Leibniz Institute on Aging –
Fritz Lipmann Institute

Press release
October 21, 2019

How intestinal cells renew themselves – the role of Klumpfuss in cell differentiation

Stem cells are essential for homeostasis and cell renewal in organs like skin, lung or intestine. During the course of life, their function decreases steadily, making this decline a main factor for the development of age-associated diseases. Researchers of the Leibniz Institute on Aging in Jena, Germany, and their colleagues of the Buck Institute for Research on Aging in Novato, USA, investigated the mechanisms of intestinal cell renewal in the model organism *Drosophila*. Their results show that the transcription factor Klumpfuss plays a key role in this process by precisely regulating the differentiation of cell types in the fly intestine.

Jena. Stem cells react to tissue damage with an increase in their proliferation rate, leading to the production of new differentiated cells. Balance between cell loss and cell renewal through strict control of stem cell division guarantees the maintenance of organ size and function. Precise control of differentiation in adult stem cell lines is important for the development and maintenance of tissue homeostasis. Stem cell dysfunction can disturb this process, which can lead to tissue degeneration and cancer.

The researchers studied the differentiation of adult stem cells during tissue homeostasis in the midgut of the fruit fly (*Drosophila melanogaster*) because it bears many similarities with the human gastrointestinal tract in both structure and function. Injuries or infections lead to damage of the intestinal mucosa, which results in an increase in proliferation and differentiation of the intestinal stem cells (ISCs) to replace damaged cells and restore homeostasis. Disruption of normal cell differentiation leads to impairment of intestinal function, as can be observed in the aging intestine. How cell differentiation is exactly regulated has not been known yet.

Researchers of the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena, Germany, together with colleagues of the Buck Institute for Research on Aging in Novato, USA, have identified a novel player in the regulation of cell renewal and differentiation in the midgut of the model organism *Drosophila*. “With its stem cells, the intestine is able to regenerate itself continuously and to ensure the function and integrity of the tissue during the lifespan of an organism”, says Dr. Jerome Korzelius, first author of the study published in *Nature Communications*.

Asymmetric cell division of intestinal stem cells

Asymmetric division of ISCs is crucial for the process of cell renewal. An ISC renews by dividing into another stem cell and an enteroblast (EB) daughter cell. This daughter cell can then differentiate into two different types of differentiated cells depending on signaling cues: absorptive enterocytes (EC), cells that take up nutrients and are responsible for immune defense or

enteroendocrine cells (EE) that produce gastrointestinal hormones. Recent work has shown that lineage choice in these EB daughter cells is likely more complex than previously thought.

Transcription factor Klumpfuss as regulator

The researchers discovered that the transcription factor Klumpfuss (Klu), which is related to the mammalian tumor-suppressor gene “Wilms’ Tumor 1” (WT1), plays an important role in the adult *Drosophila* midgut for the lineage choice of EBs. “We found Klu to be expressed specifically in EBs to regulate cellular differentiation towards the enterocyte lineage”, tells Dr. Korzelius, who is currently working at the Max Planck Institute for Biology of Ageing in Cologne, Germany. Klu suppresses the differentiation of enteroendocrine cells from EBs by downregulating genes necessary for EE differentiation. Therefore, a loss of Klu in the enteroblasts leads to differentiation of EBs in EE cells.

Interplay with Notch signaling

Furthermore, the researchers found that Klu and Notch signaling together play a role in ISC division and differentiation. ISCs produce the Notch-ligand Delta and activate Notch in the enteroblast daughter cell, the precursor of mature enterocytes. Loss of Notch in ISC lineages leads to the development of tumors, likely because of impaired EB differentiation that leads to an increased frequency of symmetric divisions and excess EE differentiation. During EB differentiation, the transcription factor Klu acts to control Notch target gene expression. This control of Notch target genes by Klu adds another layer of regulation to this complex pathway, which is also important in many diseases in humans.

“Our results give a mechanistic insight into how cell differentiation in the *Drosophila* intestine is regulated”, summarizes Dr. Heinrich Jasper, senior author of the study. These are important insights into the control mechanisms of tissue regeneration that are also relevant for mammals, including humans.

Publication

The WT1-like transcription factor Klumpfuss maintains lineage commitment of enterocyte progenitors in the Drosophila intestine. Korzelius J, Azami S, Ronnen-Oron T, Koch P, Baldauf M, Meier E, Rodriguez-Fernandez IA, Groth M, Sousa-Victor P, Jasper H. Nat Commun. 2019 10(1), 4123. doi: 10.1038/s41467-019-12003-0.

