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Revealing how organs self-repair could lead to safer regenerative therapies

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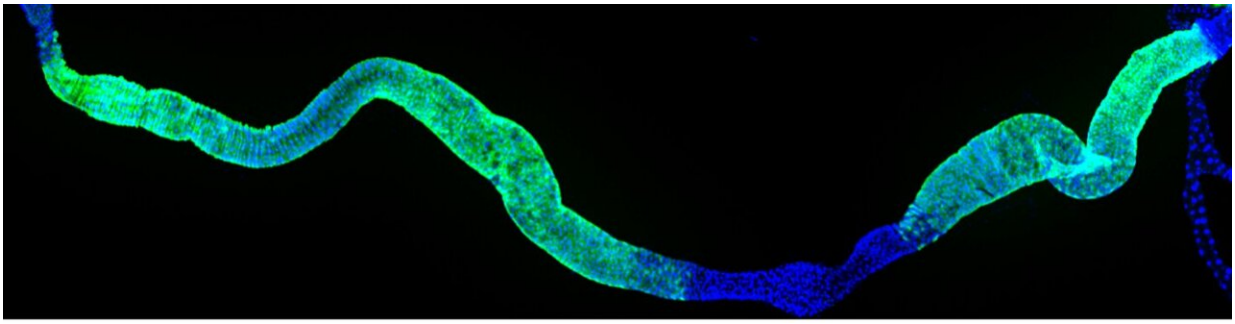

Cells in a fruit fly GI tract glow under a microscope. Credit: Afroditi Petsakou

Understanding how damaged organs heal themselves is important for scientists trying to develop treatments that regenerate injured, diseased, or aged tissue.

That includes understanding how self-healing stops when complete. Organs need to generate new cells for repair, but uncontrolled proliferation can lead to cancer.

Researchers in the lab of Harvard Medical School geneticist Norbert Perrimon have just provided new insight into how regeneration ends by revealing that nerves play a role in helping the injured gut finish healing and return to normal function.

"It's exciting to make progress on this unresolved question in regenerative biology," said first author Afroditi Petsakou, HMS research fellow in genetics.

Results were published Sept. 18 in *Nature.*

Petsakou and colleagues made their discovery in the fruit fly gut, which is similar to the human intestine but easier to study.

If the findings hold true for humans, they could lead to better ways to treat or prevent diseases that arise from improper healing, including inflammatory bowel diseases and some colorectal cancers.

How it works

The team chose the gut because it's "one of the most regenerative organs," regularly repairing damage from viruses, bacteria, and toxins in food, Petsakou said.

She fed fruit flies a chemical known to cause intestinal damage in both flies and people and studied how the gut repaired itself.

She identified a group of gut nerves that detected inflammatory molecules, such as tumor necrosis factor, known to be released by human and fly cells in response to injury.

The nerves responded by releasing acetylcholine—a neurotransmitter with many roles, including making the gut contract to move food along—into the flies' gut cells.

At the same time, the team found, the gut cells increased their sensitivity to acetylcholine by lowering levels of an enzyme that breaks down acetylcholine and raising levels of a protein that responds to

acetylcholine.

These changes caused small channels between gut cells to open and allowed an electrical current containing positively charged calcium ions to flow across the cells and stimulate healing.

When the team boosted the current, the gut finished healing and returned to normal function faster. By contrast, disrupting the current:

- Increased death of mature gut cells.
- Made gut stem cells proliferate excessively.
- Hampered the gut's ability to restore healthy functions such as absorbing nutrients.
- Caused too much inflammation.
- Raised the likelihood of tumor development in the gut.

"Without the current, the flies developed a condition similar to inflammatory bowel disease," said Petsakou.

What it means for regenerative medicine

Although flies are obviously not the same as people, each link in the chain of events the researchers pieced together has a direct counterpart in humans, and some of the proteins involved are already being tested as anti-inflammatory treatments for various diseases.

Those similarities increase the likelihood that stimulating nerve release of acetylcholine or boosting calcium currents in the gut could help treat inflammatory bowel diseases and the cancers they sometimes progress to.

The findings also suggest that such methods would work for ensuring healthy tissue healing in the body more broadly.

The work feeds into growing interest in manipulating electrical signals in the body to fight injury and disease.

"Bioelectric regenerative signaling is an exciting upcoming field," said Petsakou. "It's motivating to consider what triggering calcium-ion currents in the gut could achieve."

More information: Afroditi Petsakou et al, Cholinergic neurons trigger epithelial Ca2+ currents to heal the gut, *Nature* (2023). DOI: 10.1038/s41586-023-06627-y

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