An imbalance of cellular bioenergetics in pancreatic beta-cells links to type 2 diabetes

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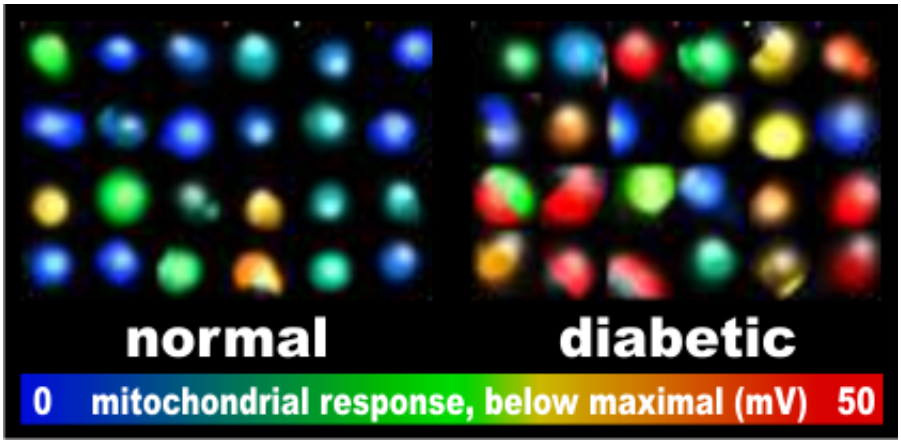

The illustration shows individual pancreatic beta-cells from a patient with type 2 diabetes and a patient without the disease. Cells were visualized by artificially coloring their fluorescence image according to the deficit in the response of their mitochondria to glucose. Warmer colors show a larger deficit, indicating how much more response is possible when intracellular energy demand is experimentally shut off. Beta-cells from each of the observed type 2 diabetic donors underperformed beta-cells from normal donors in this respect. Interestingly, the maximal possible response in the absence of intracellular energy demand was not impaired, demonstrating that the mitochondrial polarization and downstream insulin secretion is determined by the supply-demand balance of the intracellular energetics in whole. Credit: Akos Gerencser, Ph.D.

Impaired activation of mitochondrial energy metabolism in the presence of glucose has been demonstrated in pancreatic beta-cells from patients

with type 2 diabetes. The cause of this dysfunction has been unknown. Publishing online in *Endocrinology*, Buck Institute assistant research professor Akos Gerencser, PhD, shows that in patients with type 2 diabetes the balance between supply and demand of the mitochondrial membrane potential ($\Delta\psi M$) is altered causing a decrease in the signaling that turns on insulin secretion.

Gerencser said the altered balance makes the beta-cells from the patients with type 2 diabetes perform like an economy car - as opposed to a full-size vehicle. "Both cars will do fine on a level freeway, but the economy car will respond more sluggishly when you press the gas, and will fall behind on an uphill road," he said. "An increase in blood sugar is the equivalent to stepping on the gas, the $\Delta\psi M$ is the RPM of the engine, and the response makes for a real-life uphill road." Gerencser said.

Gerencser utilized new fluorescence microscopic assays to quantify $\Delta\psi M$ and its response to glucose in pancreatic beta-cells from four normal and three type 2 diabetic organ donors. Observation of individual cells under the microscope allowed simultaneous recording of $\Delta\psi M$ and plasma membrane potential - a mediator of insulin secretion - while the supply or the demand in cellular energy metabolism was altered. His findings suggest that the failure of pancreatic beta-cells to secrete sufficient amounts of insulin in patients with type 2 diabetes may be explained by the cellular level disturbance of energy metabolism, a process whereby multiple supply and demand pathways interplay in a complex network of metabolic reactions. The research showed that mitochondrial energy metabolism did not harbor a substantial defect, but that a more subtle disharmony between bioenergetic supply and demand pathways dampened the response to glucose in the observed individuals. "Type 2 diabetes is a multi-etiological disease," Gerencser said. "The demonstration of a cellular systems-level dysfunction of energy metabolism suggests that a shift towards systems-level approaches is needed to fight the disease." The current reductionist paradigm is aimed

at understanding type 2 diabetes on a molecular level, he said.

Dr. Gerencser designed and utilized the novel fluorescence microscopic assays to quantify $\Delta\psi M$ and its response to glucose in single pancreatic beta-cells from normal and type 2 diabetic organ donors. Determination of the absolute magnitude of $\Delta\psi M$ that is required for the comparison of diseased and normal individuals has been previously unattainable due to fundamental biophysical processes interfering with the readout of otherwise commonly used fluorescence sensor molecules. The novel assay technology enables researchers to untwine these interfering factors and to interpret fluorescence signals correctly as millivolt potentials. The previously published (J Physiology 2012 590:2845-71) technology became practical when it was implemented into Image Analyst MKII (Image Analyst Software, Novato, CA), a fluorescence time-lapse microscopy analysis and assay software. This allowed unbiased comparison of $\Delta\psi M$ and its response to experimental interventions in thousands of individual cells in minuscule pancreatic samples from human organ donors.

"I hope these findings and the newly introduced technology will prompt others to seek a better understanding of the systems-level regulation of cellular energy metabolism," said Gerencser, "My goal is to help reveal etiologies that may affect this central mediator of insulin secretion in human type 2 diabetes."

More information: *Endocrinology*: Bioenergetic Analysis of Single Pancreatic Beta-Cells Indicates an Impaired Metabolic Signature in Type 2 Diabetes Subjects (2015)

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