipotent intestinal stem cells (Fig. 1). The intestinal stem cells produce the two differentiated cell types required for organ function: the enterocytes and enteroendocrine cells. The differentiated cells are replaced approximately once a week in healthy animals but can be stimulated to rapidly regenerate the intestine upon infection by pathogenic bacteria or treatment with damaging agents (DSS, paraquat). Thus, this is an excellent
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and simple model for mammalian tissues such as the intestine, lung or skin that need to regenerate in response to environmental stimuli.

We are using this model system to address several important questions:

1. How is the self-renewal of the stem cell regulated? What is the role of chromatin-remodelling in this process?
2. What controls the differentiation choice of the stem cell?
3. What is the impact of somatic mutations on adult stem cells? How does this impact tissue aging and cancer initiation?

Self-renewal control: In order to gain broader insight into self-renewal and differentiation control of ISC s, we have conducted an EMS-based genetic screen to identify novel regulators. We are currently focusing on several genes identified in this screen including regulators of chromatin remodeling that are conserved in mammals, mutated in human cancers and are essential in the fly intestine to limit stem cell proliferation.

Differentiation control: Our past work (Bardin, AJ, 2010) has identified the achaete-scute transcription factors as being essential for stem cell differentiation into enteroendocrine cells. We have now identified additional factors controlling enteroendocrine differentiation and are studying their mechanisms of action (Sallé, et al, EMBOJ, 2017). This will provide insight into how an accurate balance of terminal cell fates is achieved in homeostatic adult tissues.

Spontaneous mutation: Aging and cancer: We are using the adult fly intestine to understand the mechanisms underlying spontaneous mutation. Stem cell mutation is clearly linked with cancer initiation and has been proposed to contribute to age-related decline of tissue renewal. We have recently shown that intestinal stem cells acquire spontaneous mutations during aging, resulting in frequent mutation of the tumor suppressor gene Notch and driving neoplasia formation (Fig. 2). We are using whole-genome sequencing approaches to determine the nature and mechanisms driving stem cell somatic mutation (Fig 3). In particular, we would
like to understand the role of diet, pathogenic bacteria, and additional environmental components in promoting mutation. Importantly, using this simplified model system, we aim to understand the role that somatic mutation may play in stem cell, tissue and organismal aging.

Key publications

Year of publication 2017

Louis Gervais, Allison Bardin (2017 Jun 30)
**Tissue homeostasis and aging: new insight from the Fly intestine**
*Current Opinion in Cell Biology*: DOI: 10.1016/j.ceb.2017.06.005

Jérémy Sallé, Louis Gervais, Benjamin Boumard, Marine Stefanutti, Katarzyna Siudeja, Allison J. Bardin (2017 May 22)
**Intrinsic regulation of enteroendocrine fate by Numb**
*EMBO Journal*: DOI: 10.15252/embj.201695622

Year of publication 2016

Katarzyna Siudeja, Allison J Bardin (2016 Nov 12)
**Somatic recombination in adult tissues: What is there to learn?**
*Fly*: 1-8 : DOI: 10.1080/19336934.2016.1249073

Year of publication 2015

**Frequent Somatic Mutation in Adult Intestinal Stem Cells Drives Neoplasia and Genetic Mosaicism during Aging.**
*Cell stem cell*: 663-74 : DOI: 10.1016/j.stem.2015.09.016

Delphine Gogendeau, Katarzyna Siudeja, Davide Gambarotto, Carole Pennetier, Allison J Bardin, Renata Basto (2015 Nov 17)
**Aneuploidy causes premature differentiation of neural and intestinal stem cells.**
*Nature communications*: 8894 : DOI: 10.1038/ncomms9894

Year of publication 2013

Juliette Mathieu, Clothilde Cauvin, Clara Moch, Sarah J Radford, Paula Sampaio, Carolina N Perdigoto, François Schweisguth, Allison J Bardin, Claudio E Sunkel, Kim McKim, Arnaud Echard, Jean-René Huynh (2013 Aug 12)
Aurora B and cyclin B have opposite effects on the timing of cytokinesis abscission in Drosophila germ cells and in vertebrate somatic cells.

*Developmental cell*: 250-65 : [DOI: 10.1016/j.devcel.2013.07.005]