Année de publication : 2019

Gervais L, van den Beek M, Josserand M, Sallé J, Stefanutti M, Perdigoto CN, Skorski P, Mazouni K, Marshall OJ, Brand AH, Schweisguth F, Bardin AJ (2019 May 20)

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

Résumé

Chromatin remodeling accompanies differentiation, however, its role in self-renewal is less well understood. We report that in Drosophila, the chromatin remodeler Kismet/CHD7/CHD8 limits intestinal stem cell (ISC) number and proliferation without affecting differentiation. Stem-cell-specific whole-genome profiling of Kismet revealed its enrichment at transcriptionally active regions bound by RNA polymerase II and Brahma, its recruitment to the transcription start site of activated genes and developmental enhancers and its depletion from regions bound by Polycomb, Histone H1, and heterochromatin Protein 1. We demonstrate that the Trithorax-related/MLL3/4 chromatin modifier regulates ISC proliferation, colocalizes extensively with Kismet throughout the ISC genome, and co-regulates genes in ISCs, including Cbl, a negative regulator of Epidermal Growth Factor Receptor (EGFR). Loss of kismet or trr leads to elevated levels of EGFR protein and signaling, thereby promoting ISC self-renewal. We propose that Kismet with Trr establishes a chromatin state that limits EGFR proliferative signaling, preventing tumor-like stem cell overgrowths.

Année de publication : 2018

Maheva Andriatsilavo, Marine Stefanutti, Katarzyna Siudeja, Carolina N Perdigoto, Benjamin Boumard, Louis Gervais, Alexandre Gillet-Markowska, Lara Al Zouabi, François Schweisguth, Allison J Bardin (2018 Nov 20)

Spen limits intestinal stem cell self-renewal.

PLoS genetics : e1007773 : DOI : 10.1371/journal.pgen.1007773

Résumé

Precise regulation of stem cell self-renewal and differentiation properties is essential for tissue homeostasis. Using the adult Drosophila intestine to study molecular mechanisms controlling stem cell properties, we identify the gene split-ends (spen) in a genetic screen as a novel regulator of intestinal stem cell fate (ISC). Spen family genes encode conserved RNA recognition motif-containing proteins that are reported to have roles in RNA splicing and transcriptional regulation. We demonstrate that spen acts at multiple points in the ISC lineage with an ISC-intrinsic function in controlling early commitment events of the stem cells and functions in terminally differentiated cells to further limit the proliferation of ISCs. Using two-color cell sorting of stem cells and their daughters, we characterize spen-dependent changes in RNA abundance and exon usage and find potential key regulators downstream of spen. Our work identifies spen as an important regulator of adult stem cells in

the Drosophila intestine, provides new insight to Spen-family protein functions, and may also shed light on Spen's mode of action in other developmental contexts.

Année de 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

Résumé

Adult somatic stem cells facilitate tissue homeostasis throughout the life of the organism. The mechanisms controlling stem cell activity are under intense scrutiny, with the aims of elucidating how they mediate tissue homeostasis, contribute to age-related decline of adult tissues, and promote tumorigenesis. Recently, the use of model systems such as the Drosophila intestine has enriched our understanding of how stem cells integrate local and systemic signals to maintain tissue and organs function in physiological conditions of homeostasis or after damage. Here we highlight recent advances made on this model allowing a better understanding of stem cell lineage decisions, their regulation by epithelial and intra-organ cues, and their altered activity during aging.

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

Résumé

How terminal cell fates are specified in dynamically renewing adult tissues is not well understood. Here we explore terminal cell fate establishment during homeostasis using the enteroendocrine cells (EEs) of the adult Drosophila midgut as a paradigm. Our data argue against the existence of local feedback signals and we identify Numb as an intrinsic regulator of EE fate. Our data further indicate that Numb, with alpha-adaptin, acts upstream or in parallel of known regulators of EE fate to limit Notch signaling, thereby facilitating EE fate acquisition. We find that Numb is regulated in part through its asymmetric and symmetric distribution during stem cell divisions, however its de novo synthesis is also required during the differentiation of the EE cell. Thus, this work identifies Numb as a crucial factor for cell fate choice in the adult Drosophila intestine. Furthermore, our findings demonstrate that cell-intrinsic control mechanisms of terminal cell fate acquisition can result in a balanced tissue-wide production of terminally differentiated cell types.

Année de 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

Résumé

Somatic recombination is essential to protect genomes of somatic cells from DNA damage but it also has important clinical implications, as it is a driving force of tumorigenesis leading to inactivation of tumor suppressor genes. Despite this importance, our knowledge about somatic recombination in adult tissues remains very limited. Our recent work, using the Drosophila adult midgut has demonstrated that spontaneous events of mitotic recombination accumulate in aging adult intestinal stem cells and result in frequent loss of heterozygosity (LOH). In this Extra View article, we provide further data supporting long-track chromosome LOH and discuss potential mechanisms involved in the process. In addition, we further discuss relevant questions surrounding somatic recombination and how the mechanisms and factors influencing somatic recombination in adult tissues can be explored using the Drosophila midgut model.

