Researchers discover birth-and-death life cycle of neurons in the adult mouse gut

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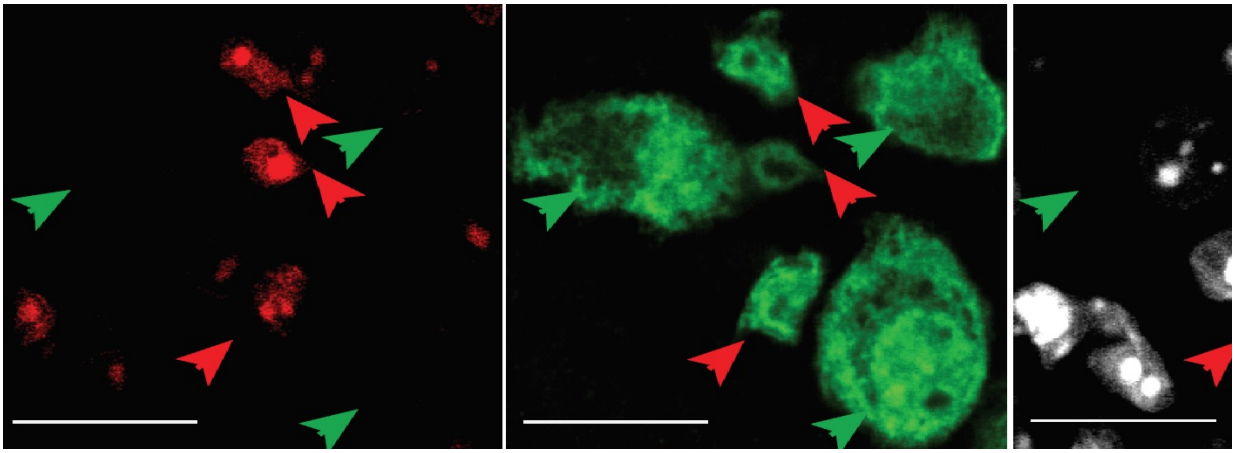


In the first-ever images of the death and birth of intestinal nerve cells, the first photograph depicts the loss of adult mouse enteric nerve cells. The red shapes are dead neurons. Neurons that are stained with a green nuclear dye are marked for programmed cell death. Credit: Pankaj Jay Pasricha lab, Johns Hopkins Division of Gastroenterology

Johns Hopkins researchers today published new evidence refuting the long-held scientific belief that the gut nerve cells we're born with are the same ones we die with.

In a report published in the journal *Proceedings of the National Academy of Sciences*, the investigators say the finding has profound implications for the understanding and treatment of disorders and diseases that affect

the digestive system.

Pankaj Jay Pasricha M.B.B.S., M.D., , professor of medicine and director of the Johns Hopkins Center for Neurogastroenterology, and Subhash Kulkarni, M.S., Ph.D., assistant professor at the Johns Hopkins University School of Medicine, led a research team that discovered the birth-and-death cycle of the neurons that form the network of millions of nerve cells throughout the digestive tract.

Previous studies have suggested that a healthy adult gut generates few or no new neurons. According to Pasricha, the Johns Hopkins study demonstrates that a healthy adult small intestine loses and regenerates about five percent of its nerve cells every day, or a third of them every week.

"Scientific dogma believed that gut neurons don't regenerate and that this 'brain,' known as the enteric nervous system, remained relatively static shortly after birth," Pasricha says. "We now have proof that, not only do they regenerate, but the whole network turns completely over every few weeks in adult animals."

The enteric nervous system controls and regulates vital gastrointestinal functions such as digestion, immunity and inflammation. After the brain, the digestive tract contains the largest nervous system in the human body.

"The yin and the yang of neuronal loss and birth keeps us going," Kulkarni says.

Pasricha, Kulkarni and their team confined their research to the small intestines of healthy adult mice. Using a variety of techniques, they found proteins associated with neural cell death and were able to observe the loss of neurons. Their work provided irrefutable evidence of ongoing

