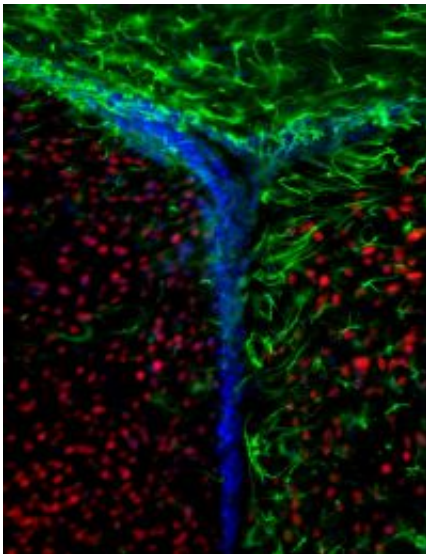


Researchers uncover new links between stem cells, aging and cancer

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This microscope image shows stem cells (blue) in a mouse brain. The stem cells persist throughout adult life and form new brain cells. Other types of mouse brain cells are shown in green (astrocytes) and red (neurons). Stem-cell function in this brain region declines with age, due the process explained by the Morrison team. Photo credit: U-M Center for Stem Cell Biology

(PhysOrg.com) -- Four genes previously implicated in the control of cancer have been shown by University of Michigan scientists to play key roles in the aging process and stem-cell regulation.

It's a case of genetic multiple personalities: Four genes that suppress tumor formation also regulate the ability of adult stem cells to replace

worn-out tissues, as well as the shut-down of stem cells during aging.

The genes switch on and off in a coordinated fashion as cells age to reduce the risk of cancer. In the process, they also shut down stem-cell function in aging tissues, reducing their capacity to regenerate.

The findings, reported in the Oct. 17 edition of the journal *Cell*, clarify and highlight the links between cancer, aging and stem-cell function by revealing some of their shared genetic pathways.

"All four of these genes had been implicated in the regulation of cancer, but only one of them had been implicated in the regulation of stem cells and aging," said Sean Morrison, director of the U-M Center for Stem Cell Biology and senior author of the *Cell* paper.

"So this is a pretty significant expansion of our mechanistic understanding of the connections between these vital processes," said Morrison, whose center is housed in the U-M Life Sciences Institute.

The three-year study of mouse brain cells also helped explain why human adult stem cells can't match the embryonic stem cell's potential to regenerate damaged tissues in patients, Morrison said.

"The genes identified in this study work together to reduce the function of adult stem cells as they age," he said. "Embryonic stem cells offer the advantage of not aging, not turning on this pathway. If you need to generate large numbers of cells to treat a major public health problem—such as juvenile diabetes—this is a big advantage."

The four genes examined in the study were *Ink4a*, *Arf*, *Hmga2* and *let-7b*. The work involved breeding mice that lacked combinations of these genes, then measuring the effects on stem-cell function and brain-cell formation at different life stages.

"We have now identified an entire pathway that changes gene expression within stem cells as they age, and that helps to explain why old tissues have less stem-cell function and less regenerative capacity," said Jinsuke Nishino, a postdoctoral fellow in the Morrison lab and first author of the Cell paper.

Two years ago, Morrison's team demonstrated that Ink4a, well known for its role as a tumor suppressor, becomes increasingly active with age and shuts down stem-cell replication in older mice. Flicking that genetic switch likely serves as a defense against cancer-causing genetic mutations, which accumulate as cells repeatedly divide.

The main question remaining after the 2006 Nature paper was: What causes Ink4a to turn on with age?

In the new Cell paper, the U-M researchers show that Ink4a's activity in mouse neural stem cells is regulated by Hmga2, which in turn is controlled by let-7b. The same relationship is likely at work in humans, who possess the same four genes.

"The tumor-suppressor mechanisms ramp up with age," Morrison said. "And the good news is that it allows us to get older before getting cancer. The bad news is that your tissues lose their regenerative capacity, making you older.

"The more we study this issue, the more we think that tissue aging exists as a by-product of mechanisms that were created to protect us against cancer," he said.

The paper's other authors are Kiran Chada and Injune Kim. Chada, a pioneer in the study of Hmga2, is a professor of biochemistry at the Robert Wood Johnson Medical School in New Jersey. Kim is a former postdoctoral fellow in Morrison's lab who now works at the Korea

Advanced Institute of Science and Technology.

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