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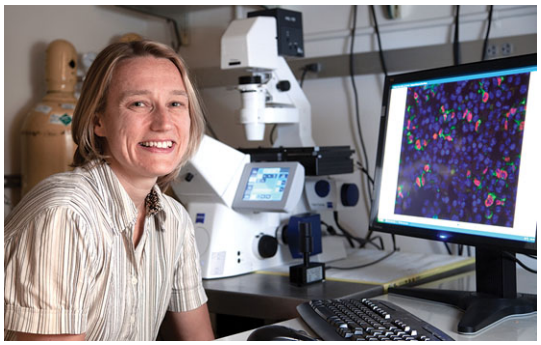
Protein Essential for Maintaining Beta Cell Function Identified

Finding underlies concept that loss of beta cell-specific traits contributes to diabetes



Maike Sander, MD

Researchers at the Pediatric Diabetes Research Center (PDRC) at the University of California, San Diego School of Medicine have shown that the pancreatic protein Nkx6.1 – a beta-cell enriched transcription factor – is essential to maintaining the functional state of beta cells.

Type 2 diabetes is characterized by impaired insulin secretion by pancreatic beta cells in response to a rise in blood glucose levels. The study, to be published in September 26 edition of *Cell Reports*, shows that loss of Nkx6.1 in mice caused rapid onset diabetes.

UC San Diego scientists – led by PDRC director Maike Sander, MD, professor in the UCSD Departments of Pediatrics and Cellular and Molecular Medicine – studied the molecular mechanisms that underlie loss of beta cell functional properties, such as regulated insulin secretion, during the progression of type 2 diabetes. They concluded that – by impairing beta cell function – reduced Nkx6.1 levels, as seen in type 2 diabetes, could contribute to its pathogenesis.

Inactivating the Nkx6.1 transcription factor in adult mice, then conducting a genome-wide analysis of Nkx6.1-regulated genes and functional assays, the scientists revealed the critical role of this protein in the control of insulin biosynthesis, insulin secretion and beta cell proliferation. Their findings demonstrate an intricate link between the beta cell's ability to import glucose and beta cell proliferation, supporting an emerging concept that glucose metabolism plays a critical role in regulating beta cell mass.

“We found the loss of Nkx6.1 activity had an immediate and dramatic impact on the expression of genes that give beta cells their ability to synthesize and release insulin in a regulated fashion,” said Sander. They discovered that genes involved in insulin biosynthesis, glucose import and glucose metabolism are direct transcriptional target genes of Nkx6.1. Its ablation also indirectly impacted the expression of numerous genes important for the function and proliferation of beta cells.

Over time, a subset of Nkx6.1-deficient beta cells acquired the molecular characteristics of somatostatin-producing delta cells, suggesting a link between impaired beta cell function and loss of cell identity. The sequential loss of first functional beta cell traits followed by the adoption of alternative endocrine cell fates closely mirrors the events previously observed in models of type 2 diabetes.

“Given that levels of Nkx6.1 are also reduced in human type 2 diabetic beta cells, our study lends support to the growing concept that loss of beta cell features could contribute to the onset of diabetes,” Sander said.

Additional contributors to the paper include Brandon L. Taylor and Fen-Fen Liu, of the UC San Diego Departments of Pediatric and Cellular and Molecular Medicine, and the UCSD Pediatric Diabetes Research Center.

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