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Researchers Uncover Cellular Metabolism Triggers that Lead to Type 2 Diabetes

While legions of medical researchers have been looking to understand the genetic basis of disease and how mutations may affect human health, a group of biomedical researchers at UC Santa Barbara is studying the metabolism of cells and their surrounding tissue to ferret out ways in which certain diseases begin. This approach, which includes computer modeling, can be applied to

Type 2 diabetes, autoimmune diseases, and neurodegenerative diseases, among others.
Scientists at UCSB have published groundbreaking results of a study of Type 2 diabetes that point to changes in cellular metabolism as the triggering factor for the disease, rather than genetic predisposition. Type 2 diabetes is a chronic condition in which blood sugar or glucose levels are high. It affects a large and growing segment of the human population, especially among the obese. The team of scientists expects the discovery to become a basis for efforts to prevent and cure this disease.

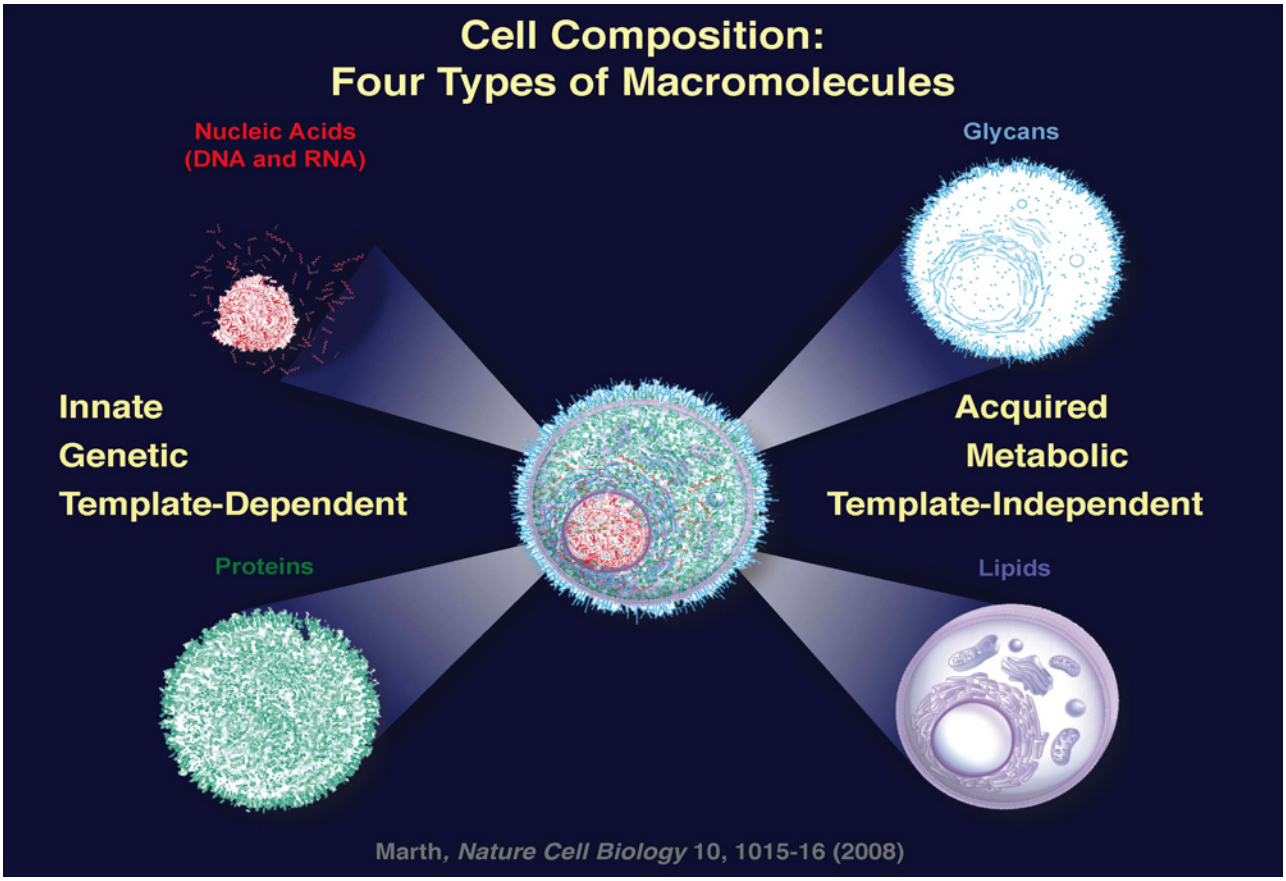
The current work is based on a previous major finding by Jamey Marth
, UCSB professor of molecular, cellular, and developmental biology, who determined the identity of the molecular building blocks needed in constructing the four types of macromolecules of all cells when he was based at the Howard Hughes Medical Institute in La Jolla in 2008. These include the innate, genetic macromolecules, such as nucleic acids (DNA and RNA) and their encoded proteins, and the acquired metabolic macromolecules known as glycans and lipids.

