Predicting the fate of personalized cells next step toward new therapies

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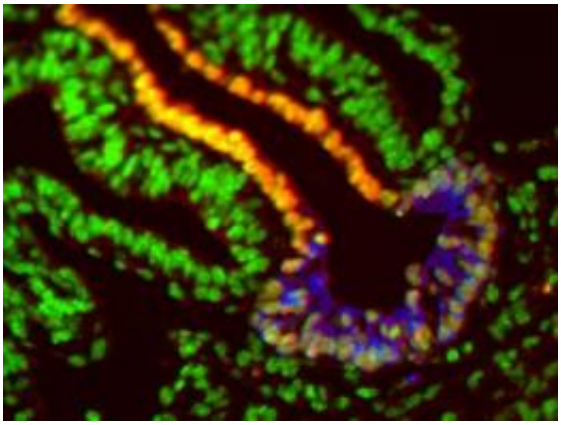

Earliest cells that form the liver (blue) emerging from progenitor cells (yellow) in the early embryo (green). Credit: Ken Zaret, PhD, Perelman School of Medicine at the University of Pennsylvania

Discovering the step-by-step details of the path embryonic cells take to develop into their final tissue type is the clinical goal of many stem cell biologists. To that end, Kenneth S. Zaret, PhD, professor of Cell and Developmental Biology at the Perelman School of Medicine at the University of Pennsylvania, and associate director of the Penn Institute for Regenerative Medicine, and Cheng-Ran Xu, PhD, a postdoctoral researcher in the Zaret laboratory, looked at immature cells called progenitors and found a way to potentially predict their fate. They base this on how the protein spools around which DNA winds -- called histones -- are marked by other proteins. This study appeared this week

in *Science*.

In the past, researchers grew progenitor cells and waited to see what they differentiated into. Now, they aim to use this marker system, outside of a cell's DNA and genes, to predict the eventual fate. This extra-DNA system of gene expression control is called epigenetics.

"We were surprised that there's a difference in the epigenetic marks in the process for liver versus pancreas before the cell-fate 'decision' is made." says Zaret. "This suggests that we could manipulate the marks to influence fate or look at marks to better guess the fate of cells early in the differentiation process."

"How cells become committed to particular fates is a fundamental question in developmental biology," said Susan Haynes, PhD, program director in the Division of Genetics and Developmental Biology at the National Institutes of Health, which funds this line of research. "This work provides important new insights into the early steps of this process and suggests new approaches for controlling stem-cell fate in regenerative medicine therapies."

A Guiding Path

How the developing embryo starts to apportion different functions to different cell types is a key question for developmental biology and regenerative medicine. Guidance along the correct path is provided by regulatory proteins that attach to chromosomes, marking part of the genome to be turned on or off. But first the two meters of tightly coiled DNA inside the nucleus of every cell must be loosened a bit. Regulatory proteins help with this, exposing a small domain near the target gene.

Chemical signals from neighboring cells in the embryo tell early progenitor cells to activate genes encoding proteins. These, in turn, guide

the cells to become liver or pancreas cells, in the case of Zaret's work. Over several years, his lab has unveiled a network of the common signals in the mouse embryo that govern development of these specific cell types.

Zaret likens the complexity of this system to the 26-letter alphabet being able to encode Shakespeare or a menu at a restaurant. Many investigators are now trying to broadly reprogram cells into desired cell fates for potential therapeutic uses.

The researchers had previously shown that a particular growth factor that attaches to the cell surface, gives a specific chemical signal for cell-type fate, promoting development along the liver-cell path and suppressing development along the pancreas-cell path. Liver and pancreas cells originate from a common progenitor cell type.

Zaret's group figured out which enzymes -- called histone acetyl transferases or methyl transferases (that add methyl groups or acetyl groups to histones) are relevant to the pancreas arm of the liver-pancreas fate decision. They used mice in which they knocked out the function for one enzyme type versus the other to induce the development of fewer liver cells and more pancreas cells.

The transferases mark genes for liver and pancreas fates differently before a cell moves into the next intermediate type along the way to becoming a mature liver or pancreas cell.

Investigators want to make embryonic stem cells for liver or pancreatic beta cells for therapies and research. To do this, they mimic the embryonic developmental steps to proceed from an embryonic stem cell to a mature cell, but have no way of knowing if they are on the right track. The hope is that the findings from this study can be applied to assess the epigenetic state of intermediate progenitor cells.

"By better understanding how a cell is normally programmed we will eventually be able to properly reprogram other cells," notes Zaret. In the near term, the team also aims to generate liver and pancreas cells for research and to screen drugs that repair defects or facilitate cell growth.

With regenerated cells, researchers hope to one day fill the acute shortage in pancreatic and liver tissue available for transplantation in cases of type I diabetes and acute liver failure.

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