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Human Stem Cells Used to Elucidate Mechanisms of Beta-Cell Failure in Diabetes

Mechanisms that impair insulin production in diabetes identified using a human stem cell model of Wolfram syndrome, a rare form of diabetes

NEW YORK, NY (November 13, 2013) – Scientists from the New York Stem Cell Foundation (NYSCF) Research Institute and Columbia University Medical Center (CUMC) have used stem cells created from the skin of patients with a rare form of diabetes—Wolfram syndrome—to elucidate an important biochemical pathway for beta-cell failure in diabetes. The findings by Linshan Shang and colleagues were published today in *Diabetes*.

Scientists from NYSCF produced induced pluripotent stem (iPS) cells from skin samples from individuals with a rare form of diabetes, Wolfram syndrome. They then derived insulin-producing cells (beta cells) from these iPS cells, creating a human diabetes model in vitro. Next, they showed that the beta cells failed to normally secrete insulin because of protein-folding—or endoplasmic reticulum (ER) —stress. They found that a chemical, 4-phenyl butyric acid, that relieves this stress, prevents the cells from failing, suggesting a potential target for clinical intervention.

"These cells represent an important mechanism that causes beta-cell failure in diabetes. This human iPS cell model represents a significant step forward in enabling the study of this debilitating disease and the development of new treatments," said Dieter Egli, PhD, principal investigator of the study, and Senior Research Fellow at NYSCF and NYSCF–Robertson Stem Cell Investigator.

Wolfram syndrome is a rare, often fatal genetic disorder characterized by the development of insulin-dependent diabetes, vision loss, and deafness. Since all forms of diabetes are ultimately the result of an inability of pancreatic beta cells to provide sufficient insulin in response to blood sugar concentrations, this Wolfram patient stem cell model enables analysis of a specific pathway leading to beta-cell failure in more prevalent forms of diabetes. It also enables the testing of strategies to restore beta-cell function that may be applicable to all types of diabetes.

"Utilizing stem cell technology, we were able to study a devastating condition to better understand what causes the diabetes symptoms as well as discover possible new drug targets," said Susan L. Solomon, Co-Founder and Chief Executive Officer of The New York Stem Cell Foundation.

"This report highlights again the utility of close examination of rare human disorders as a path to elucidating more common ones," said co-author Rudolph L. Leibel, MD, the Christopher J. Murphy Professor of Diabetes Research and co-director of the Naomi Berrie Diabetes Center at CUMC. "Our ability to create functional insulin-producing cells using stem cell techniques on skin cells from patients with Wolfram's syndrome has helped to uncover the role of ER stress in the pathogenesis of diabetes. The use of drugs that reduce such stress may prove useful in the prevention and treatment of diabetes."

Clinicians from the Naomi Berrie Diabetes Center recruited Wolfram syndrome patients to donate a skin sample. All Wolfram patients had childhood-onset diabetes requiring treatment with injected insulin, and all had vision loss. Additional cell lines were obtained from Coriell Institute for Medical Research. The researchers at NYSCF "reprogrammed," or reverted, the skin cells to an embryonic-like state to become iPS cells. An iPS cell line generated from a healthy individual was used as a normal control.

The researchers differentiated the iPS cells from the Wolfram subjects and the controls into beta cells, an intricate process that took several weeks. They implanted both Wolfram and control iPS cell-derived beta cells under the kidney capsule of immuno-compromised mice. Beta cells from the Wolfram subjects produced less insulin in the culture dish and secreted less insulin into the bloodstream of the mice when they were challenged with high blood-sugar levels.

A key finding was that these beta cells showed elevated markers of ER stress. Treatment with 4-phenyl butyric acid reduced the ER stress and increased the amount of insulin produced by the beta cells, thereby increasing the ability to secrete insulin in response to glucose.

Direct evidence in mice, as well as circumstantial evidence in humans with both type 1 and type 2 diabetes, highlights the role of the ER stress response mechanism in the survival of insulin-producing beta cells. The ER stress response mechanisms oppose both the stress of immune assault in type 1 diabetes and the metabolic stress of high blood glucose in both types of diabetes. When the ER stress response fails cell death occurs, potentially reducing the number of insulin-producing cells.

The other contributors to the study are: Linshan Shang, Hector Martinez, David Kahler and Matthew Zimmer of the New York Stem Cell Foundation Research Institute; Haiqing Hua of The New York Stem Cell Foundation Research Institute and of the Division of Molecular Genetics, Department of Pediatrics, and the Naomi Berrie Diabetes Center at CUMC; and Kylie Foo, Kazuhisa Watanabe, Matthew Freeby, Wendy Chung, Charles LeDuc, Robin Goland, of the Division of Molecular Genetics, Department of Pediatrics, and the Naomi Berrie Diabetes Center at CUMC.

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The authors report no financial or other conflict of interest.

About The New York Stem Cell Foundation

The New York Stem Cell Foundation (NYSCF) is an independent research institute founded in 2005 that accelerates cures and better treatments for patients through stem cell research. NYSCF has over 45 researchers in its New York laboratory and is an acknowledged world leader in stem cell research and in developing pioneering stem cell technologies, including the NYSCF Global Stem Cell Array™. Additionally, NYSCF supports another 60 researchers at other leading institutions worldwide through its Innovator Programs, including the NYSCF – Druckenmiller Fellowships and the NYSCF – Robertson Investigator Awards. NYSCF focuses on translational research in a model designed to overcome the barriers that slow discovery and encourage multi-institutional collaboration.

NYSCF researchers have achieved five major discoveries in the field, including: the recent creation of patient-specific bone substitutes from skin cells; the discovery of a clinical cure to prevent transmission of maternal mitochondrial diseases in December 2012; the derivation of the first-ever patient specific embryonic stem cell line (named the #1 Medical Breakthrough of 2011 by Time magazine); the discovery

of a new way to reprogram stem cells; and the creation of the first disease model from induced pluripotent stem cells (also named the #1 Medical Breakthrough by Time magazine in 2008).

About the Naomi Berrie Diabetes Center at CUMC

The Naomi Berrie Diabetes Center at CUMC opened in 1998 to serve the 1.6 million people with diabetes in the New York area, by combining world-class diabetes research and education programs with family-oriented patient care. Founded with support from the Russell Berrie Foundation and other friends, and named in honor of the mother of the late Russell Berrie, founder of RUSS™ Toys, the center has been designated a national "Diabetes Center of Excellence." The Center's more than 100 faculty and students conduct basic and clinical research related to the pathogenesis and treatment of all forms of diabetes and its complications. For more information, visit www.nbdiabetes.org.

About Columbia University Medical Center

Columbia University Medical Center provides international leadership in basic, preclinical, and clinical research; medical and health sciences education; and patient care. The medical center trains future leaders and includes the dedicated work of many physicians, scientists, public health professionals, dentists, and nurses at the College of Physicians and Surgeons, the Mailman School of Public Health, the College of Dental Medicine, the School of Nursing, the biomedical departments of the Graduate School of Arts and Sciences, and allied research centers and institutions. Columbia University Medical Center is home to the largest medical research enterprise in New York City and State and one of the largest faculty medical practices in the Northeast. For more information, visit cumc.columbia.edu or columbiadoctors.org.

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