How cells coordinate their action to build epithelial tissues during development, tissue morphogenesis and remodeling is a fundamental question that remains only superficially understood. We study the signals controlling adult stem cell homeostasis and lineage specification, with the final goal of gaining mechanistic insights into organ morphogenesis, and also into the critical steps of malignant transformation. Our research is particularly focused on epithelial stem cells in the intestine and the mammary gland, as well as in tumors derived from them. In these epithelia, the Notch signaling pathway has a central role in tissue development and cell fate decisions. Our studies aim at gaining insights into the molecular control of adult stem cell maintenance, as well as into the mechanisms by which Notch signaling controls cell plasticity in both normal and pathological conditions.

A deep comprehension of the cellular hierarchies originating from tissue-specific stem cells and the factors that regulate their behaviour will have a major impact in exploring therapeutic avenues for cancer. Given the very well documented involvement of Notch signaling in the maintenance and differentiation of stem and progenitor cells in a broad organ spectrum, the in vivo identification of Notch lineages provides an essential tool to discover critical early progenitors both for organ homeostasis and cancer development. Our group seeks to examine the behaviour of normal stem cells in the mouse intestine and the mammary gland, with the goal of gaining insights into the cellular hierarchy of the highly heterogeneous tumor cell populations. We have chosen to focus our research on
these two epithelial tissues because they are very dynamic and contain highly active stem cells, to ensure extremely rapid and continuous cell renewal in the case of the intestinal epithelium and to guarantee remarkable tissue remodeling upon hormonal stimulation for the mammary gland. Our studies on one hand, use Notch as a tool to study stem/progenitor cells homeostasis in vivo, and on the other, aim at revealing if and how Notch signals can change the fate of normal and cancer stem cells, a possibility with important therapeutic implications, given that colon and breast cancer are among the most common tumors.

Our questions:

1) Can we use Notch to trace specific stem/progenitor cells as well as “stem-cell like” tumor cell populations? We are addressing this question through the systematic identification and functional characterization of Notch-expressing lineages in vivo in normal and tumor cells of the mouse intestinal and mammary epithelia.

2) How are stem cell division and differentiation dynamically coordinated within a crypt and during mammary tubulogenesis? In order to visualize stem cell behaviour and response to injury by time-lapse imaging, we use 3D organoids and embryonic tissue explants derived from normal or malignant Notch-expressing cells.

3) Are Notch signals required for stem cell survival in normal tissues and in tumors? We aim at establishing, by in vivo genetic ablation and gain of function studies, the functional role of Notch signaling in maintaining stem/progenitor cells and in the transformation of the intestinal and mammary epithelia.

4) Can niche signals affect the establishment of a stem cell pool during development and do they influence cell plasticity? We study how paracrine factors from the mesenchyme can influence lineage specification and plasticity of intestinal and mammary stem cells both temporally, during embryonic development, and topologically, as regional differences are established along the antero-posterior axis.

Our Tools: novel knock-in transgenic mice
We have recently generated and characterized a novel collection of transgenic mice that offers the opportunity to assess Notch expression and function in vivo in an unprecedented fashion. Specifically, these mice permit the conditional expression of a given transgene in the cells where the promoters of the four Notch receptor paralogues are endogenously active. In addition, we have also developed reporter mice, allowing us to visualize cells with an active Notch pathway and transgenic animals allowing conditional activation of the four Notch receptors. We share these useful mouse tools with several collaborators, as they allow to probe the relationship between Notch-related activity and normal and cancer stem cells in vivo.

Key publications

Year of publication 2019

Bethan Lloyd-Lewis, Philippos Mourikis, Silvia Fre (2019 Jul 20)
Notch signalling: sensor and instructor of the microenvironment to coordinate cell fate and organ morphogenesis.

Larissa Mourao, Guillaume Jacquemin, Mathilde Huyghe, Wojciech J Nawrocki, Naoual Menssouri, Nicolas Servant, Silvia Fre (2019 Jan 31)
Lineage tracing of Notch1-expressing cells in intestinal tumours reveals a distinct population of cancer stem cells.
Scientific reports : 888 : DOI: 10.1038/s41598-018-37301-3
Clonal analysis of Notch1-expressing cells reveals the existence of unipotent stem cells that retain long-term plasticity in the embryonic mammary gland.

Nature cell biology : DOI : 10.1038/s41556-018-0108-1

Mechanical induction of the tumorigenic β-catenin pathway by tumour growth pressure.

Nature : 92-5 : DOI : 10.1038/nature14329

Luminal progenitors restrict their lineage potential during mammary gland development.

PLoS biology : e1002069 : DOI : 10.1371/journal.pbio.1002069
Silvina Dos Reis Tavares, Giuseppe-Fulvio Boccia, Wulfran Cacheux, Didier Meseure, Silvia Fre, Loredana Martignetti, Patricia Legoix-Né, Elodie Girard, Luc Fetler, Emmanuel Barillot, Daniel Louvard, Andreï Zinovyev, Sylvie Robine (2014 Apr 9)

**Concomitant Notch activation and p53 deletion trigger epithelial-to-mesenchymal transition and metastasis in mouse gut.**

*Nature communications* : 5005 : DOI : 10.1038/ncomms6005