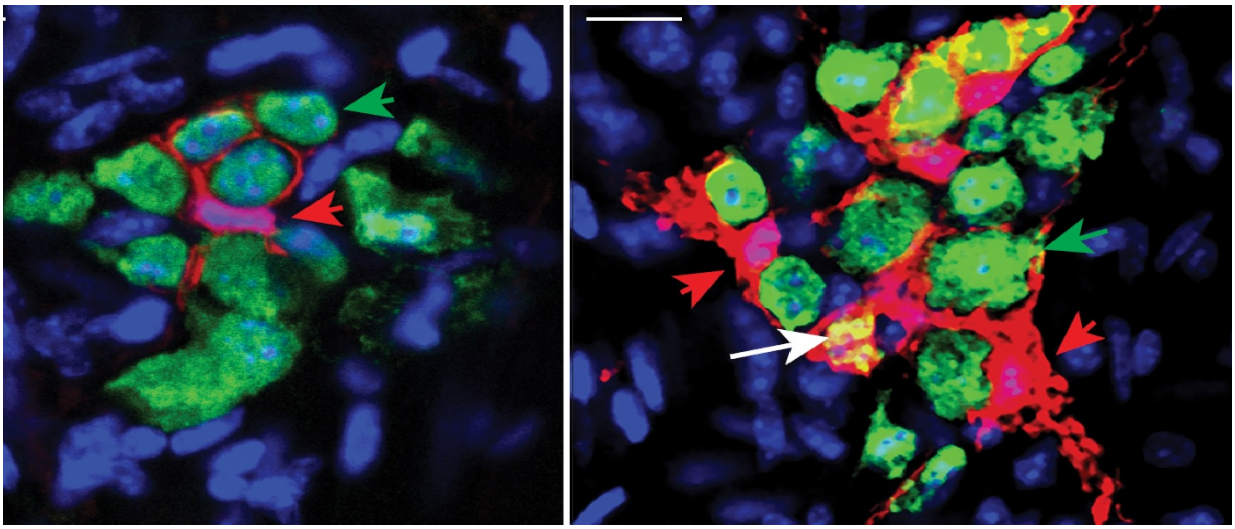
neuronal death due to apoptosis in the adult gut.

This significant rate of nerve cell loss left the research team with the question of how the gut maintains its relatively constant number of neurons.

"There could be only one answer," says Kulkarni. "The high turnover of neurons in the gut could only be reconciled by birth of newborn neurons, or neurogenesis."

Despite years of research, proof of neurogenesis in the healthy digestive system has been elusive. Scientists knew that the numbers of enteric neurons in a healthy small intestine remain remarkably constant for most of the adult life. While previous studies have shown that the adult gut contains cells that can generate neurons in lab settings outside of living organisms, finding whether such cells truly give birth to neurons in healthy adult animals eluded scientists for years.

Pasricha says the key to finding the process came when the team focused on tracing and following the behavior of cells that expressed Nestin, a protein typically associated with brain stem cells.



The green shapes are new neurons emerging from their precursor cells, highlighted in red. Credit: Credit: Pankaj Jay Pasricha lab, Johns Hopkins Division of Gastroenterology

After years of "staking out" these Nestin-expressing cells and studying their location, behavior and fate in the adult gut tissue, the research team found that some of them, called "enteric neural precursor cells," generated new neurons rapidly, shoring up and maintaining the large neuronal population that would otherwise dwindle fast in light of ongoing neuronal death.

The study also shows that any aberration that tilts the cells' birth-and-death balance may cause disease.

"Although previous studies have shown that regeneration of adult neurons may happen in an injured gut," Kulkarni says, "by and large, this appeared a relatively isolated and rare phenomenon. We now provide evidence that this happens continually and robustly in the adult healthy gut. It helps explain how this nervous system maintains itself, despite constant exposure to dietary factors, toxins, microbes and mechanical forces."

"We didn't believe it ourselves, at first," Pasricha, whose lab has been working on these neural stem cells for many years, says of the findings. "It's an extraordinary result; the mice get an entirely new 'brain' in the gut every few weeks."

He cautions that their study was limited to the mouse small intestine and that further research is necessary to determine whether other

species—including humans—and other regions of the gut experience the same cellular birth and death processes. Such studies are underway in Pasricha's Johns Hopkins lab.

The researchers hope the findings will help identify new regenerative and other therapies for gastrointestinal motility disorders like achalasia, gastroparesis, pseudo-obstruction, colonic inertia and other problems related to the digestive system.

"And as we dig deeper into this research," says Kulkarni, "we will gain new insights into a whole host of other diseases that affect not just the gut, but other organ systems with which this nervous system communicates, such as the brain."

More information: Subhash Kulkarni el al., "Adult enteric nervous system in health is maintained by a dynamic balance between neuronal apoptosis and neurogenesis," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1619406114

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