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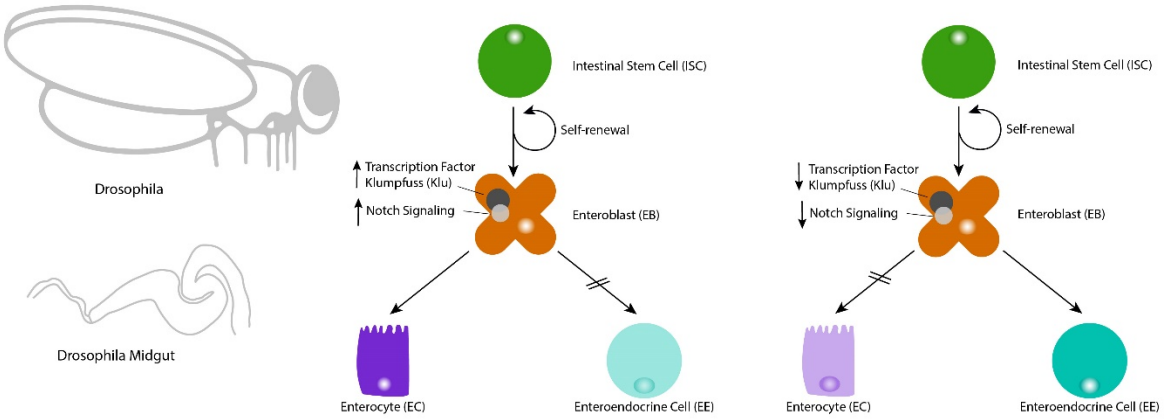
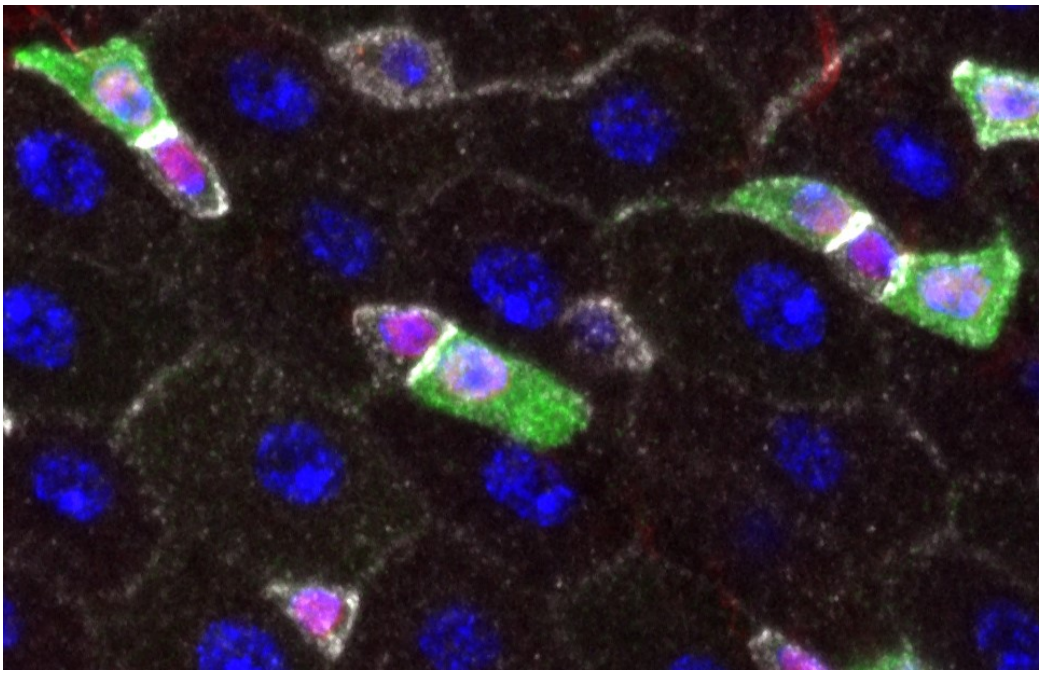


Picture 1

Schematic representation of the cell differentiation of adult stem cells in the intestine of the fruit fly (*Drosophila melanogaster*). The transcription factor Klumpfuss (Klu) together with Notch signaling regulates cell differentiation and precisely controls cell specification in enterocytes (ECs) or enteroendocrine cells (EEs). (Graphic: Magdalena Voll / FLI)



Picture 2:

The transcription factor Klu (green) is exclusively expressed in the EB precursor cell. Another transcription factor called Escargot is marked in red and labels both the EB cells and the Intestinal Stem Cells (ISC), which together play a crucial role in the regeneration of this tissue upon damage. (Source: Jerome Korzelius)

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Background information

The Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) – upon its inauguration in 2004 – was the first German research organization dedicated to research on the process of aging. More than 350 employees from around 40 nations explore the molecular mechanisms underlying aging processes and age-associated diseases. For more information, please visit www.leibniz-fli.de.

The Leibniz Association connects 95 independent research institutions that range in focus from the natural, engineering and environmental sciences via economics, spatial and social sciences to the humanities. Leibniz Institutes address issues of social, economic and ecological relevance. They conduct knowledge-driven and applied basic research, maintain scientific infrastructure and provide research-based services. The Leibniz Association identifies focus areas for knowledge transfer to policy-makers, academia, business and the public. Leibniz Institutes collaborate intensively with universities – in the form of “WissenschaftsCampi” (thematic partnerships between university and non-university research institutes), for example – as well as with industry and other partners at home and abroad. They are subject to an independent evaluation procedure that is unparalleled in its transparency. Due to the institutes’ importance for the country as a whole they are funded jointly by the Federation and the Länder, employing some 20,000 individuals, nearly half of whom are researchers. The entire budget of all the institutes is approximately 1.9 billion EUR. See https://www.leibniz-gemeinschaft.de/en/ for more information.