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A molecule central to diabetes is uncovered

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(Medical Xpress) -- At its most fundamental level, diabetes is a disease characterized by stress — microscopic stress that causes inflammation and the loss of insulin production in the pancreas, and system-wide stress due to the loss of that blood-sugar-regulating hormone.

Now, researchers led by scientists at the University of California, San Francisco (UCSF) have uncovered a new key player in amplifying this stress in the earliest stages of diabetes: a molecule called thioredoxin-interacting protein (TXNIP). The molecule, they've discovered, is central to the inflammatory process that leads to the death of the cells in the human pancreas that produce insulin.

"This molecule does something remarkable — it takes stress and makes it worse," said the senior author of the study, UCSF's Feroz Papa, MD, PhD, an associate professor of medicine at UCSF and a member of the UCSF Diabetes Center and the California Institute for Quantitative Biosciences (QB3).

The study is published this week in the journal *Cell Metabolism*, with a parallel study by researchers at Washington University in St. Louis. Both studies were funded by the Juvenile Diabetes Research Foundation (JDRF).

The work provides a roadmap for finding new drugs that could target and shut down the action of TXNIP, thus preventing or stalling the inflammatory processes it amplifies. Researchers in the field believe that this strategy could benefit people in the early days of the disease, when

diabetes is first developing or is soon to develop — a time referred to as the “honeymoon” period.

Clinical studies have already shown that dietary changes and other approaches can extend the honeymoon period in some people and prevent diabetes in others. The overarching goal of Papa’s research, he said, is to find a way to extend this honeymoon period indefinitely.

Diabetes and the Loss of Beta Cells

Diabetes is a major health concern in the United States, affecting an estimated 8.3 percent of the U.S. population — some 25.8 million Americans — and costing U.S. taxpayers more than $200 billion annually. In California alone, an estimated 4 million people (one out of every seven adults) has type 2 diabetes, and millions more are at risk of developing it. These numbers are poised to explode in the next half century if more is not done to prevent the disease.

At the heart of diabetes is the specialized hormone-producing beta cells, which dot the human pancreas and produce the insulin that helps regulate a person’s blood sugar.

These beta cells are like tiny biological factories that churn out insulin. A single beta cell might make a million molecules of insulin a minute. That means the billion or so beta cells in the average healthy pancreas will make more copies of insulin every year than there are grains of sand on every beach and in every desert in the world.

They are part of a delicate balance, however, and if the beta cells are lost, the pancreas may not be able to produce enough insulin and the body may not be able maintain proper blood sugar levels. That’s exactly what happens in diabetes.

Stress to the Cells

Papa and his colleagues have found in recent years that underlying beta cell destruction and diabetes is stress within a part of the cell known as the endoplasmic reticulum (ER).

All cells have these structures, and the enveloped folds of the ER are easily spotted under a microscope. They play a crucial role in all human cells by helping to process and fold proteins the cells produce. But for beta cells, this structure is critical to their specialized function of secreting insulin.

If one thinks of a beta cell as a little factory, the ER would be like the shipping warehouse — the packaging place where the end products are nicely wrapped, tagged with address labels, and sent to their final destination.

A healthy ER is like a well-run warehouse. Items are processed, packaged and shipped efficiently. A stressed ER, however, resembles a warehouse in shambles, with unboxed cargo accumulating everywhere. The longer this continues, the worse it becomes, and the body's solution to the problem is somewhat drastic: it essentially burns the factory down and closes the warehouse.

In scientific terms, the cell initiates what is known as the "unfolded protein response" in the ER, which activates inflammation through a protein known as interleukin-1 (IL-1). This process ultimately leads to apoptosis, the self-implosion of the beta cell.

For a whole organism, this is not as drastic as it sounds — with a billion or more beta cells in the pancreas, most people can afford to lose a few. The problem is that for far too many people, there are far too many warehouses burning down.

“There’s not a lot of reserve in the human pancreas — if these cells start dying, the remaining cells have to work harder,” Papa said. Past some tipping point, the balance is lost and diabetes develops.

The Discovery of TXNIP’s Role

Recognizing the importance of the inflammatory process in the development of diabetes, several pharmaceutical companies already have clinical trials underway to test potential new drugs that target the IL-1 protein.

In the new work, the UCSF team highlighted the protein TXNIP as a potential new target, until now an underappreciated central player in this process. TXNIP is involved in initiation of this destructive process of ER stress, unfolded protein response, inflammation and cell death.

They found that, as this process begins, a protein called IRE1 induces TXNIP, which leads directly to IL-1 production and inflammation. Removing TXNIP from the equation protects cells from death. In fact, when mice without this protein are bred with mice prone to developing diabetes, the offspring are completely protected against the disease because their insulin-producing beta cells survive.

What this suggests, said Papa, is that inhibiting TXNIP in people may protect their beta cells, perhaps delaying the onset of diabetes — an idea that that will now have to be developed, translated and tested in clinical trials.

More information:
http://www.sciencedirect.com/science/article/pii/S1550413112002847