Trio of signals converge to induce liver and pancreas cell development in the embryo

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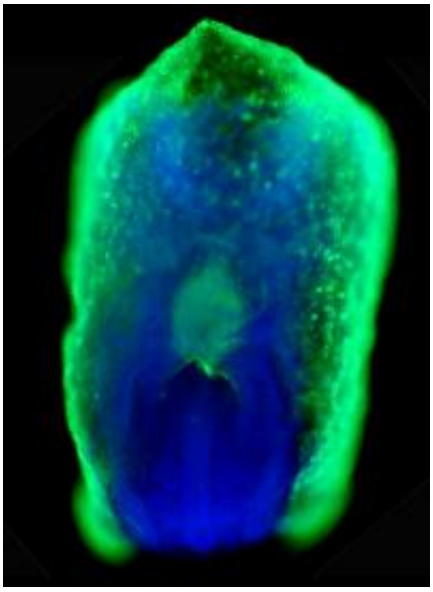

Distribution of the genetic regulatory protein, Smad4, in a mouse embryo at 8.5 days gestation. The green stain in the center is Smad4 expressed in the liver and pancreas progenitor cells. The green on the periphery is Smad4 in the extraembryonic yolk sac tissue. Credit: Ken Zaret, PhD; Ewa Wandzioch, PhD, University of Pennsylvania School of Medicine

(PhysOrg.com) -- Understanding the molecular signals that guide early cells in the embryo to develop into different organs provides insight into ways that tissues regenerate and how stem cells can be used for new therapies. 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.

Previous studies on pancreas and liver development have focused on individual molecular signals that induce these tissues to mature from a common precursor cell population. In a new study, published this week in *Science*, researchers investigated a trio of cell-signaling pathways that work simultaneously, converging to direct pancreas and liver progenitor cells to mature into their final state. They looked at how BMP, TGF-beta, and FGF signaling pathways turn on genes that guide cells to ultimately become pancreas or liver tissue.

The structure of the cell-signaling network provides insight into the basis of tissue development and how it can be manipulated to facilitate pancreas and liver-cell regeneration and development from embryonic stem cells.

"For my entire scientific life, I've been intrigued by how cells early in development make 'decisions' to turn on one genetic program and exclude others," says Kenneth S. Zaret, PhD, Professor of Cell and Developmental Biology and Associate Director, Institute for Regenerative Medicine at the University of Pennsylvania School of Medicine.

The work was conducted while Zaret and co-author Ewa Wandzioch, PhD, Research Associate in the Department of Cell and Developmental Biology, were at the Fox Chase Cancer Center in Philadelphia.

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 genetic 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. The regulatory proteins help with this, exposing a small domain near the target gene. They then act as a landing pad on which other proteins assemble to continue the gene activation process.

The Science paper addresses how chemical signals from neighboring cells in the embryo tell early progenitor cells to activate genes encoding the regulatory proteins. The regulatory proteins, in turn, guide the cells to become a liver cell or a pancreas cell. "In the current study we mapped the signaling pathways being turned on before they connected with the target genes," explains Zaret. "We monitored these cues before the cell displayed any overt signs of differentiation. While my lab and others had previously looked at individual signals that influence development, in this paper we simultaneously mapped three signal paths that converge to induce liver and pancreas cells. We're starting to construct a network of the common signals that govern development of these specific cell types. The complexity of this system is somewhat like our 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. "By better understanding how a cell is normally programmed we will eventually be able to directly reprogram other cells," notes Zaret. "An analogy I use here is if a watch is broken and you want to know how to reassemble it, the best thing is to go the factory and see how it is assembled in the first place. That may not be the solution to fixing it, but it's a good place to start."

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.

Source: University of Pennsylvania School of Medicine