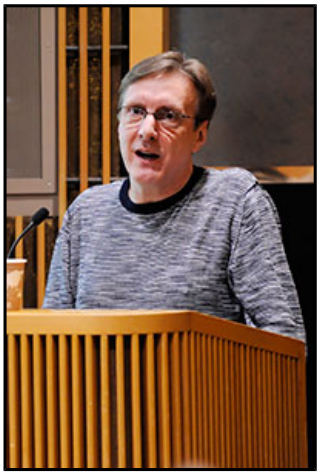
Understanding organ development

By Robin Arnette

For a mouse embryo to develop properly, many molecular events must occur within its body. Scientists have identified some of the steps, but one developmental biologist wants to fully understand the transition from endoderm, an early embryonic cell layer, to fully-functioning organs, a process known as differentiation.

Using a combination of real-time imaging and snapshot-style evaluation of organ differentiation, Christopher Wright, D.Phil. *(https://medschool.vanderbilt.edu/pdb/person/christopher-v-wright-dphil)* studies what happens as the pancreas develops in a mouse embryo. He believes that studying cell fate in mice will help researchers create cell-based therapies that combat human disease, such as diabetes and pancreatic cancer. Wright discussed his work May 6 as part of the NIEHS Distinguished Lecture Series. NIEHS Laboratory of Respiratory Biology lead Anton Jetten, Ph.D., hosted the seminar.



Wright holds several positions at Vanderbilt University, including director of the Program in Developmental Biology, professor in the Department of Cell and Developmental Biology, and the Louise B. McGavock Endowed Chair in Cell and Developmental Biology. (Photo courtesy of Steve McCaw)

Growing in 3-D

The pancreas is a glandular organ with two functions - it produces hormones, such as insulin, that circulate in the bloodstream, as well as digestive enzymes that flow into the small intestine. Wright said that one of the most important recent discoveries was that the pancreas doesn't grow like the kidneys or lungs in an outward-branching formation with new growth at the ends of the epithelium. Instead, it grows from a complex meshwork of epithelial tubes, at the interior, middle, and exterior, simultaneously.

Wright explained that pancreatic and duodenal homeobox gene 1 (Pdx1) and pancreas specific transcription factor 1a (Ptf1a) are among the most critical early-acting transcription factors that drive pancreas development. Researchers have used knowledge of the regulation of these genes in attempts to culture beta cells, the insulin-producing cells that are lost or dysfunctional in type 1 and type 2 diabetes. Unfortunately, none have been successful.

"When the stem cells are differentiated in flat culture conditions, they tend to pile up on each other without any sense of collaborative organization," Wright said. "Since they are not in the proper three-dimensional context, the only thing we get is immature beta cells."

Jetten also studies transcription factors as head of the NIEHS Cell Biology Group. (Photo courtesy of Steve McCaw)

New technology reveals pancreas development

Using a microscope with real-time video imaging capability, Wright and his team made several discoveries, including that a third transcription factor called neurogenin 3 (Ngn3) was also needed for proper pancreatic growth and differentiation. It turns out that endodermal cells express Ngn3 at low levels, and when daughter cells that are committed to becoming pancreas beta cells split off from the parent cells, the daughters express high levels of Ngn3.

Communication between parent and daughter cells taking place in the epithelium, the birthplace of beta cells, was also discovered. In other epithelial tissues, such as the developing nervous system, it usually takes an hour or so for daughter cells to fully separate from their parent cells, but Wright's lab determined that daughter cells maintain a connection that may last 20 hours or more after cell mitosis, or division.

"We didn't know that such a close, prolonged parent-daughter cellular contact was possible before our real-time imaging made it inescapably clear," Wright said, while showing the audience a short video clip of the process. "Perhaps young beta cells are instructing their parent cells to produce another beta cell in the next round of cell division."

Timing is everything

Another exciting finding to come from Wright's research was that he could completely transform an organ into a different organ. By using the antibiotic doxycycline to carefully time the production of Ptf1a, Wright was able to convert almost all of the stomach into pancreas tissue. Only the right timing and level of Ptf1a expression caused this remarkable organ conversion. At

slightly later stages, when stomach differentiation had progressed further, no amount of doxycycline could induce the conversion, and stomach tissue formed as normal.

Wright's work has uncovered pivotal information about how cells differentiate into specific organs, and how the gene regulatory networks and intercellular signaling molecules control that development.

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