

In this issue:**Molecular Link Found Between High Blood Sugar and Retinopathy****Two Studies Suggest Method For Increasing Immune Tolerance****Researchers Find Cause for Blood Vessel Damage in People With Diabetes****MOLECULAR LINK FOUND BETWEEN HIGH BLOOD SUGAR AND RETINOPATHY**

Researchers at the JDRF Center for Diabetic Complications Research at Albert Einstein College of Medicine identified a molecular link that ties high blood sugar inside cells to the beginning of diabetic retinopathy. The research showed that hyperglycemia triggers overproduction of this molecule, which can cause retinopathy in the diabetic eye. This finding suggests that drugs targeting the molecule could be effective in the treatment and possible prevention of the complication.

The study, led by Michael Brownlee, M.D., and reported in *Cell*, found that cells damaged by high blood sugar produce excessive amounts of methylglyoxal (MG). The abnormal build-up of MG turns on a gene, *angiopoietin-2*, which plays a central role in the loss of oxygen-bearing blood vessels in the retina. The body compensates for that loss by growing new blood vessels, which can break and bleed into the eye and eventually lead to blindness.

Blocking MG production could prevent this harmful cascade in its earliest stage. And because this same mechanism may also be at the root of other diabetic complications, such as nerve and kidney damage, researchers think the finding could result in treatments for those complications, as well. (In addition, drugs targeting MG might lead to cancer-fighting agents, as stemming the growth of blood vessels could choke off tumors trying to tap into the blood supply to sustain growth.)

“We believe that by reducing MG levels, we would normalize damaging patterns of gene expression in complication-prone diabetic cells,” Dr. Brownlee said. “Control of changes in the concentration of MG also has implications beyond the realm of retinopathy since abnormal MG metabolism has been linked to kidney failure, cancer and malaria. We’re very excited to see where this research will lead.”

Dr. Brownlee said the next step may be an attempt to identify all the genes and proteins affected by MG. This would speed the development of effective drugs and treatments.

TWO STUDIES SUGGEST METHOD FOR INCREASING IMMUNE TOLERANCE

Two JDRF-funded research teams have made discoveries that could prove important in controlling the autoimmune response in established diabetes, or in preventing the disease altogether. The advances also could eventually point to ways to make the immune system more tolerant, or to prevent the rejection of transplanted islets.

Both studies, published in *Diabetes*, achieved immune tolerance in mice by boosting the effects of immune cells known as regulatory T cells. When these cells are activated, they restrain the immune system from attacking and destroying other cells. The studies show that with the right prompting, the regulatory T cells can block the onset of diabetes as well as prevent rejection of transplanted material.

“This is further evidence that one of the most effective strategies for modifying immune function will be to exploit the power of the body’s own regulatory T cells, rather than solely blocking the actions of destructive cells,” says JDRF Executive Vice President for Research Richard Insel, M.D. “Induction of regulatory T cells may provide immune tolerance without the need for continuous drug therapy.”

One study, conducted in Milan, Italy, used a cocktail of two drugs to spur the regulatory T cells into action. One day after receiving islet transplants, the mice received doses of rapamycin, an immunosuppressant drug, and interleukin (IL)-10, an immunosuppressive protein produced within the body.

While the rapamycin prevented rejection immediately after transplant, the IL-10 activated the regulatory T cells in the mouse, causing the cells themselves to secrete high levels of IL-10 as well as other factors that dampen the immune response. This enabled the mice to tolerate the transplanted islets over the long term—much longer than they would if treated with rapamycin alone. Later, when the same mice were given a drug that blocked the effects of IL-10, the animals immediately rejected the islets, confirming IL-10’s essential role in maintaining tolerance.

The research was led by Maria-Grazia Roncarolo, M.D., Ph.D., at the San Raffaele Telethon Institute for Gene Therapy in Milan.

The other study, conducted at the University of Alberta, used antibodies in a two-pronged approach to target two immune system molecules simultaneously. The therapy blocked CD40 ligand, which carries signals to immune cells by binding to their surface, and inducible costimulator (ICOS), a molecule that plays a critical role in activating “killer” T cells into a destructive mode.

When the researchers gave antibodies blocking the two molecules to mice receiving islet transplants, the grafts survived for more than 200 days in almost all of the animals. While the recipients tolerated the islets, their immune response appeared to be functioning normally, otherwise. The researchers detected regulatory T cells at the transplant site, as if they were drawn there to suppress rejection.

The researchers also tested anti-ICOS and anti-CD40 therapy in nonobese diabetic (NOD) mice, which spontaneously develop type 1 diabetes if left untreated. Sets of NOD mice were given anti-ICOS and anti-CD40 either alone or in combination for 14 days.

The groups receiving only one drug had a slight reduction in the number that developed diabetes. The mouse group receiving both drugs had a dramatic reduction in the number that developed the disease.

The Alberta study was led by Sulaiman Nanji, M.D., Ph.D., in the laboratory of James Shapiro, M.D., Ph.D., at the JDRF Center for Clinical Islet Transplantation at the University of Alberta.

Both approaches to inducing tolerance and blocking the autoimmune attack will move to large animal models before researchers can begin human trials.

RESEARCHERS FIND CAUSE FOR BLOOD VESSEL DAMAGE IN PEOPLE WITH DIABETES

JDRF-funded researchers at the University of Florida have made a potentially major discovery about why blood vessels in people with diabetes become damaged. They found that primitive repair cells that normally mend the damaged lining of blood vessels become too rigid to move in people with diabetes, leading to heart disease and complications that harm the eyes, kidneys, and nerves. Just as important, a simple laboratory procedure might be able to undo the damage, according to a study in the scientific journal *Diabetes*.

“These research findings present a new mechanism underlying the development of diabetic microvascular complications, showing that the damage caused by defects in blood vessel repair is potentially reversible,” said Antony Horton Ph.D., JDRF’s Program Director for Diabetes Complications. “The finding holds great importance for understanding and treating a broad range of diabetic complications.”

The Florida researchers, led by Mark Segal, Ph.D., showed they can restore the repair cells’ flexibility by dosing them with nitric oxide, a signaling molecule that occurs naturally in blood. Scientists have observed that people with diabetes have low levels of nitric oxide, so their primitive repair cells, called endothelial progenitor cells (EPCs), may have become too rigid to migrate to restore the damaged endothelial layer lining the blood vessels. The repair cells, made in the bone marrow, normally travel throughout the body to sites where blood vessels need mending and are drawn to those spots by signals from a protein called SDF-1.

The researchers isolated EPCs from blood samples drawn from patients with diabetes. They found that the cells were rigid and unable to move properly in response to SDF-1 signals. When the cells were exposed to nitric oxide, they became more supple, and their ability to move improved dramatically. The scientists found that nitric oxide affects the cytoskeleton, or scaffold, of the cell, and that by adding nitric oxide, they were able to rearrange the scaffold.

Dr. Segal said that many drugs already on the market have been shown to affect nitric oxide levels within EPCs. This suggests that medications could be effective at restoring EPC mobility and thus help to block vascular complications. He said that there might be ways to harvest EPCs from a patient, treat them with nitric oxide outside the body and then return them to the patient, where they would perform capably.