The role of the prostaglandin PGE2 in pancreatic β-cell death in the context of type 2 diabetes

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Type 2 diabetes mellitus (T2DM) is a complex disease characterized by β-cell failure in the setting of insulin resistance. The underlying causes of β-cell failure are complex and result from the interplay between genetic and environmental factors. Consumption of foods high in saturated fatty acids (FFAs) and the elevation of circulating FFAs have been implicated as an important causative link among obesity, insulin resistance and β-cell dysfunction. Moreover, cumulative evidence indicates that there is a decrease in β-cell mass due to β-cell death in T2DM patients. FFAs can induce β-cell death by apoptosis, even in the absence of high glucose, whereas unsaturated fatty acids are usually protective. Several mechanisms have been implicated in palmitate-induced β-cell death, including ceramide formation leading to altered lipid partitioning, oxidative stress, and inflammation. Mild inflammation has been suggested to play a role in the pathogenesis of T2DM. Another family of molecules involved in inflammation is prostaglandins, but their role in the development of T2DM is poorly understood. The present research aims at understanding the impact of prostaglandins (PGE2) on β-cell death. We show that PGE2-induced apoptosis is mediated by p38MAPK. To further elucidate the downstream signaling pathway of prostaglandins in β-cells, we studied the differential expression of PGE2 receptors (EP1-EP4) and found that the EP3 receptor is differentially upregulated in islets from T2DM patients. The significance of this receptor in β-cell apoptosis was tested by using EP3 specific siRNA or EP3 antagonist, and found that they led to a significant rescue of these cells from apoptosis.

Biography

Danielle Melloul has completed her PhD from the Weizmann Institute of Sciences (Rehovot, Israel) and postdoctoral studies from the Hormone Research Institute at UCSF (San Francisco, USA). She is Senior lecturer and head of the Biochemistry, Endocrinology and Metabolism at the Hadassah Medical School and Scientist at the Hadassah University Hospital (Hebrew University, Jerusalem). She has received a number of awards and has published more than 32 papers in high impact journals as well as a series of invited reviews in the fields of physiology and pathophysiology of the pancreatic β-cell.

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