

HIF1 β /PFKFB3 pathway is a novel mechanism to account for slow β -cell loss and β -cell dysfunction in type-2 diabetes



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 IAPP toxicity activates the conserved hypoxia inducible factor 1 α (HIF1 α) 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 protective posture from the stress-induced increase in cytosolic Ca²⁺. Silencing of PFKFB3 in β -cells expressing IAPP toxic oligomers rescues mitochondrial form, relative metabolite composition and glucose-dependent compartment Ca²⁺-increase, but fails to rescue pyruvate anaplerosis, indicating that PFKFB3 is central to the β -cell metabolic reprogramming in stress. Conditional disruption of PFKFB3 in mouse β -cells heterozygous for IAPP (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 IAPP 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 HIF1 α injury repair. Instead, β -cells in T2D remain trapped in the first phase of the HIF1 α 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 HIF1 α /PFKFB3 stress response pathway in beta cells in type 1 diabetes

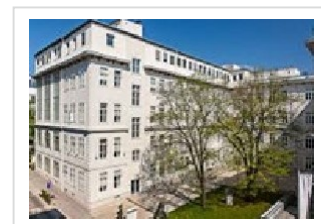
Publisher Correction: IAPP toxicity activates HIF1 α /PFKFB3 signaling delaying β -cell loss at the expense of β -cell function

Slavica Tudzarova¹, Chiara Montemurro², Hiroshi Nomoto³, Lina Pei⁴, Vishal Parekh⁵, Kenny Vongbunyong⁶, Suryakiran Vadrevu⁷, Tatyana Gurlo⁸, Alexandra Butler⁹, Rohan Subramaniam¹⁰, Eleni Ritou¹¹, Orjan Shirihai¹², Leslie Satin, Peter Butler

University of California, Los Angeles

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



International Conference on Endocrinology disorders, Diabetes complications and Hypertension | Dublin, Ireland | July 31st-August 1st, 2020

Citation: Slavica Tudzarova, *HIF1 β /PFKFB3 pathway is a novel mechanism to account for slow β -cell loss and β -cell dysfunction in type-2 diabetes*, Endocrinology 2020, International Conference on Endocrinology disorders, Diabetes complications and Hypertension, Dublin, Ireland, 31st July- August 1st, 2020, 5