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Insulin-Producing Pancreatic Cells Are Replenished by Duplication

Howard Hughes Medical Institute (HHMI) researchers at Harvard University have discovered that insulin-producing beta cells in the pancreas that are attacked in type 1 diabetes are replenished through duplication of existing cells rather than through differentiation of adult stem cells.

Although the experiments, which were done using mice, do not rule out the possibility that there are adult stem cells in the pancreas, the researchers say that they do suggest strongly that embryonic stem cells or mature beta cells may be the only way to generate beta cells for use in cell replacement therapies to treat diabetes.

The research team, which was led by HHMI investigator [Douglas A. Melton](#) at Harvard University, reported its findings in a research article published in the May 6, 2004, issue of the journal *Nature*. Melton's co-authors include Yuval Dor, Juliana Brown and Olga I. Martinez, all of Harvard.

In cell culture, embryonic stem (ES) cells retain the properties of undifferentiated embryonic cells. ES cells have the capacity to make all cell types found in an adult organism. One of the most hotly debated questions in biology is whether adult stem cells, which have been isolated from blood, skin, brain and other organs, have the same developmental capacity as ES cells.

Researchers have known for some time that ES cells can give rise to pancreatic beta cells during development. “But the more interesting question for us has been what happens in mature pancreatic tissue to both maintain the pancreas and to regenerate it,” said Melton. “Previous studies have suggested that there are sources of adult stem cells that might give rise to beta cells. However, those studies had largely depended on histological ‘snapshots’ of tissues.” Those snapshots can only suggest the “geographic” origin of new beta cells and not the identity of the cells from which they arise, Melton noted.

Melton and his colleagues knew that they could finally put such questions to rest if they could tag beta cells in such a way that they could determine unequivocally whether the new cells were made from existing beta cells or

from a different reservoir of stem cells. For these studies, they devised a “genetic lineage tracing” technique that involved engineering a mouse whose beta cells contained a telltale genetic marker that could be switched on by administering the drug tamoxifen to the mice.

The logic behind the technique is relatively straightforward: When the researchers administer tamoxifen to the adult mice, they can easily follow the marker to determine whether it is inherited by subsequent generations of beta cells. If it is inherited, then the cells expressing the marker are the offspring of pre-existing beta cells.

When the researchers applied their technique to the mice, they discovered that all the new beta cells they examined—whether arising in the usual process of renewal or during regeneration following partial removal of the pancreas - were generated from pre-existing beta cells. According to Melton, the finding highlights a largely unappreciated capability of beta cells.

“No one has really paid much attention to the replicative capacity of the beta cell,” he said. “And this work shows the cells to have a significant proliferative capacity that could be clinically useful.”

According to Melton, the findings might have implications for developing treatments for type 1 diabetes, a disease that destroys beta cells. “If such people have residual beta cells, these findings suggest that a useful clinical direction would be to find a way to boost the proliferative capacity of those beta cells, to restore insulin production in such patients.

“On the other hand, if type 1 diabetics don't have any beta cells left, then these findings suggest that the only source of new beta cells is probably going to be embryonic stem cells, because there don't appear to be adult stem cells involved in regeneration.”

Melton emphasized that although the results by his group cannot rule out the existence of beta-cell-producing adult stem cells, “they raise the bar on trying to demonstrate their existence. In these experiments, we find no evidence for the existence of adult pancreatic stem cells,” he said.

The genetic lineage tracing technique devised by Melton's group is a tool that can now be used to trace the origin of cells involved in the maintenance and repair of other types of tissue. Melton and his colleagues are already using the technique to determine the origin of new cells in lung tissue. And it should be possible to apply the technique to understand the origin of cancer cells in tumors or to understand the role of stem cells in such malignancies, Melton said.