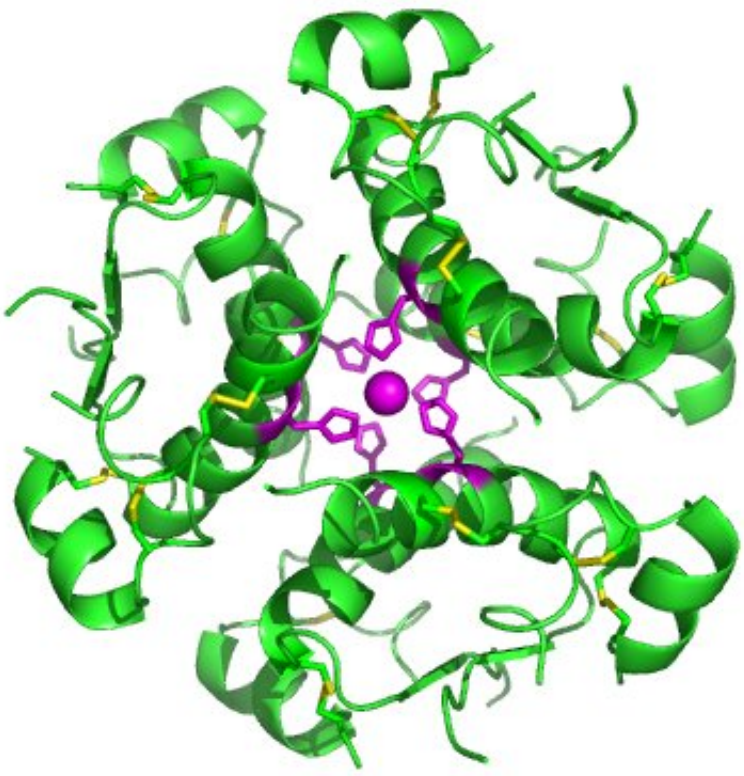
Newly identified biochemical pathway could be target for insulin control

September 24 2015



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

In the final event leading to the development of Type 2 diabetes, the pancreas loses its ability to secrete insulin and clear glucose from the blood. Preventing this breakdown in insulin secretion is a key goal in the

fight to reduce the burden of a disease that afflicts an estimated 29 million people in the United States.

Now researchers at Duke Medicine and the University of Alberta are reporting the identification of a new biochemical pathway to control insulin secretion from islet beta cells in the pancreas, establishing a potential target for insulin control.

The study, published online Sept. 24 in the journal *Cell Reports*, results from a field of work called metabolomics, which uses mass spectrometry instruments to measure and trace intermediate molecules in key metabolic pathways of cells and tissues.

"The Duke group focused on metabolites in islet cells that changed in response to elevated external glucose concentrations," said co-senior author Christopher B. Newgard, Ph.D., director of the Sarah W. Stedman Nutrition and Metabolism Center and the Duke Molecular Physiology Institute. "We found a strong increase in an intermediate in the purine/nucleotide metabolic pathway—known as adenylosuccinate, or S-AMP—in islets stimulated with glucose."

Impairment of S-AMP production was shown to interfere with normal glucose-stimulated insulin secretion. The Duke and University of Alberta Diabetes Institute teams were also able to demonstrate that S-AMP is capable of rescuing impaired insulin secretion in islets from people with Type 2 diabetes.

Newgard said the collaborative effort between the Duke and Alberta teams also yielded a separate finding, reported online Sept. 21 in the *Journal of Clinical Investigation*, which describes another molecular pathway that could be a potential metabolic target for insulin control.

In that study, the research teams identified a process that works

essentially like a dimmer switch to adjust how much or how little insulin is secreted when blood sugar increases. This dimmer switch appears to be broken in Type 2 diabetes, but the researchers found that its function can be restored.

"For the moment, we have two separate mechanisms, but with further study we may find that they are more connected," Newgard said. "Whether they are independent, additive or synergistic is unknown, so we are eager to bring the two projects together to see where that may lead."

Provided by Duke University Medical Center