Circadian clock controls insulin and blood sugar in pancreas

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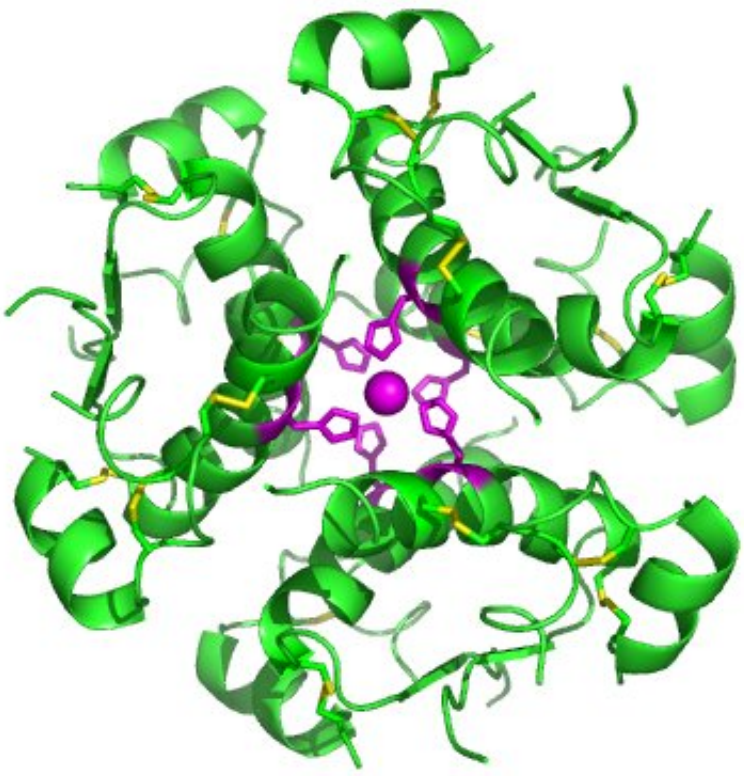

High-resolution model of six insulin molecules assembled in a hexamer. Credit: Isaac Yonemoto/Wikipedia

A new Northwestern Medicine study has pinpointed thousands of genetic pathways an internal body clock takes to dictate how and when our pancreas must produce insulin and control blood sugar, findings that

could eventually lead to new therapies for children and adults with diabetes.

The body's circadian clocks coordinate behaviors like eating and sleeping, as well as physiological activity like metabolism, with the Earth's 24-hour light-dark cycle. There's a master clock in the brain, as well as peripheral clocks located in individual organs. When genetics, environment or behavior disrupt the synchrony of these clocks, metabolic disorders can develop.

In a previous publication in *Nature*, Northwestern Medicine investigators showed that a circadian clock in the pancreas is essential for regulating insulin secretion and balancing blood sugar levels in mice. The scientists demonstrated that knocking out clock genes led to obesity and type 2 diabetes, but they still had much to learn if they wanted to manipulate clock action to treat the conditions.

"We knew that the pancreas didn't work if we removed these clock genes , but we didn't know how the genes were affecting the normal function of the pancreas," said principal investigator Dr. Joe Bass, chief of endocrinology at Northwestern University Feinberg School of Medicine and a Northwestern Medicine physician.

Clock genes are responsible for producing transcription factors, special proteins that help tell a cell how to function.

In the new study, published Nov. 6 in *Science*, Bass's laboratory revealed thousands of genes in the pancreas that the clock's transcription factors control in rhythm with the planet's daily rotation from light to dark.

"We established a new gene map that shows how the entire repertoire of factors produced in the pancreas maintain and anticipate daily changes in the external environment," Bass said. "These factors are all tied to the

rotation of the Earth—to the timekeeping mechanism that has evolved to control when we sleep, wake up, eat and store nutrients each day."

Bass's team focused on cells in the pancreas called beta cells, which secrete insulin into the blood stream to help the body absorb glucose—sugar—to use for energy. Using genome-wide sequencing technology on beta cells with both intact and disrupted clock gene function, the scientists were able to lay out the map of transcription factors and genes.

In ongoing research, Bass's group continues to study how the body's circadian clocks interact and how their rhythm is thrown off—not just in diabetes, but also during the normal aging process and from day-to-day conditions like jetlag, stress or dietary changes.

"This study reinforces the idea that clocks operating in cells are fundamental to health," Bass said. "They represent an important untapped target for improving the functions of cells in the pancreas."

More information: "Pancreatic β cell enhancers regulate rhythmic transcription of genes controlling insulin secretion" *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.aac4250

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