The Peroxisome: a new player in intestinal epithelial repair.

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Abstract

Stem cells drive tissue regeneration due to their capacity to proliferate and differentiate in response to damage. In this issue of *Developmental cell*, Du et al. (2020) reveal a mechanism regulating intestinal stem cell differentiation and epithelial repair following injury, which depends on peroxisomes and their action inducing JAK/Stat signalling and Sox21a.

Main text

The robust regenerative capacity of the intestinal epithelium is essential to maintain tissue integrity and function in face of a wide range of challenges, such as bacterial or viral infections, chemical damage and radiation. This process relies on tissue resident stem cells, which self-renew and give rise to multiple specialised cell types. However, as deregulation of stem cells proliferation can lead to chronic inflammation and cancer, a tight control of intestinal stem cell (ISC) proliferation is important to maintain tissue homeostasis and allow acute proliferative responses to injury, while preventing malignancy. Identification of the molecular and cellular mechanisms controlling intestinal regeneration is key to the understanding and prevention of intestinal disorders.

While multiple studies have comprehensively characterised the role of conserved signalling pathways in intestinal regeneration (Jiang et al., 2016; Vanuytsel et al., 2013), less is known about how changes in intracellular compartments may affect this process. Previously, Berger and colleagues (Berger et al., 2016) demonstrated a constitutive role of mitochondria in intestinal proliferation and stemness, through the use of a conditional mouse model of mitochondrial dysfunction caused by loss of the mitochondrial chaperone heat shock protein 60 (HSP60). Here, Du et al. (2020) uncover the importance of organelle dynamics in intestinal epithelial repair following damage.

Peroxisomes are intracellular organelles present in all eukaryotic cells and known for their role in lipid biogenesis, fatty acids oxidation and reactive oxygen metabolism. Peroxisomes are remarkably adaptable by their capacity to modulate their number, composition, shape and size in response to environmental stimuli, Du et al. (2020) showed that peroxisomal plasticity in the intestine is reflected by dynamic changes in organelle numbers in response to tissue damage. Importantly, using *Drosophila* models of peroxisomal dysfunction caused by loss of *pex2* and *pex10*, the authors demonstrated a functional role of peroxisomes in the differentiation of intestinal stem/progenitor cells (ISCs/EBs) into mature enterocytes (ECs) during tissue regeneration (Figure 1). Transcriptional profiling and *in situ* gene expression analysis of control and *pex* mutant midguts followed by genetic and functional experiments linked peroxisomes function to known regulators of stem/progenitor cell differentiation: JAK-STAT signalling and its downstream effector, the transcription factor Sox21a (Zhai et al., 2015). To further address the mechanisms mediating the effect of peroxisomes on signal transduction in the intestine, the authors performed mass spectrometry studies, which revealed *pex*-dependent interaction of peroxisomes with components of the intracellular endocytic transport machinery. Previously, endosomal sorting of the JAK/STAT pathway receptor, Domeless, was correlated with signalling activation during border cell migration in the *Drosophila* egg chamber (Devergne et al., 2007).

Interestingly, Du et al. (2020) noticed an increase in RAB7 positive late endosomes upon intestinal damage, which was disrupted upon loss of peroxisomal function. Consistently, RAB7 activation rescued ISC/EBs differentiation in *pex* mutant animals and was required for

JAK/STAT signalling and Sox21a activation following intestinal damage. Through a multimethod approach, Du et al. (2020) delineated a comprehensive pathway leading to the execution of intestinal regeneration by peroxisomes in *Drosophila*. In their working model, the authors propose that peroxisome elevation is required for intestinal regeneration by modulating endosomes maturation, activation of JAK/STAT signalling and expression of *Sox21a* (Devergne et al., 2007; Figure 1). Is this mechanism of intestinal repair conserved? Analysis of intestines from patients with inflammatory bowel diseases showed a consistent elevation of peroxisomes and upregulation of *RAB7* and *Sox21* expression. Furthermore, oral administration of peroxisome-proliferating agents improved intestinal repair and overall organismal wellbeing in *Drosophila* and mouse models of colitis. This elegant study presents compelling evidence of a conserved role of peroxisomes in the intestine and points to the use of peroxisome proliferation agents as a potential therapeutic avenue to restore intestinal regeneration and function in conditions of chronic tissue damage. Further studies in genetically modified pre-clinical models will be needed to categorically assess the translational potential of targeting peroxisome function in intestinal disease.

