New stem cell mechanism discovered in the gut

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A special layer of cells that coats the insides of the small and large intestines takes in nutrients and water while keeping anything bad from circulating. This layer is called the intestinal epithelium. It completely

renews itself every four to seven days using stem cells. But scientists still do not know how, exactly, these stem cells work, or even what defines a stem cell.

Bernat Corominas-Murtra, previously postdoc at the Institute of Science and Technology Austria (ISTA) and now assistant professor at the University of Graz, and Edouard Hannezo, professor at ISTA, worked with an international group of experimental researchers led by the Jacco Van Rheenen team in Amsterdam to study the stem cells in the intestinal epithelium. They found an exciting new mechanism that could change our understanding of what a stem cell is. Their findings have now been published in the journal *Nature*.

The intestinal epithelium is just one layer of cells thick and is constantly renewed. It is all over the villi which look like tiny tentacles covering the insides of the small and large intestines. Between the villi, there are tiny pockets in the tissue called intestinal crypts. The name invokes mystery, which is a good description for what really happens there. "At the bottom of the crypts, stem cells in the epithelium are constantly dividing. Some of the resulting cells remain as stem cells in the crypt and the others are pushed outwards toward the tip of the surrounding villi," Corominas-Murtra explains, "there, in the end, they differentiate into functional cell types that allow intestinal function and which are discarded after a few days. This happens all the time inside your body, and if this mechanism breaks down, you can get into serious medical trouble."

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While studying these stem cells in the small and large intestines, the scientists were initially perplexed. "How we usually think of stem cells is that being a stem cell is determined by intrinsic biochemical properties of a cell—something like a biochemical marker we can identify," Corominas-Murtra says.

"We found that among the cells that had this traditional stem cell marker, many of them never actually worked as stem cells but were pushed out of the crypts to be discarded instead, without contributing at all to the long-term renewal of the gut. We also saw that while classical markers predicted about the same number of stem cells in both the small

and large intestines, there were about twice as many of them actually working as stem cells in the small intestine than in the large intestine." The scientists therefore wanted to understand what determines which cells actually act as stem cells and they found a surprising new mechanism that regulates the stem cells in the crypts.

"We found that whether these cells behave as a stem cell or not is all about their location. Cells in the epithelium are not just pushed outward from the crypt by the cell divisions below them—like on a conveyor belt—but there is another kind of motion involved," Corominas-Murtra explains. The scientists found that cells in the epithelium layer also actively move around in random directions—back and forth along the conveyor belt. This way, cells that were already pushed along the conveyor belt for a bit can end up back at the base of the crypt, and act there again as stem cells to divide and replenish the epithelium.

Edouard Hannezo explains the possible implications of these findings, "These movements constitute a new environmental mechanism that determines which cells get to functionally act as stem cells. In the small intestine, the molecular signal regulating the movements is stronger than in the large intestine, so cells can move more frequently back into the crypt. This explains why there are more actually working stem cells in the small intestine than in the large ones. This could have major implications for our understanding of what a stem cell actually is and how to use them in medical applications."

This insight builds on previous research by Bernat Corominas-Murtra and Edouard Hannezo at ISTA and the work of the Van Rheenen group. Originally coming from a physics background, Corominas-Murtra and Hannezo created an advanced mathematical model of the intestinal epithelium layer which included the motion of the cells both away from and back toward the crypt. Using their model, they predicted the number of working stem cells in the small and large intestines. A number of

other research groups in Europe designed experiments using the latest methods in microscopy and genetics to test the predictions and found them to be accurate. They even tried to inhibit the chemical signal in the crypts and saw that this reduced the number of working stem cells, as predicted.

More information: Jacco van Rheenen, Retrograde movements determine effective stem cell numbers in the intestine, *Nature* (2022). DOI: 10.1038/s41586-022-04962-0.
www.nature.com/articles/s41586-022-04962-0

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