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Researchers find novel mechanism regulating replication of insulin-producing beta cells

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Bringing scientists a step closer to new treatments for diabetes, researchers at the University of Pittsburgh School of Medicine and The Mount Sinai Medical Center have discovered a novel mechanism that regulates the replication of insulin-producing beta cells in the pancreas. The findings were recently published online ahead of print in *Diabetes*, a journal of the American Diabetes Association.

Regenerating beta cells to restore insulin production has moved to center stage in the quest for therapies for both Type 1 and 2 diabetes, said lead author Nathalie Fiaschi-Taesch, Ph.D., assistant professor, Division of Endocrinology and Metabolism, Pitt School of Medicine.

"Ideally, we would be able to do this by collecting cells from donor pancreatic tissue and growing them in the lab or better yet, giving a patient a pill to stimulate their own beta cells to replicate," she said. "In the past, this has proven to be very challenging. Our findings provide new insights into how one may be able to do this. "

After a 2009 paper in which a team led by Dr. Fiaschi-Taesch and Andrew F. Stewart, M.D., formerly of Pitt and now Irene and Dr. Arthur M. Fishberg Professor of Medicine and director of the Diabetes, Obesity and Metabolism Institute at The Mount Sinai Medical Center in New York, successfully induced human beta cells to replicate in the lab by elevating the level of a protein called cdk-6. In two current reports in *Diabetes*, they continued to examine the workings of the cell cycle proteins involved in the replication machinery.

What they found surprised them. Scientists had assumed the proteins resided in the cell's nucleus, where they could act upon genes and molecules to stimulate – or in the case of beta cells, prevent – cell replication. Their experiments showed that the cell cycle proteins were actually in the cell's cytoplasm, the fluid around the nucleus and contained within the cell membrane.

"It's like looking under the hood of a car for the engine and instead finding all the parts scattered around the back seat: it's no wonder the car won't go," Dr. Stewart explained. "Now we have to find ways to get those parts hooked up and back under the hood so that they can once again function as the engine that drives beta cell replication."

Increasing levels of cdk-6 led that molecule and other key (or critical) cell cycle proteins to move into the nucleus to foster replication, but in the quiescent or non-replicating cell, the only ones that remained in the nucleus were inhibitors of replication. Understanding how and why those inhibiting proteins block replication could in turn lead to ways to block their activity, providing a novel approach for reviving beta cell regeneration, Dr. Fiaschi-Taesch said.

Dr. Stewart noted that the relocation of cell cycle proteins outside the nucleus in the beta cell might hold true for other kinds of cells.

"It makes me curious about whether we can turn replication back on in other cells that aren't known to regenerate, such as neurons," he said. "I'd also like to know why these proteins continue to be produced by the quiescent cell if they aren't playing a role in cell replication."

In the second *Diabetes* paper, the team described the intracellular localization of all the cell cycle proteins in the beta cell, a biochemical atlas that could guide other researchers.