Tribbles a new hope for type 2 diabetes patients?

Research shows promising targeted therapies for type 2 diabetes patients.

Named for the fur balls whose astonishing fecundity made them stars in early Star Trek episodes, the tribbles protein, first identified in fruit flies, aids in regulating many cell processes in humans. Joslin Diabet Centre researchers now have identified mechanisms triggered by a variant of the tribbles gene that cause trouble in insulin-producing pancreatic beta cells and that offer a promising target for therapies for people with type 2 diabetes, even if they don't carry that gene variant.

Earlier work by scientists at Joslin and elsewhere pinpointed a variant of the tribbles gene called 84 TRB3 that is linked to an increased risk of type 2 diabetes. People with this genetic variant also displayed signs c decreased insulin secretion.

These findings intrigued Joslin Principal Investigator Rohit N. Kulkarni, M.D., Ph.D., an expert in beta-cell biology and senior author on the paper published online in the *Journal of Clinical Investigation* on July 1. His lab began work in collaboration with the lab of Andrzej Krolewski, M.D., Ph.D., head of Joslin's Genetic and Epidemiology Research Section.

Chong Wee Liew, Ph.D., lead author and a postdoctoral researcher in the Kulkarni lab, first examined the expression of the tribbles protein in pancreatic islets (which house beta cells and other hormone-producin cells) in both humans and mice. He found that expression was elevated only in beta cells both in humans with type 2 diabetes and in mice that model the disease.

Tribbles binds to ATF4

Next, the scientists found that genetically engineered mice that over-express the tribbles protein develope glucose intolerance (often a prelude to diabetes). The mice also held fewer beta cells and secreted less insulin than normal mice.

Researchers then tested human and mouse beta cells modified to express genetic variants of tribbles, an found that insulin secretion was blunted in both.

In beta cells, insulin is packaged in granules that dock onto the cell membrane before being released whe necessary. But in the genetically modified cells that carried the genetic variants of the tribble protein, seve proteins that are critical to the 'docking' process were being affected. When these cells were further altere to over-express key docking proteins, insulin secretion returned to normal.

Searching for details on underlying mechanisms, the scientists found that tribbles was binding to ATF4, a "transcription factor" protein that regulates the creation of the key docking proteins.

The tribbles factor

"In our model, stress conditions, such as a genetic variant or insulin resistance or a high-fat diet, lead to increased availability of the tribbles protein by as yet poorly understood mechanisms," says Dr. Kulkarni, w is also an Assistant Professor of Medicine at Harvard Medical School. "That in turn blocks the function of t

ATF4 transcription factor, which ultimately leads to reduced insulin secretion."

In addition to revealing details on how the tribbles protein may hamper insulin secretion, the study suggest ways in which it may increase beta cell death and decrease beta cell proliferation. Tribbles normally binds and blocks the action of AKT, an insulin signaling protein directly involved in cell death and proliferation - a the tribbles genetic variants bound more strongly to AKT, thereby blocking proliferation and promoting cell death.

"While our research started out looking at one particular genetic variant of tribbles, our findings may have a broader impact on patients with type 2 diabetes, because they highlight ways in which elevated levels of tribbles have an effect on the beta cell," Dr. Kulkarni adds. "The higher the protein, the greater the defect. Yes, the more the tribbles, the more the trouble for beta cells."

Source: Joslin Diabetes Centre