Année de publication : 2015

Katarzyna Siudeja, Sonya Nassari, Louis Gervais, Patricia Skorski, Sonia Lameiras, Donato Stolfa, Maria Zande, Virginie Bernard, Thomas Rio Frio, Allison J Bardin (2015 Dec 3)

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

Résumé

Adult stem cells may acquire mutations that modify cellular behavior, leading to functional declines in homeostasis or providing a competitive advantage resulting in premalignancy. However, the frequency, phenotypic impact, and mechanisms underlying spontaneous mutagenesis during aging are unclear. Here, we report two mechanisms of genome instability in adult Drosophila intestinal stem cells (ISCs) that cause phenotypic alterations in the aging intestine. First, we found frequent loss of heterozygosity arising from mitotic homologous recombination in ISCs that results in genetic mosaicism. Second, somatic deletion of DNA sequences and large structural rearrangements, resembling those described in cancers and congenital diseases, frequently result in gene inactivation. Such modifications induced somatic inactivation of the X-linked tumor suppressor Notch in ISCs, leading to spontaneous neoplasias in wild-type males. Together, our findings reveal frequent genomic modification in adult stem cells and show that somatic genetic mosaicism has important functional consequences on aging tissues.

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

Résumé

Aneuploidy is associated with a variety of diseases such as cancer and microcephaly. Although many studies have addressed the consequences of a non-euploid genome in cells, little is known about their overall consequences in tissue and organism development. Here we use two different mutant conditions to address the consequences of aneuploidy during tissue development and homeostasis in Drosophila. We show that aneuploidy causes brain size reduction due to a decrease in the number of proliferative neural stem cells (NSCs), but not through apoptosis. Instead, aneuploid NSCs present an extended G1 phase, which leads to cell cycle exit and premature differentiation. Moreover, we show that this response to aneuploidy is also present in adult intestinal stem cells but not in the wing disc. Our work highlights a neural and intestine stem cell-specific response to aneuploidy, which prevents their proliferation and expansion.

Année de 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

Résumé

Abscission is the last step of cytokinesis that physically separates the cytoplasm of sister cells. As the final stage of cell division, abscission is poorly characterized during animal development. Here, we show that Aurora B and Survivin regulate the number of germ cells in each Drosophila egg chamber by inhibiting abscission during differentiation. This inhibition is mediated by an Aurora B-dependent phosphorylation of Cyclin B, as a phosphomimic form of Cyclin B rescues premature abscission caused by a loss of function of Aurora B. We show that Cyclin B localizes at the cytokinesis bridge, where it promotes abscission. We propose that mutual inhibitions between Aurora B and Cyclin B regulate the duration of abscission and thereby the number of sister cells in each cyst. Finally, we show that inhibitions of Aurora B and Cyclin-dependent kinase 1 activity in vertebrate cells also have opposite effects on the timing of abscission, suggesting a possible conservation of these mechanisms.

Carolina N Perdigoto, Allison J Bardin (2013 Feb 4)

Sending the right signal: Notch and stem cells.
Biochimica et biophysica acta : 2307-22 : DOI : 10.1016/j.bbagen.2012.08.009

Résumé

Notch signaling plays a critical role in multiple developmental programs and not surprisingly, the Notch pathway has also been implicated in the regulation of many adult stem cells, such as those in the intestine, skin, lungs, hematopoietic system, and muscle.

Mahéva Andriatsilavo, Louis Gervais, Clara Fons, Allison J Bardin (2013 Jan 25)
[The Drosophila midgut as a model to study adult stem cells].
Médecine sciences : M/S : 75-81 : DOI : 10.1051/medsci/2013291016

Résumé

Constant renewal of cells occurs in most tissues throughout the adult lifetime and is insured by the activity of resident stem cells. Recent work has demonstrated the presence of adult stem cells in the Drosophila intestine and consequently, the Drosophila intestine has become a powerful model to understand adult stem cells in vivo. In this review, we summarize our current understanding of the mechanisms controlling cell fate decisions of the intestinal stem cells with a particular focus on the role of the Notch pathway in this process. We also summarize what is known about proliferation control of the intestinal stem cells, which is crucial to maintain tissue homeostasis during normal and environmentally stressful conditions.

Année de publication : 2012

Joaquín de Navascués, Carolina N Perdigoto, Yu Bian, Markus H Schneider, Allison J Bardin, Alfonso Martínez-Arias, Benjamin D Simons (2012 May 30)
Drosophila midgut homeostasis involves neutral competition between symmetrically dividing intestinal stem cells.
The EMBO journal : 2473-85 : DOI : 10.1038/emboj.2012.106

Résumé

The Drosophila adult posterior midgut has been identified as a powerful system in which to study mechanisms that control intestinal maintenance, in normal conditions as well as during injury or infection. Early work on this system has established a model of tissue turnover based on the asymmetric division of intestinal stem cells. From the quantitative analysis of clonal fate data, we show that tissue turnover involves the neutral competition of symmetrically dividing stem cells. This competition leads to stem-cell loss and replacement, resulting in neutral drift dynamics of the clonal population. As well as providing new insight into the mechanisms regulating tissue self-renewal, these findings establish intriguing parallels with the mammalian system, and confirm Drosophila as a useful model for studying

adult intestinal maintenance.

