

Mitochondria deliver a gut check to intestinal stem cells

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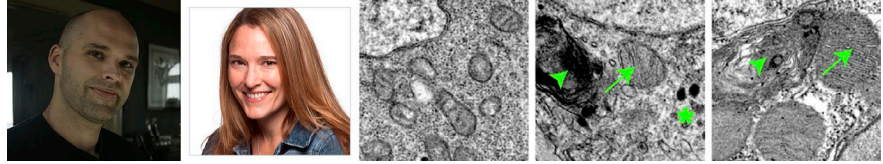
Mitochondrial turnover regulates stem cell proliferation and tissue homeostasis in *Drosophila* intestines.

Adult tissues are maintained by the carefully coordinated activity of stem cells. In the midgut of adult fruit flies, for instance, intestinal stem cells (ISCs) asymmetrically divide to yield both a new stem cell and an enteroblast capable of differentiating into the intestine's other main cell types. ISCs can undergo a burst of proliferation to repair the intestinal epithelium if it is damaged by chemicals or invading pathogens. But as flies grow older, a constitutive increase in ISC proliferation, with a concomitant reduction in enteroblast differentiation, disrupts the organization and function of the intestine. In this issue, Koehler et al. reveal that this process is regulated by mitochondrial turnover in ISCs, which enter a senescence-like state when they accumulate damaged mitochondria, delaying intestinal aging (1).

Stem cell activity is regulated, in part, by the cell's metabolic state. A few years ago, for example, Leanne Jones and colleagues, working with David Walker's laboratory at UCLA, found that boosting mitochondrial function in *Drosophila melanogaster* ISCs by overexpressing *spargel/PGC1 α* , the master regulator of mitochondrial biogenesis, delayed the age-related dysregulation of ISC and intestinal function (2). "That raised a big question for us: What role(s) do mitochondria play in adult stem cells?" Jones says.

To address this question, Jones and colleagues, led by graduate student Christopher Koehler, decided to perform a small-scale RNAi screen, depleting a number of genes in ISCs that regulate various aspects of mitochondrial function (1). The only genes whose knockdown affected ISC function were *pink1* and *parkin*, both of which promote the turnover of damaged mitochondria via a process called mitophagy.

"It was really striking," Koehler recalls. "When I dissected the guts from older flies lacking *pink1* or *parkin*, they looked like the intestines of 5–10-day-old flies. They hadn't aged a day!"



Focal Point Christopher Koehler, Leanne Jones, and colleagues demonstrate that *Drosophila* intestinal stem cells (ISCs) unable to degrade damaged mitochondria via the process of mitophagy can enter a senescence-like state where they are unable to proliferate. Compared with wild-type cells (left), ISCs lacking the key mitophagy proteins Pink1 (center) or Parkin (right) accumulate dysfunctional mitochondria with abnormal morphologies. These damaged mitochondria produce elevated levels of reactive oxygen species, which typically trigger ISC proliferation, a hallmark of intestinal aging. However, because loss of *pink1* or *parkin* suppresses ISC proliferation by inducing senescence, intestinal aging is delayed.

PHOTOS COURTESY OF THE AUTHORS.

"That was surprising to us," Jones says. "We had assumed that inhibiting mitophagy by depleting *pink1* or *parkin* would be detrimental."

"When I dissected the guts from older flies . . . they hadn't aged a day!"

As expected, ISCs lacking *pink1* or *parkin* accumulated damaged mitochondria until, in older flies, they contained large numbers of swollen or collapsed organelles with misshapen cristae. Yet, even though the ISCs themselves had an aged appearance, the flies' intestines showed no signs of aging. "Typically, one of the hallmarks of aging is unregulated ISC proliferation, which ultimately disrupts the intestinal epithelium," Koehler explains. "But when we depleted *pink1* or *parkin*, we saw a severe reduction in ISC proliferation in older flies, leading to a preservation of gut integrity."

Similarly, the researchers found that depleting *pink1* or *parkin* limited the ability of ISCs to proliferate in response to intestinal injury caused by the DNA damaging agent bleomycin. "So ISCs have a strategy to block their proliferation when they accumulate damaged mitochondria," Jones says.

What might that strategy be? Koehler et al. found that the dysfunctional mitochondria that accumulate in *pink1*- or *parkin*-deficient ISCs produce increased amounts of reactive oxygen species (ROS). Elevated ROS levels can stimulate ISC proliferation (3), but researchers have recently discovered that ROS can cause other *Drosophila* cell types to cease dividing and become senescent (4).

Koehler et al. therefore stained fly intestines for several markers of cellular senescence and saw that a subset of ISCs enter a senescence-like state in the absence of *pink1* or *parkin*. This explains why mitophagy-deficient ISCs do not increase their proliferation rate in response to aging or intestinal injury. In effect, it uncouples cellular and tissue aging: ISCs accumulate damage and cease dividing but the intestinal epithelium is able to maintain its organization.

Jones and colleagues now want to investigate whether other types of damage or cellular defects can induce ISCs to enter a senescence-like state, and whether similar mechanisms exist in the stem cells of other adult tissues.

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4. Nakamura, M., et al. 2014. *Nat. Commun.* 5:5264. <http://dx.doi.org/10.1038/ncomms6264>

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