"By studying the four types of components that make up the cell, we can, for the first time, begin to understand what causes many of the common grievous diseases that exist in the absence of definable genetic variation, but, instead, are due to environmental and metabolic alterations of our cells," said Marth. UCSB is the only institution studying these four types of molecules in the cells while also using computational modeling to determine their functions in health and disease, according to Marth.

The new study, published in the December 27 issue of PLOS ONE, relies on computational systems biology modeling to understand the pathogenesis of Type 2 diabetes.

"Even in the post-genomic era, after the human genome has been sequenced, we're beginning to realize that diseases aren't always in our genes ?? that the environment is playing a major role in many of the common dise ases," said Marth.

Normally, beta cells in the pancreas sense a rise in blood sugar and then secrete insulin to regulate blood glucose levels. But in Type 2 diabetes, the beta cells fail to execute this important function and blood sugar rises, a trend that can reach life-threatening levels. The researchers identified a "tipping point," or metabolic threshold, that when crossed results in the failure of beta cells to adequately sense glucose in order to properly secrete insulin.



Obesity has long been linked to Type 2 diabetes, but the cellular origin of the disease due to beta cell failure has not been described until now. "In obesity there's a lot of fat in the system," said Marth. "When the cell is exposed to high levels of fat or lipids, this mechanism starts, and that's how environment plays a role, among large segments of the population bearing ?normal' genetic variation. We're trying to understand what actually ca uses disease, which is defined as cellular dysfunction. Once we understand what causes disease we can make a difference by devising more rational and effective preventative and therapeutic approaches."

The research was based on a unique approach. "This project illustrates the power of systems biology; namely, how a network perspective combined with computational modeling can shed new light on biophysical circuits, such as this beta-cell glucose transport system," said co-author Frank Doyle, professor of chemical engineering. "It cannot be done by molecular biology alone, nor computational modeling alone; rather, it requires the uniquely interdisciplinary approach that is second-nature here at UCSB." Doyle is associate dean for research of the College of Engineering, director of UCSB's Institute for Collaborative Biotechnologies, and the Duncan and Suzanne Mellichamp Chair in Process Control.

"We are excited to bring our 20 years of expertise on Type 1 diabetes and systems biology methods to look at the networks responsible for the onset of Type 2 diabetes," said Doyle.

According to the American Diabetes Association, 8.3 percent of the U.S. population has diabetes. The disease can lead to nerve loss, blindness, and death.

Marth is a professor in the Department of Molecular, Cellular, and Developmental Biology and the Biomolecular Science and Engineering Program; and holds the John Carbon Chair in Biochemistry and

Molecular Biology and the Mellichamp Chair in Systems Biology. He is also a professor with the Sanford-Burnham Medical Research Institute in La Jolla.

The first author of the paper is Camilla Luni, who was a UCSB postdoctoral researcher at the time of the study, and is now with the University of Padova, in Italy. The research was funded by a grant from the U.S. Army Research Office to UCSB's Institute for Collaborative Biotechnologies, and a grant from the U.S. National Institutes of Health.

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