Mechanisms of Cytokine-mediated ß-cell Death

John A Corbett,

Saint Louis University School of Medicine
Department of Biochemistry, St. Louis, MO 63104

There currently is controversy regarding the mechanisms by which -cells are killed in response to cytokines. A number of reports suggest that the process is mediated by apoptosis, other suggest necrosis, and the role of nitric oxide in each type of death has been debated. To ascertain the mechanisms of cell death, the effects of IL-1 (rat islets) or IL-1 + IFN- (human islets) and known activators of apoptosis on -cell viability were examined. While cytokines stimulates -cell DNA damage (as determined by TUNEL staining), they fail to activate caspase 3 or to induce phosphatidylserine externalization (annexin staining); however, apoptosis inducers activate caspase 3 and the externalization of phosphatidylserine on -cells. In contrast, cytokines stimulate the release of the immunological adjuvant high mobility group box 1 protein (HMGB1; a biochemical maker of necrosis) in a nitric oxide-dependent manner, while apoptosis inducers fail to stimulate HMGB1 release. The release of HMGB1 by -cells treated with cytokines is not sensitive to caspase 3 inhibition, while inhibition of this caspase attenuates -cell death in response to known inducers of apoptosis. These studies were preformed following short exposures to cytokines. The form of -cell death appears to shift from nitric oxide-dependent necrosis to apoptosis following longer incubations. The mechanisms responsible for this shift in the type of cell death are currently being examined. These findings indicate that short exposures of cytokines induce -cell necrosis and support the hypothesis that macrophage-derived cytokines may participate in the initial stages of diabetes development by inducing -cell death by a mechanism that promotes antigen release (necrosis) and islet inflammation (HMGB1 release).