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One molecule, many more insulin-producing cells to treat diabetes, says Pitt team

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With a single stimulatory molecule, human insulin-producing beta cell replication can be sustained for at least four weeks in a mouse model of diabetes, according to researchers at the University of Pittsburgh School of Medicine in *Diabetes*, a journal of the American Diabetes Association.

They also found several cocktails of molecules that drive human beta cells to replicate, as well as important differences between mouse and human beta cells that could influence how these approaches are best used to treat diabetes, which is caused by insufficient insulin production leading to abnormal blood sugar levels.

"Our team was the first to show that adult human beta cells can be induced to proliferate or grow at substantial rates, which no one thought possible before," said senior authorAndrew F. Stewart, M.D., professor of medicine and chief of the Division of Endocrinology and Metabolism, Pitt School of Medicine. "Now our effort has been to unravel these regulatory pathways to find the most effective strategy that will allow us to treat - and perhaps cure - diabetes by making new insulin-producing cells."

In a series of experiments, lead author Nathalie M. Fiaschi-Taesch, Ph.D., assistant professor of endocrinology, and the team discovered that combining elevated amounts of the regulatory molecules cdk4 or cdk6 with a variety of D-cyclin proteins, particularly cyclin D3, stimulates human beta cell replication in test tubes.

"We didn't expect cyclin D3 to ramp up beta cell replication so strongly when it was used with either cdk4 or cdk6," Dr. Fiaschi-Taesch said. "There was no known role for cyclin D3 in human beta cell physiology."

Cyclin D2 is present in and essential for rodent beta cell replication and function, but the team showed that molecule is barely detectable in human cells, and beta cell replication could be sustained for at least four weeks in a model in which mice were transplanted with human beta cells engineered to overproduce cdk6. Blood sugar normalized in the diabetic mice transplanted with surprisingly small numbers of human beta cells, indicating that the cells functioned properly to produce needed insulin.

Mice don't appear to make cdk6 naturally, but they do have cdk4 and cyclins D1 and D2, so standard rodent studies of beta replication might have led scientists to pursue the wrong molecules in their quest to stimulate human beta cell replication, Dr. Stewart noted.

He and his colleagues continue to explore many other regulatory proteins that could play a role in encouraging or thwarting beta cell replication.

Provided by University of Pittsburgh

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