Stem cells crucial to diabetes cure in mice

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More than five years ago, Dr. Lawrence C.B. Chan and colleagues in his Baylor College of Medicine laboratory cured mice with type 1 diabetes by using a gene to induce liver cells to make insulin.

"Now we know how it works," said Chan, director of the federally designed Diabetes and Endocrinology Research Center at BCM and chief of the division of endocrinology in BCM's department of medicine. "The answer is adult stem cells."

A gene called neurogenin3 proved critical to inducing cells in the liver to produce insulin on a continuing basis, said Chan and Dr. Vijay Yechoor, assistant professor of medicine-endocrinology and first author of the report that appears in the current issue of the journal *Developmental Cell*. The research team used a disarmed virus called a vector to deliver the gene to the livers of diabetic mice by a procedure commonly known as gene therapy.

"The mice responded within a week," said Yechoor. The levels of sugar in their blood plummeted to normal and stayed that way for the rest of their normal lives.

The quick response generated more questions as did the length of time that the animals stayed healthy.

They found that there was a two-step response. At first, the neurogenin3 gene goes into the mature liver cells and causes them to make small quantities of insulin - enough to drop sugar levels to normal, said

Yechoor.

"This is a transient effect," he said. "Liver cells lose the capacity to make insulin after about six weeks."

However, they found that other cells that made larger quantities of insulin showed up later, clustered around the portal veins (blood vessels that carry blood from the intestines and abdominal organs to the liver).

"They look similar to normal pancreatic islet cells (that make insulin normally)," said Yechoor.

They found that these "islet" cells came from a small population of adult stem cells usually found near the portal vein. Only a few are needed usually because they serve as a safety net in case of liver injury. When that occurs, they quickly activate to form mature liver cells or bile duct cells.

However, neurogenin3 changes their fates, directing them down a path to becoming insulin-producing islet cells located in the liver. The mature liver cell cannot make this change because its fate appears to be fixed before exposure to neurogenin3.

The islet cells in the liver look similar to those made by pancreas after an injury, said Yechoor.

"If we didn't use neurogenin3, none of this would happen," he said. "Neurogenin3 is necessary and sufficient to produce these changes."

Chan cautioned that much more work is needed before similar results could be seen in humans. The gene therapy they undertook in the animals used a disarmed viral vector that could still have substantial toxic effects in humans.

"The concept is important because we can induce normal adult stem cells to acquire a new cell fate. It might even be applicable to regenerating other organs or tissues using a different gene from other types of adult stem cells," he said.

Finding a way to use the treatment in human sounds easier than it is, he said. The environment in which cells grow appears to be an important part of the cell fate determination.

However, he and Yechoor plan to continue their work with the eventual goal of providing a workable treatment for people with diabetes.

More information: www.cell.com/developmental-cell/home

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