JDRF Juvenile Diabetes Research Foundation International
dedicated to finding a cure

research frontline

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In this issue:

NATURAL COMPOUNDS PREVENT DIABETES BY BLOCKING IMMUNE CELL CHANNEL

Using natural compounds derived from a shrub and the venom of a sea anemone, JDRF-funded researchers at the University of California-Irvine thwarted the autoimmune attack causing type 1 diabetes in experiments with human cells and animals.

In the research, the compounds blocked an ion channel in immune T cells that plays a critical role in allowing the cells to multiply and gear up for an immune attack. These results in human cells and animals suggest that the ion channel could be an important target for diabetes therapies.

The study, led by George Chandy, M.D., Ph.D., and Christine Beeton, Ph.D., showed that the compounds selectively stop white blood cells called effector memory T lymphocytes, which play a major role in type 1 diabetes and autoimmune diseases such as arthritis. Other white blood cells are left free to fight disease and infection. The results were published in the *Proceedings of the National Academy of Sciences*.

In their study, the Irvine researchers found that in people with type 1 diabetes or rheumatoid arthritis, some effector memory T lymphocytes had elevated levels of the ion channel protein, suggesting its role in autoimmune disease.

The researchers administered modified compounds from the rue shrub plant and a Cuban sea anemone extract to blood samples from type 1 patients. Both compounds suppressed the function of the T cells without affecting other T cells.

Ion channels are proteins that rest in the cell membrane, like tiny doughnuts floating in oil. They allow the passage of ions into and out of the cell, movement essential to many cellular functions, including the activation of T cells that prime them for attack against beta cells.

In tests using rats, the compound from the rue plant delayed the onset and reduced the incidence of diabetes, while the anemone venom stopped diabetes from progressing. The venom also improved joint function of rats with autoimmune arthritis. Both compounds proved nontoxic to the animals.

The Chandy laboratory is collaborating with AIRMID, a biotech company near San Francisco, to conduct preclinical safety studies for humans with both compounds.

AMNIOTIC FLUID-DERIVED STEM CELLS SHOW POTENTIAL

Researchers at Wake Forest and Harvard reported that stem cells collected from amniotic fluid have been used to create different cell types, including fat, bone, muscle, nerve, and liver cells. The research, published in *Nature Biotechnology*, was led by Antony Atala M.D., a Wake Forest scientist, in collaboration with colleagues at Wake Forest and Harvard University and represents "an important development for the field of regenerative medicine," said JDRF Executive Vice President for Research. Richard Insel, M.D.

In this study, the research team did not report creating pancreatic beta cells from the new stem cell source; it is still not known whether stem cells from amniotic-derived fluid have the capacity to develop into beta cells. JDRF, however, has been funding Dr. Atala to investigate whether this can be accomplished. In addition, JDRF has formed a partnership with the Pittsburgh biotechnology company Stemnion to conduct similar research on a similar cell also from the womb—an amnion-derived stem cell.

"That stem cells from amniotic fluid have the ability to become many cell types is a significant finding," added Dr. Insel. "It confirms how critical it is for JDRF to support research exploring the potential and promise of all types of stem cells- embryonic stem cells, adult stem cells, and amniotic fluid-derived and amnion-derived stem cells- to become mature functional cells to cure diabetes."

DRUG SHOWN TO PROTECT AGAINST DIABETIC RETINOPATHY

For the first time, an oral drug has been shown in human studies to protect against progression of diabetic retinopathy, the most common and serious eye-related complication of diabetes, and the leading cause of adult blindness in the U.S.

The drug, ruboxistaurin, was found to be effective in a three-year, Phase III clinical trial funded by Eli Lilly and Company and conducted at 70 sites across the U.S. Patients treated with the compound fared significantly better than those who received a placebo, suffering sustained visual loss at about half the rate of the placebo group. The study was led by Lloyd Aiello, M.D., Ph.D., of Joslin Diabetes Center, and published in the journal *Ophthalmology*.

Despite the positive results of the Lilly study, it is unclear when the drug might be approved for use by people with diabetes, as the FDA has asked that additional testing be conducted.

Ruboxistaurin inhibits an enzyme in the body called protein

kinase C beta or PKC beta, which contributes to blood vessel damage leading to diabetic retinopathy. JDRF funded early research on PKC's effect by George King, M.D. professor of medicine at Harvard Medical School. Dr King's work and collaboration with Lilly led to ruboxistaurin's development.

Retinopathy often has no overt symptoms in the earliest stages ("background retinopathy") but progresses over time to a proliferative phase in which blood vessels of the eye leak and rupture easily, eventually causing blindness. A related condition, diabetic macular edema, results when swelling in the center of the retina, known as the "macula," disrupts forward vision. Currently, the only effective treatments are laser surgery and vitrecomy, both of which inflict minor damage on part of the eye.

Ruboxistaurin was originally tested with the expectation that it would delay progression from background to proliferative retinopathy. The new study shows that the compound does not actually inhibit this progression, but it does reduce worsening of macular edema and visual acuity.

In an editorial published in *Ophthalmology*, Thomas Gardner, M.D., and David Antonetti, Ph.D., of the JDRF Center for Diabetic Retinopathy at Penn State College of Medicine, emphasize that the positive results—even for unexpected reasons—demonstrate the importance of testing basic laboratory discoveries with rigorous hypothesis-driven clinical trials: "Does the failure to support the original hypothesis make the findings any less important for patients? Not at all. In fact, this is the best possible outcome for patients because the drug improved the parameter with which they are most concerned—vision."

Drs. Gardner and Antonetti also note that the effects of ruboxistaurin represent "the beginning of a new era in diabetes complications treatments," with more emphasis on drugs and medical therapy and less emphasis on surgical procedures.