Abstract

Pancreatic beta-cells are specialized for the production and regulated secretion of insulin to control blood-glucose levels. Pancreatic beta-cells are strongly involved in protein secretion and have highly developed endoplasmic reticulum (ER). Proper folding of polypeptide into a three-dimensional structure is essential for cellular function and protein misfolding can threaten cell survival. Various conditions can perturb the protein folding in the ER, which is collectively called ER stress. In order to adapt ER stress conditions, the cells respond in three distinct ways such as transcriptional induction of ER chaperone, translational attenuation, and ER-associated degradation (ERAD). Components of the unfolded protein response (UPR) play a dual role in beta-cells, acting as beneficial regulators under physiological conditions or as triggers of beta-cell dysfunction and apoptosis under situation of chronic stress. However, when ER functions are severely impaired, the cell is eliminated by apoptosis. The beta-cell is one of the most susceptible cells for ER stress, and ER stress-mediated apoptosis in beta-cells can be a cause of diabetes.

Under *in vitro* conditions, cytokines such as IL-1beta in combination with IFN-gamma induced NO production by activating iNOS expression. NO-induced apoptosis in beta-cells is mediated by the ER-stress pathway. Using NO donor SNAP depletes ER Ca$^{2+}$ in MIN-6 cells. Severe ER Ca$^{2+}$ depletion will impair the quality of
ER protein folding and assembly and trigger CHOP expression and apoptosis. Overexpression of calreticulin increased the Ca\textsuperscript{2+} content of ER and afforded protection to cells against NO-mediated apoptosis.

Interestingly, low concentrations of NO, as induced by activation of constitutive NOS by glucose, protect against ER stress by dissipating ROS, suggesting that the effect of NO of beta-cell ER stress are concentration- and time-dependent.

The mechanisms causing beta-cell dysfunction and death in diabetes are complex, and ER stress is probably only one of several factors contributing to beta-cell loss in diabetes. But a comprehensive understanding of the mechanism of protein folding and how they relate to the development of diabetes will contribute to provide new targets for the prevention and management of diabetes.

Reference


