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DIABETES AND APOPTOSIS

Apoptosis in diabetes

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The number of people suffering from diabetes is on the increase due to population growth, aging, urbanization, and increasing obesity and physical inactivity. The prevalence of diabetes worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is anticipated to rise from 171 million in 2000 to 366 million in 2030 (Wild S. et al. *Diabetes Care* 2004;27: 1047–1053).

Diabetes mellitus is a complex disease characterized by absolute insulin deficiency or resistance leading to hyperglycemia. Two major forms of diabetes exist, namely type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM occurs when the insulin-producing β-cells in the pancreas are destroyed, resulting in insufficient insulin production. T2DM is caused by development of cellular resistance to insulin combined with insufficient insulin production. T2DM is commonly linked to obesity, which can cause insulin resistance. Diabetic patients show altered metabolism of glucose, fat and protein. These metabolic dysfunctions result in a range of long-term effects known as "diabetic complications". These manifest itself in multiple disorders in for instance the vasculature, different organs and inflammatory cells. This special issue focuses on the mechanisms and effects of apoptosis in diabetes on a (sub)cellular level in the pancreas and other organs.

Thomas H. et al. discuss apoptosis of beta cells that occurs both in T1DM and T2DM as well as in transplanted islets. In T1DM, β-cells are destroyed by immunological mechanisms, whereas in T2DM metabolic abnormalities contribute to β-cell failure and subsequent apoptosis. Regardless of the diabetes type, highly conserved intracellular pathways of apoptosis are triggered. In their review Thomas et al. will outline these molecular mediators of β-cell apoptosis and the intracellular pathways activated.

Szabadkai G. et al. focus on mitochondrial dysfunction and its role in the pathogenesis of the survival/death pathways in both in T1DM and T2DM. They discuss the apparently distinct mechanisms governing β-cell life/death decisions during the development of diabetes and provide a remarkable example where remote metabolic, immune and stress signaling meet with mitochondria mediated apoptotic/necrotic death pathways to determine the fate of the β-cell. Furthermore, they clarify that deranged glucose stimulated insulin secretion (GSIS) and over-nutrition-induced apoptotic/necrotic β-cell death are the result of mitochondrial dysfunction, representing hallmarks of T2DM.

Endoplasmic reticulum (ER) stress is increasingly acknowledged as an important mechanism in the development of diabetes. Van der Kallen C.J.H. et al. explain that ER stress is important not only for β-cell loss but also for insulin resistance. They highlight the role of ER stress-induced apoptosis in liver

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and adipose tissue and discuss the exact interactions between environmental signals, ER stress and apoptosis in these organs.

Ryan A. et al. focus on the importance of inflammation in the development of diabetes. In addition, experiments have shown that inflammation also plays a prominent role in diabetes related target organ damage, in which both elements of the innate and the adaptive immune system are involved. They describe how inflammatory cell-mediated apoptosis contributes to this target organ damage, from β-cell destruction to both micro- and macrovascular disease complications.

An important target organ in diabetes is the kidney. Hyperglycemia can induce apoptosis of renal cells and result in diabetic nephropathy. Wagener F.A.D.T.G. et al. show the importance of redox balance shifts in renal cells in diabetes related kidney damage. Reactive oxygen species (ROS) lead to considerable cellular damage and to a point of no return in apoptosis when insufficient cytoprotective and ROS scavenging molecules are available. Here, they discuss mechanisms of apoptosis and several strategies that have been tested to prevent apoptosis in the diabetic kidney.

Another important target organ in diabetes is the liver. End stage liver disease is characterized by fibrosis or cirrhosis and occurs more often in patients with insulin resistance than in patients with physiological insulin sensitivity. In their review Schattenberg J.M. et al., focus on the molecular mechanisms that connect insulin resistance with hepatocellular injury. The mechanisms that advance hepatocellular injury, related to decreased insulin sensitivity, are not well known. Here, the authors summarize insulin signaling in the context of liver disease and apoptotic hepatocellular injury and underline the importance of understanding such signaling with respect to therapy development.

Diabetes also affects the neural system, including its development. Chappell J.H. et al. discuss defects of the neural tube resulting from diabetic pregnancy. These defects are associated with apoptosis early in its formation. Maternal diabetes inhibits expression of the Pax3 gene that encodes a transcription factor which is expressed in neural crest and neuroepithelial cells. As a result of insufficient Pax3, cardiac neural crest and neuroepithelial cells undergo apoptosis.

In addition to hyperglycemia, elevated systemic levels of fatty acids are considered significant contributors towards the pathophysiological aspects associated with insulin resistance. In their paper, Kusminski C.M. et al. explain that over accumulation of unoxidized long-chain fatty acids can result in a lipid 'spill over' to non-adipose tissues, such as the liver, muscle, heart and pancreatic-islets. This ectopic lipid deposition can promote metabolically relevant cellular dysfunction (lipotoxicity) and programmed cell-death (lipoapoptosis). The authors focus on how both of these processes are major mediators of insulin resistance and diabetes.

This collection of excellent reviews highlights the importance of apoptosis in the induction of diabetes and in the pathophysiology of different diabetes related complications. Understanding these processes can offer new targets for therapeutic intervention and are of increasing necessity, regarding the growing world-wide burden of diabetes.