Stem Cells and Tissue Homeostasis

U934/UMR3215 - Genetics and Developmental Biology

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.

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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Figure 2: During aging, spontaneous mutations arise in adult stem cells. This leads to the frequent inactivation of the tumor suppressor gene, Notch, promoting neoplasia formation (in red) in 10% of aged male flies.

Figure 3: We use whole-genome deep sequencing approaches to define molecular events occurring during aging in stem cells. An example of whole-genome sequencing of a neoplasia (red) and its control (green) showing large scale rearrangement of the Notch locus.

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 ISCs, 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 2019**


**Stem Cell Proliferation Is Kept in Check by the Chromatin Regulators Kismet/CHD7/CHD8 and Trr/MLL3/4**

*Developmental Cell* : [DOI](https://doi.org/10.1016/j.devcel.2019.04.033)

**Year of publication 2018**


**Spen limits intestinal stem cell self-renewal.**

*PLoS genetics* : e1007773 : [DOI](https://doi.org/10.1371/journal.pgen.1007773)

**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](https://doi.org/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](https://doi.org/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](https://doi.org/10.1080/19336934.2016.1249073)

**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]