Année de publication : 2011

Carolina N Perdigoto, Francois Schweisguth, Allison J Bardin (2011 Sep 28)
Distinct levels of Notch activity for commitment and terminal differentiation of stem cells in the adult fly intestine.
Development (Cambridge, England) : 4585-95 : DOI : 10.1242/dev.065292

Résumé

Tight regulation of self-renewal and differentiation of adult stem cells ensures that tissues are properly maintained. In the Drosophila intestine, both commitment, i.e. exit from self-renewal, and terminal differentiation are controlled by Notch signaling. Here, we show that distinct requirements for Notch activity exist: commitment requires high Notch activity, whereas terminal differentiation can occur with lower Notch activity. We identified the gene GDP-mannose 4,6-dehydratase (Gmd), a modulator of Notch signaling, as being required for commitment but dispensable for terminal differentiation. Gmd loss resulted in aberrant, self-renewing stem cell divisions that generated extra ISC-like cells defective in Notch reporter activation, as well as wild-type-like cell divisions that produced properly terminally differentiated cells. Lowering Notch signaling using additional genetic means, we provided further evidence that commitment has a higher Notch signaling requirement than terminal differentiation. Our work suggests that a commitment requirement for high-level Notch activity safeguards the stem cells from loss through differentiation, revealing a novel role for the importance of Notch signaling levels in this system.

Silvia Fre, Allison Bardin, Sylvie Robine, Daniel Louvard (2011 May 13)
Notch signaling in intestinal homeostasis across species: the cases of Drosophila, Zebrafish and the mouse.
Experimental cell research : 2740-7 : DOI : 10.1016/j.yexcr.2011.06.012

Résumé

Notch signaling has been recently shown to have a fundamental role in stem cell maintenance and control of proper homeostasis in the intestine of different species. Here, we briefly review the current literature on Notch signals in the intestine of Drosophila, Zebrafish and the mouse, and try to highlight conserved and divergent Notch functions across species. Notch signals show a remarkably conserved role in skewing cell fate choices in intestinal lineages throughout evolution. Genetic analysis demonstrates that loss of Notch signaling invariably leads to increased numbers of secretory cells and loss of enterocytes, while gain of Notch function will completely block secretory cell differentiation. Finally, we discuss the potential contribution of Notch signaling to the initiation of colorectal cancer by controlling the maintenance of the undifferentiated state of intestinal neoplastic cells and speculate on the therapeutic consequences of affecting cancer stem cells.

Année de publication : 2010

Allison J Bardin, Carolina N Perdigoto, Tony D Southall, Andrea H Brand, François Schweisguth
(2010 Feb 12)

Transcriptional control of stem cell maintenance in the Drosophila intestine.

Development (Cambridge, England) : 705-14 : DOI : 10.1242/dev.039404

Résumé

Adult stem cells maintain tissue homeostasis by controlling the proper balance of stem cell self-renewal and differentiation. The adult midgut of Drosophila contains multipotent intestinal stem cells (ISCs) that self-renew and produce differentiated progeny. Control of ISC identity and maintenance is poorly understood. Here we find that transcriptional repression of Notch target genes by a Hairless-Suppressor of Hairless complex is required for ISC maintenance, and identify genes of the Enhancer of split complex [E(spl)-C] as the major targets of this repression. In addition, we find that the bHLH transcription factor Daughterless is essential to maintain ISC identity and that bHLH binding sites promote ISC-specific enhancer activity. We propose that Daughterless-dependent bHLH activity is important for the ISC fate and that E(spl)-C factors inhibit this activity to promote differentiation.

Année de publication : 2006

Allison J Bardin, François Schweisguth (2006 Feb 7)

Bearded family members inhibit Neuralized-mediated endocytosis and signaling activity of Delta in Drosophila.

Developmental cell : 245-55

Résumé

Endocytosis of Notch receptor ligands in signaling cells is essential for Notch receptor activation. In Drosophila, the E3 ubiquitin ligase Neuralized (Neur) promotes the endocytosis and signaling activity of the ligand Delta (Dl). In this study, we identify proteins of the Bearded (Brd) family as interactors of Neur. We show that Tom, a prototypic Brd family member, inhibits Neur-dependent Notch signaling. Overexpression of Tom inhibits the endocytosis of Dl and interferes with the interaction of Dl with Neur. Deletion of the Brd gene complex results in ectopic endocytosis of Dl in dorsal cells of stage 5 embryos. This defect in Dl trafficking is associated with ectopic expression of the single-minded gene, a direct Notch target gene that specifies the mesectoderm. We propose that inhibition of Neur by Brd proteins is important for precise spatial regulation of Dl signaling.