Medical Xpress

Pitt researchers identify key molecular pathway to replicate insulin-producing beta cells

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Researchers at the University of Pittsburgh School of Medicine are trailblazing the molecular pathway that regulates replication of pancreatic beta cells, the insulin-producing cells that are lacking in people who have type 1 or type 2 diabetes.

Building on findings from earlier this year, a research team led by Andrew F. Stewart, M.D., professor of medicine and chief of the Division of Endocrinology and Metabolism, University of Pittsburgh School of Medicine, has now shown in mouse experiments that knocking out two cell cycle proteins leads to robust beta cell replication. The results were presented today in New Orleans at the 69th Annual Scientific Sessions of the American Diabetes Association, and in an accompanying paper published online in the ADA's journal *Diabetes*.

"These proteins act like brakes to prevent regeneration of beta cells," Dr. Stewart explained. "It's a redundant system, though, so removing just one of the proteins isn't sufficient to make beta cells replicate."

In earlier studies, Rupangi Vasavada Ph.D., an assistant professor in Pitt's endocrinology division working with Dr. Stewart, assessed mice that lacked a key regulator of cell division called retinoblastoma protein (pRB), so named because mutations in it can lead to the childhood eye cancer. But the loss of pRB alone did not make beta cells regenerate.

In the current study, lead author George Harb, Ph.D., a postdoctoral fellow in Pitt's endocrinology division, engineered mice to lack the gene for another cell cycle protein that is very similar to pRB called p130. Again, there was no impact on beta cell production. The similarity of pRB and p130 hinted that they serve the same purpose, and so his next step was to engineer mice deficient in both proteins. The result was a marked increase in beta cell replication.

"The cell cycle has yet another protein, called p107, that is much like pRB and p130," Dr. Stewart noted. "Now we want to see what happens to beta cell numbers if we knock out any two of the three or all three."

In an online publication in Diabetes in January, another of his research teams demonstrated for the first time that human beta cells could be induced to replicate by boosting levels of cell cycle proteins cdk-6 and cyclin D1 using gene therapy techniques. When study co-author Nathalie Fiaschi-Taesch, Ph.D., assistant professor in Pitt's endocrinology division, transplanted those engineered cells into diabetic mice, blood sugar levels normalized. She will give a symposium at the ADA meeting describing that work.

The Pitt researchers also plan to examine the effects of gain or loss of other cell cycle proteins in an ongoing effort to better understand the regulatory pathway of beta cell replication and to identify targets that might make it possible one day to treat diabetes by giving patients more insulin-producing cells, perhaps by expanding cadaveric donor cells in the lab.

"It's now clear that both type 1 and type 2 diabetes are beta cell deficiency diseases," Dr. Stewart said. "And while we work on making more beta cells, our colleagues are trying to tackle the autoimmunity problems that cause a reduction in their number. Ultimately, both issues have to be addressed to develop a cure for diabetes."

Source: University of Pittsburgh Schools of the Health Sciences (news : web)