Cell reprogramming during liver regeneration

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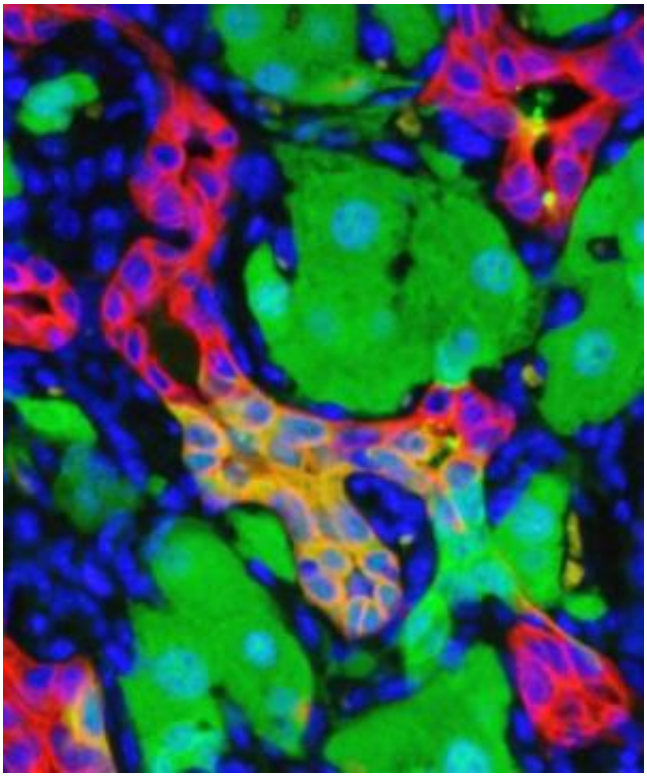

Hepatocytes are reprogrammed into biliary cells upon liver injury. Immunofluorescence analysis of yellow fluorescent protein-expressing mouse hepatocytes at 4 weeks after toxin-induced injury. YFP-expressing hepatocytes are green, biliary cells are red, cell nuclei are blue. In the center of the field is a duct containing multiple hepatocyte-derived biliary cells, which appear yellow since are expressing both green and red immunofluorescence. Credit: 2013 Cold Spring Harbor Laboratory Press

During embryonic development, animals generate many different types of cells, each with a distinct function and identity.

"Although the identities of these cells remain stable under normal conditions, some cells can be persuaded to take on new identities, through reprogramming," says Ben Stanger, MD, PhD, assistant professor of Medicine in the Division of Gastroenterology at the Perelman School of Medicine, University of Pennsylvania.

Researchers have been able to reprogram cells experimentally, but few have shown that cells can change their identities under normal physiological conditions in the body, particularly in mammals.

In the cover article of this month's issue of *Genes and Development*, Stanger, PhD candidate Kilangsungla Yanger, Yiwei Zong, PhD, and their colleagues, did just that in the liver of a mouse. Stanger is also an investigator in the Abramson Family Cancer Research Institute and the Department of Cell and Developmental Biology.

The adult liver contains two major cell types – hepatocytes and biliary cells – that differ dramatically in appearance and function. Hepatocytes are the main cell type in the liver, where they synthesize proteins and other macromolecules, and detoxify toxic substances. Biliary cells, on the other hand, line the bile ducts, which carry bile from the liver to the small intestine to help digest fats.

Using a sensitive method to tag and track how cells develop and differentiate, the researchers found that conditional expression of an activated Notch1 gene converted hepatocytes into biliary cells. Notch is an important receptor for relaying signals to tell cells how to develop.

What's more, after the researchers injured liver cells with a variety of toxins to stimulate wound healing, they found that over two to three

weeks hepatocytes activated a biliary cell program on their own, acquiring the shape and function of biliary cells. These changes were dependent on the activation of endogenous Notch signaling.

"This is direct evidence that cells can be converted from one mature cell type to another in a live animal, as part of a normal response to injury," says Stanger. "We think that augmenting pre-existing cell reprogramming relationships may be another way to engineer cells for the treatment of diseases in which there are not enough bile ducts, such as cholestasis."

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