Key protein accelerates diabetes in two ways

August 26 2013

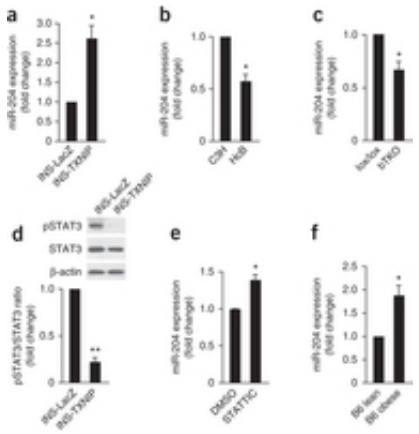

Figure 1: The effects of TXNIP and diabetes on beta-cell miR-204 expression. Credit: Nature Medicine

The same protein tells beta cells in the pancreas to stop making insulin and then to self-destruct as diabetes worsens, according to a University of Alabama at Birmingham (UAB) study published online today in the journal *Nature Medicine*.

Specifically, the research revealed that a protein called TXNIP controls the ability of beta cells to make insulin, the hormone that regulates blood-sugar levels.

"We spent years confirming that TXNIP drives beta-cell death in both Type 1 and Type 2 diabetes," said Anath Shalev, M.D., director of the UAB Comprehensive Diabetes Center and senior author of the paper.

"We were astounded to find that its action also contributes to a second major diabetic mechanism—the decrease seen in insulin production by beta cells—by a mechanism never before seen."

During their research, Shalev and colleagues discovered that high TXNIP triggers beta cells to make a specific snippet of genetic material called microRNA-204.

Genetic instructions are encoded in DNA chains and converted into ribonucleic acids (RNA) that direct the building of the proteins that comprise bodily structures and signals. A large portion of human genetic material, however, does not encode proteins and once was considered "junk DNA." RNA snippets called microRNAs are built based on this junk DNA, but instead of converting its messages into proteins, they silence targeted genes. This provides yet another level of regulation and a tool to turn genes on or off.

The study found that microRNA-204, in response to the TXNIP signal, interferes with MAFA, a transcription factor known to turn on the insulin gene. This is not the first instance of a microRNA influencing a transcription factor, but is a first for a factor critical to the expression of the human insulin gene. Taken together, the evidence argues for the existence of a previously unknown TXNIP/miR-204/MAFA pathway that dials down insulin production and drives diabetic disease.

After demonstrating that TXNIP ramps up production of miR-204 in a microarray analysis, the team confirmed the finding in beta cells, pancreatic islets of diabetic or TXNIP-deficient mice and human islets.

Based on these findings, the team redoubled its effort in 2013 to identify a new class of drugs that can regulate TXNIP levels to increase insulin production by beta cells and extend their lifespan. In partnership with the Southern Research Institute and Alabama Drug Discovery Alliance, the

researchers screened a library of 300,000 small molecules and the search has yielded lead molecules. The team expects to begin medicinal chemistry and preliminary mouse studies on the best candidates soon, with a goal of identifying a clinical compound and launching the first human clinical trials at UAB.

In early tests, the lead molecule normalizes TXNIP expression levels that have grown too high in response to elevated blood sugar without causing detrimental effects, Shalev said. Her team has also launched an effort to search for experimental compounds that interfere with microRNA-204 instead of TXNIP, opening the door for the design of novel RNA therapeutics.

Rethinking concepts

Excessive expression of the gene for TXNIP—or thioredoxin-interacting protein—has emerged as one of the most destructive forces in diabetes because it unleashes waves of highly reactive molecules—free radicals—that tell beta cells to self-destruct. Cells evolved to use oxidation to switch on cellular processes such as healing.

Disease-related oxidation, however, can create reactive particles that destroy cell components in a process called oxidative stress. By shutting down antioxidant thioredoxin, TXNIP contributes to oxidative stress; pancreatic beta cells are especially susceptible to oxidative stress and more likely to undergo programmed cell death in response to it.

Shalev favors the theory that any excessive demand on beta cells to produce insulin to counteract elevated blood sugar eventually stresses the beta cells, which become less able to make enough insulin to meet demand. This leads to an increase in blood sugar and greater levels of TXNIP production that result in even less insulin production and beta cell death.

In 2002, a team led by Shalev published a study showing that – in the face of rising glucose levels – the gene for TXNIP undergoes an 11-fold increase in expression in human pancreatic islets. A 2008 paper by the team revealed that deleting the gene for TXNIP in mice protected them against Type 1 and Type 2 diabetes and too much TXNIP-signaling shuts down the signaling pathway that keeps beta cells alive.

All that said, the mechanism revealed in this study has nothing to do with TXNIP's relationship with thioredoxin or its contribution to oxidative stress. This is the first study to suggest that TXNIP, along with being a regulator of cellular oxidation state, also regulates gene expression through a microRNA-based mechanism.

"Beyond the potential implications for diabetes drug design, our finding fundamentally alters the current understanding of the relationships between TXNIP, microRNAs, gene expression and insulin production," Shalev said. "The field may once again have to rethink its concepts of gene regulation, including that of insulin."

More information: Xu, G. et al. Thioredoxin-interacting protein regulates insulin transcription through microRNA-204, *Nature Medicine*, 25 August 2013. www.nature.com/nm/journal/vaop … nt/full/nm.3287.html

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