Scientists unlock one mystery of tissue regeneration

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The human body has a remarkable ability to heal itself. Due to the presence of dedicated stem cells, many organs can undergo continuous renewal. When an organ becomes damaged, stem cells in the organ are typically activated, producing new cells to regenerate the tissue. This activity of stem cells, however, has to be carefully controlled, as too much stem cell activity can cause diseases like cancer. Current research in stem cell biology is starting to unravel the control mechanisms that maintain a balance between efficient regeneration and proper control of stem cell function. Strikingly, it is becoming evident that oxidative stress is at the heart of this regulation. Researchers at the University of Rochester have now identified a genetic switch that controls oxidative stress in stem cells and thus governs stem cell function.

The work was done by biologists Heinrich Jasper, Christine Hochmuth and Benoit Biteau, and geneticist Dirk Bohmann of the University of Rochester Medical Center, who hoped to gain some insight into human stem cell processes by studying the intestinal stem cells of Drosophila (fruit flies), which have genetic structures that, in many ways, mimic those that are found in humans. The researchers studied the function of two genes, Nrf2 and Keap1, which were already known as regulators of cellular responses to oxidative stress. The research team was surprised to discover that, in contrast to other cell types, Nrf2 was active within the

stem cells even in the absence of stress. This finding suggested that Nrf2 might have an unusual role in the control of stem cell function.

Indeed, the researchers found that Nrf2 prevents stem cells from dividing, and that only when Nrf2 is repressed can stem cell division take place. That's where the other gene, Keap1, comes into play.

When the intestine of the fruit fly is damaged, proteins secreted from the damaged cells send signals that activate stem cells. Jasper and colleagues learned that Keap1 inhibits the function of Nrf2 in stem cells experiencing such signals, making it possible for the stem cells to divide and regenerate the intestinal tissue.

Interestingly, Nrf2 controls stem cell activity by influencing the level of ROS (reactive oxygen species) in these cells. ROS are highly reactive molecules that, though occurring naturally in cells, can harm the cell structure if their concentration increases significantly. Nrf2 reduces the ROS levels in cells—and that's the mechanism by which Nrf2 helps to determine whether stem cells divide in fruit flies: Intestinal stem cell division can only take place when ROS levels go up, and as long as Nrf2 does its job, that won't happen. But when Keap1 represses Nrf2, ROS levels increase, allowing stem cells to divide and initiate regeneration. This switch is thus a critical stress sensor that allows proper control of stem cell activity in the intestine. Accordingly, the researchers found that when Nrf2 function is disrupted, the fly intestine degenerates due to excessive production of new cells by the stem cells.

Their work is being published in the February 4 issue of the scientific journal *Cell Stem Cell*.

Jasper expects other scientists to start testing whether stem cell regulation works the same way in small vertebrates and humans. "If it does, it would encourage the adaptation of these findings to new

therapies. And scientists may eventually learn how to control stem cell function to safely replace damaged tissue in humans."

The University of Rochester researchers are now trying to learn more about the processes behind Keap1 and Nrf2 activity. "How does Keap1 know that there's a signal from the damaged tissue?" asked Jasper. "We're trying to understand what happens upstream and what happens downstream—before and after Keap1 is activated."

Provided by University of Rochester