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HIF1β/PFKFB3 pathway is a novel mechanism to account for slow β-cell loss and β-cell dysfunction in type-2 diabetes

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Abstract

The islet in Type 2 diabetes (T2D) is characterized by β-cell dysfunction and amyloid deposits from the islet amyloid polypeptide (IAPP), a protein co-secreted with insulin by β-cells.

We established that hIAPP toxicity activates the conserved hypoxia inducible factor 1 α (HIF1α) injury repair pathway that remodels the metabolism via its target, the phosphofructokinase PFKFB3, recapitulating the metabolic phenotype of β-cells in T2D.

The main adaptive metabolic response relies on the disengagement of glycolysis from the mitochondrial TCA cycle along with adaptive fragmentation of the mitochondrial network. In the presence of maintained mitochondrial membrane potential, the fragmented mitochondrial network provides a protectiveposture from the stress-induced increase in cytosolic Ca2+. Silencing of PFKFB3 in β-cells expressing hIAPP toxic oligomers rescues mitochondrial form, relative metabolite composition and glucose-dependent compartment Ca2+increase, butfailstorescuepyruvateanaplerosis, indicatingthat PFKFB3 iscentraltothe β-cell metabolic reprogramming in stress. Conditional disruption of PFKFB3 in mouse β-cells heterozygous for hIAPP (which don't develop diabetes spontaneously) facilitates onset of diabetes under high fat diet, indicating that metabolic remodeling by PFKFB3 is important for the survival of β-cells under hIAPP stress.

Given the unique dependence of β-cell function on the tight engagement of glucose with the TCA cycle, this pro-survival change in metabolism predictably induces β-cell dysfunction with relatively high insulin secretion occurring at baseline glucose and a deficient response to glucose stimulation, both characteristics of β-cells in T2D. Moreover, in contrast to tissues with the capacity to regenerate, β-cells in adult humans are minimally replicative and therefore fail to execute the pro-regenerative phase of the HIF1α injury repair. Instead, β-cells in T2D remain trapped in the first phase of the HIF1α injury repair response with pro-survival metabolism that slows down the rate of cell attrition at the expense of β-cell function.

Publications

Activation of the HIF1α/PFKFB3 stress response pathway in beta cells in type 1 diabetes

Publisher Correction: IAPP toxicity activates HIF1α/PFKFB3 signaling delaying β-cell loss at the expense of β-cell function

Biography

Slavica Tudzarova obtained her PhD in 2003 at the Medical University Vienna, Austria. In 2006 she joined University College London, in the UK, where she was postdoctoral fellow until 2013. In 2014 she established her independent research program funded by Ernst Jung Stiftung and Industrial Research collaboration before being appointed to an assistant professor at the Larry Hillblom Islet Research Center at David Geffen School of Medicine at UCLA in 2015. Dr. Tudzarova's group recently reported the discovery of a novel evolutionary-conserved injury/regeneration pathway activated in both type-1 and type-2 diabetes that explains loss of β-cell function upon misfolded protein stress

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