More insulin-producing cells, at the flip of a 'switch'

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Researchers have found a way in mice to convert another type of pancreas cell into the critical insulin-producing beta cells that are lost in those with type I diabetes. The secret ingredient is a single transcription factor, according to the report in the August 7th issue of *Cell,* a Cell Press journal.

When the gene called Pax4 is forced on in pancreatic alpha cells, the cells change their identity to become beta cells, the researchers found. The body in turn senses a loss of alpha cells, replaces them with new alpha cells and then converts those too into beta cells.

The hope is that a treatment based on the findings in mice might find its way to human patients, although "a lot of ifs remain before we will know whether it could be taken to the clinic," said Patrick Collombat of Inserm in France. For instance, it's not yet known whether the findings in mice will translate to human tissue. Even if they do, scientists would need to find a way to turn Pax4 on and then back off again once a sufficient number of beta cells were in place.

Still, the findings hold considerable promise. "The strategy we use is a good one," said Ahmed Mansouri of the Max-Planck Institute for Biophysical Chemistry in Germany. "It's a new idea that we might use one factor. Normally, we would have thought it would take more."

The results also show that the pancreas is in general capable of such regeneration. "It shows there are progenitors [in the pancreas] that can be

activated," Mansouri said.

In type I diabetes, the body essentially makes a mistake and autodestructs beta cells, the researchers explained. As those cells are lost, insulin levels drop and blood sugar soars, a condition that can lead to complications including blindness and even death.

While insulin-replacing injections can improve the situation enormously, people with the condition are left with fluctuations in blood sugar depending on their diet, exercise and other factors that can still lead to complications. "We need a better treatment," Collombat said. "We need to find a way to regenerate beta cells."

Earlier studies showed that Pax4 was important for making insulin-producing cells in the pancreas, Mansouri explained. Mice without the gene die at birth with pancreases that look normal except that they lack beta cells.

The researchers also found previously that another factor, which works against Pax4 action, could turn beta cells into alpha cells. (Alpha cells produce a hormone called glucagon when blood sugar levels fall too low, causing the liver to release glucose from storage.)

The discovery suggested to them that the opposite conversion might also be achieved. And indeed, they now show that it can. Mice with Pax4 switched on in the pancreatic cells end up with an eight-fold increase in the number of beta cells, Collombat said.

Those beta cells seem to be fully functional, they report. In mice treated with a drug that selectively kills beta cells, the conversion of alpha into beta cells can counter the effects of their diabetes, at least when the mice are treated at a young age.

Further studies are needed to show that the alpha to beta cell conversion can be kept under control, Mansouri said.

"Too many beta cells isn't good either," he said. "We'll need a strategy to trigger Pax4 and, at a certain point, also stop it."

Source: Cell Press (news : web)