

Discovery may revolutionise diabetes treatment

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About 40% of type 2 diabetics become dependent on injecting themselves with insulin to deal with the surges in blood glucose that occur after meals. Jeff Fillmore/Flickr, CC BY-NC-SA

Research [published in the journal *Nature Medicine*](#) on Monday by my team provides hope for a new approach to treating type 2 diabetes. In animal models of the disease, our treatment restores natural control of blood sugar.

Diabetes results from the inability of [beta cells](#) within the pancreas to make sufficient amounts of the hormone insulin to control the amount of sugar (glucose) in blood. High [blood glucose](#) levels are the root cause of all the medical problems associated with [diabetes](#), which is imposing an enormous burden on our health system.

Stressed cells

Inadequate insulin production in type 2 diabetes, the form of diabetes often associated with obesity, which affects around 1.7 million Australians, occurs because the beta cells become stressed. This stress is due to increased demand on the cells to make insulin, and high levels of fats and glucose in the blood.

[Previous research has shown](#) proteins from [immune cells](#) called cytokines that are released into the environment around the beta cells in diabetes also contribute to stress.

We have identified new stress-causing cytokines and shown that blocking them partially improves control of blood glucose, offering several new targets for therapy. But our major finding was the discovery that there's a specific cytokine, known as IL-22, that protects beta cells from stress and completely restores control of [blood sugar](#) when given to mice with obesity and diabetes.

One of our major challenges was to determine how IL-22 blocks stress in beta cells. To explain that, we need to step back a little and look at what these cells do.

Beta cells are clustered in groups within the pancreas, known as the [islets of Langerhans](#). And the average human pancreas contains several hundred thousand such islets, each of which contain around 200 beta cells.

Every beta cell makes about one million molecules of insulin every minute. Some quick arithmetic will tell you that a healthy human needs to make a lot of insulin to adequately control blood glucose.

The major form of stress for beta cells in diabetes is oxidative stress, a condition where reactive oxygen molecules are generated within a cell. Oxidative stress interferes with cellular metabolism, and activates the immune system.

Importantly for diabetes, oxidative stress interferes with the correct assembly of proteins (such as insulin) into their appropriate structures within a specialised organelle, the [endoplasmic reticulum](#). Stress in the endoplasmic reticulum reduces production of insulin, alerts the immune system and can even trigger suicide of beta cells.

IL-22 blocks these processes at their very start by preventing the generation of [oxidative stress](#), which explains its effectiveness against a broad range of stress inducers. It turns off genes that encode proteins causing stress while turning on genes that encode antioxidant proteins, which dispose of the activated oxygen radicals.

In other words, IL-22 is a powerful natural antioxidant for beta cells. But what does that mean for diabetes treatment?

A new treatment

There are many different forms of treatment used currently for [type 2 diabetes](#). Some of them push beta cells harder to make more insulin, while others use approaches unrelated to the pancreas, such as reducing glucose production in the liver or increasing glucose excretion in urine.

Although they lower blood glucose, these treatments don't really address the underlying problem. And about 40% of type 2 diabetics become

dependent on injecting themselves with insulin to deal with the surges in blood glucose that occur after meals.

Administering IL-22 is a completely different approach and one that promises to reduce glucose while preserving beta cells and limiting disease progression. The attraction of this therapy is that it addresses the underlying basis for the disease; IL-22 allows the system to naturally control glucose by fostering production of good quality, effective insulin.

Another key characteristic of diabetes is diminished response to insulin of cells in the muscles, fat, and liver that remove glucose from blood. We found treatment of mice with IL-22 not only restored appropriate insulin release from the pancreas, but also led to restoration of normal [insulin](#) sensitivity.

Most of our research has been conducted in cultured cells or in mice with diabetes, but it does have implications for treatment of human disease.

In collaboration with a group from Melbourne, we have obtained human pancreatic islets from organ donors and shown that IL-22 also protects human beta cells from [stress](#). While this supports the applicability of therapy to human diabetes, we still have to do much work before we can translate IL-22 into an effective and safe therapy in humans.

Interestingly, IL-22 treatment caused weight loss in obese mice by mechanisms we don't yet fully understand. Needless to say this would be a desirable effect if it were replicated in overweight individuals with diabetes. We hope our discovery will foster new approaches to diabetes therapy that reduce morbidity and ease the burden of the disease.

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