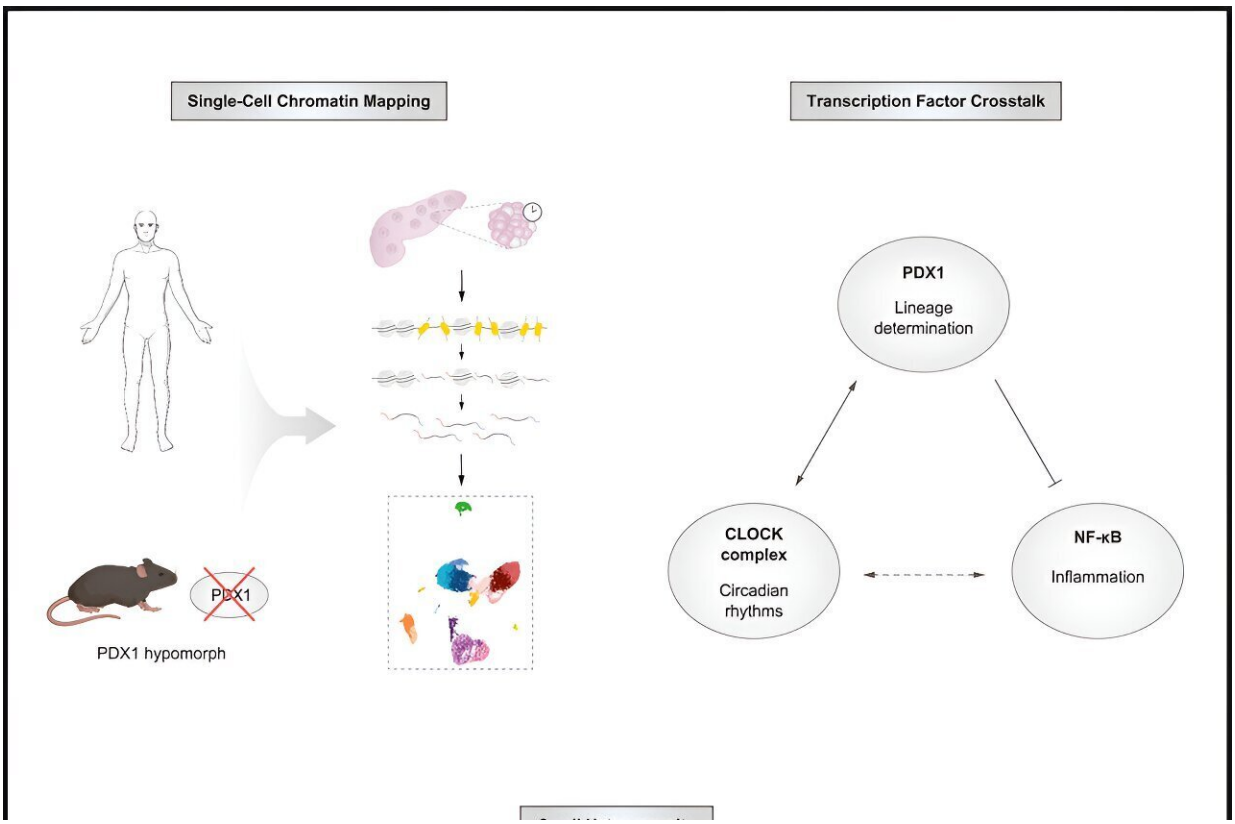
How transcription factors influence insulin-producing beta cells

January 31 2024, by Melissa Rohman



Credit: *Cell Metabolism* (2024). DOI: 10.1016/j.cmet.2023.11.018

A recent study from the laboratory of Joseph Bass, MD, Ph.D., the Charles F. Kettering Professor of Medicine and chief of Endocrinology in the Department of Medicine, has revealed how transcription factors

within individual cells influence the identity and function of insulin-producing beta cells in the pancreas. The findings are published in *Cell Metabolism*.

Previous work from the Bass lab found that a cell's circadian clock—the set of transcription factors that either turn on or turn off genes every 24 hours—is essential for beta cells to regulate insulin production in the pancreas.

Specifically, the scientists discovered that certain regions in the genome of beta cells contain specialized transcription factors that control the cells' production and release of insulin at specific times of the day and night.

In the current study, the investigators aimed to understand how this circadian timing determines both the type and function of cells within multicellular tissues, such as the pancreas.

Using single-cell sequencing to analyze beta cells from human islet cells, clusters of cells in the pancreas that contain beta and other hormone-producing cells, the investigators observed the expression one of two unique molecular signatures: An inflammatory state (supporting cell survival) or a cell signaling state involving "lineage-determining" transcription pathways (supporting cell function).

"We had always known that the circadian clock, at least in the beta cell, was really important, but here we discovered that there seems to be an additional role to help reinforce or control cell identity and help it possibly switch between these two different states: This inflammatory state and this more lineage-determining state where it appears to be more functional," said Benjamin Weidemann, a student in the Medical Scientist Training Program (MSTP) and lead author of the study.

In mouse models, the investigators also found that the fundamental signals that determine the development of beta cells that are encoded by the transcription factor PDX1 interact with these pathways to repress, or turn off, inflammation signaling.

"If beta cells begin to lose their function as insulin producing cells, what emerges is a set of genes that are involved in determining whether a cell survives or dies and belong to the signal transduction pathways that we call inflammatory," said Bass, who is also director of the Center for Diabetes and Metabolism and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The findings demonstrate how PDX1 protects beta cells from stress and inflammation and, furthermore, induces circadian signaling to support proper beta cell function and growth.

"We think that some of these principles may turn out to be involved in the signals that are important in telling a cell what its identity should be, in sustaining that identity, and turning on and off cell growth. So those are very general processes that probably will find applications in different tissue contexts, especially in immune cells," Bass said.

The findings may also have implications for metabolic diseases, particularly type 2 diabetes, the most common form of diabetes, and type 1 or juvenile diabetes, and may inform future therapeutic strategies, according to Bass.

As a beta cell loses its ability to turn off, or repress, the signals for inflammation and cell survival, they become more vulnerable to incoming signals that trigger cell death and inflammation pathways. One of the main entry points for these signals in the beta cell is a receptor called the IL-1 beta receptor.

The findings suggest that blocking this IL-1 beta receptor may enhance insulin production in the cell and could be an effective strategy for treating hypoinsulinemia, which is characterized by a low concentration of insulin in the blood. However, additional research is needed, according to Bass.

"What we think we have learned is something fundamental about what may determine the basic properties of cells that function well and make up a healthy pancreas versus those that are incompetent to produce insulin," Bass said.

More information: Benjamin J. Weidemann et al, Repression of latent NF-κB enhancers by PDX1 regulates β cell functional heterogeneity, *Cell Metabolism* (2024). DOI: 10.1016/j.cmet.2023.11.018

Provided by Northwestern University