Pyruvate oxidation is critical determinant of pancreatic islet number and beta-cell mass

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Researchers at the University at Buffalo, led by Dr. Mulchand Patel and also at Lawson Health Research Institute and Western Ontario, London, Canada, led by Dr. David Hill, collaboratively evaluated the role of the mitochondrial multienzyme pyruvate dehydrogenase complex in the regulation of pancreatic β-cell development and maturation in the immediate postnatal period in mice. This study, reported in the August 2014 issue of *Experimental Biology and Medicine*, demonstrated that the pyruvate dehydrogenase complex is not only required for insulin gene expression and glucose-stimulated insulin secretion, but also directly influences β-cell growth and maturity. This places glucose metabolism as a direct regulator of β-cell mass and plasticity.

Glucose metabolism within the pancreatic β-cells is crucial for insulin gene expression and hormone exocytosis, but there is increasing evidence that glucose metabolic pathways are also important for β-cell development and the maintenance of β-cell mass in adult life. A targeted deletion of glucokinase in mouse β-cells not only prevents glucose-stimulated insulin secretion, but also β-cell proliferation and is associated with increased apoptosis. A direct manipulation of glucose availability to the embryonic pancreas in tissue culture showed that it was necessary for both α- and β-cell development through the regulation of the transcription factors Neurogenin 3 (Neurog3) and NeuroD.

In the article by Patel et al., the authors show that a targeted β-cell deletion of the α subunit of the pyruvate dehydrogenase component, a major rate-limiting enzyme for the pyruvate dehydrogenase complex

that regulates pyruvate metabolism from glucose in the mitochondria, in mouse resulted in reduced insulin availability and glucose-sensitive release as would be expected. But they also demonstrate that β-cell number was reduced postnatally as was the expression of Neurog3, NeuroD and Pdx1. Interestingly, there was also a reduction in the numbers of insulin-immunopositive, extra-islet small endocrine cell clusters, a possible source of new β-cells from progenitors. The new findings reinforce the concept that pathways controlling glucose metabolism in β-cells are as important for maintenance of β-cell mass as are hormones and growth factors, such as glucagon-like polypeptide 1 (GLP1). "These findings show that glucose metabolism is a major regulator of β-cell mass which is likely to act independently of other signaling pathways, such as insulin receptor substrate 2", said Dr. Mulchand Patel, senior author of the study and SUNY Distinguished Professor, Department of Biochemistry, School of Medicine and Biomedical Sciences, University at Buffalo, the State University of New York.

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "the study by Patel et al utilizes a mouse knockout model to disrupt the pyruvate dehydrogenase complex (PDC) activity to study the role of PDC in pancreatic β-cell development. They demonstrate that PDC has a direct impact upon the regulation of β-cell mass as well as plasticity."

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