Multiple questions emerge from the findings presented by Du et al. (2020), such as the nature of the mechanisms involved in peroxisomes elevation and those by which peroxisomes induce maturation of late endosomes. A bigger and perhaps related issue is if and how the newly identified function of peroxisomes in intestinal regeneration is connected to the well-known role of these organelles in cellular metabolism. Previous studies in *Drosophila* and mice have demonstrated the importance of dietary lipids and fatty acid oxidation in ISCs proliferation and survival (Beyaz et al., 2016; Singh et al., 2016). In mice, the regenerative capacity of ISCs is induced by the peroxisome proliferator-activated receptor (PPAR) (Beyaz et al., 2016). Once activated, these receptors regulate the expression of a wide range of genes including genes involved in lipid metabolism and peroxisome proliferation. Metabolic studies on *pex* mutant midguts and dietary lipid supplementation of mutant animals are possible approaches to address a potential co-dependence between peroxisomal function and lipid metabolism during intestinal regeneration. The importance of the interaction between peroxisomes and other intracellular organelles such as mitochondria (Fransen et al., 2017) and early endosomes (Guimaraes et al., 2015) should be considered in that context. Peroxisomes may represent key executors of metabolic adaptations of the intestine to multiple intrinsic and external stimuli.

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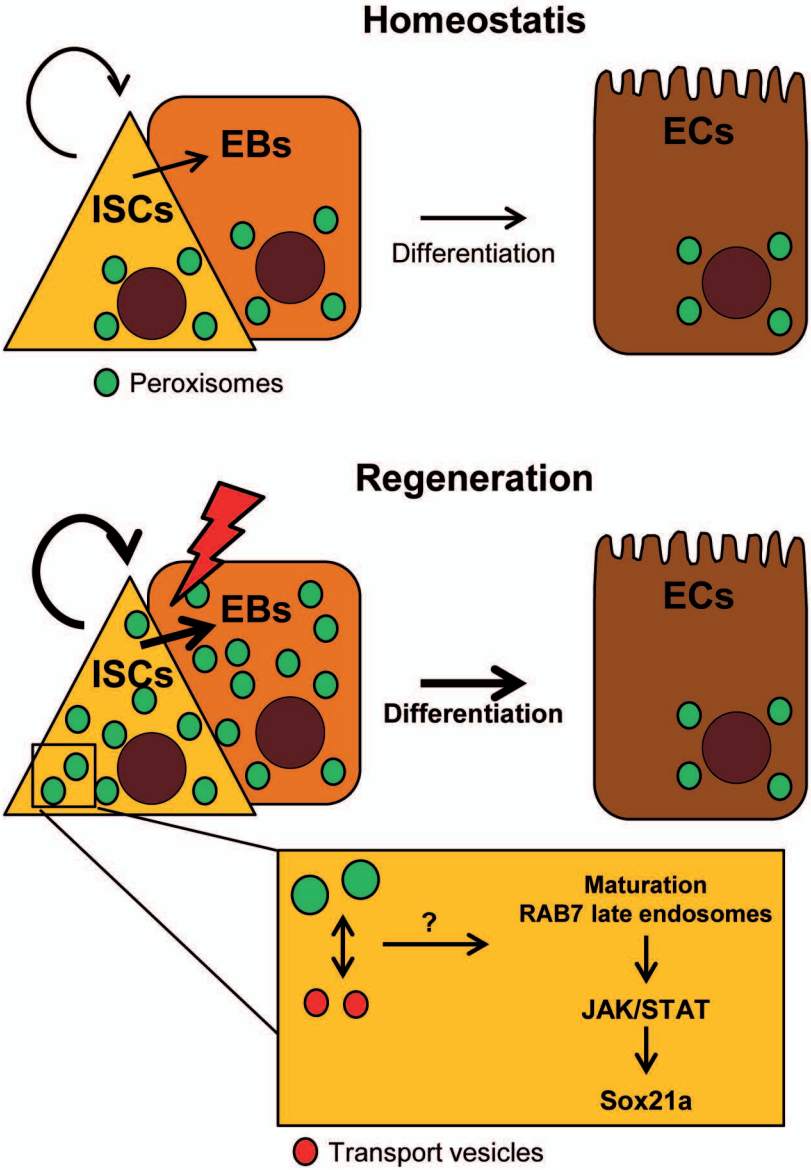
Figure Legend

Figure 1. Peroxisomes elevation in intestinal stem cells/progenitor cells promotes cell differentiation during tissue repair.

Schematic representation of proposed working model. Peroxisomes number increases within stem/progenitor cells following intestinal damage and interact with proteins from the vesicular transport machinery promoting maturation of RAB7 endosomes. This peroxisome-driven process induces differentiation of intestinal stem/progenitor cells through JAK/STAT signalling and Sox21a activation. Peroxisome dependent mechanisms involved in late endosomes maturation remain to be elucidated.


Homeostatis
EBs
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Maturation
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JAK/STAT
Sox21a
Transport vesicles