Molecular Regulation of Fas Expression in β-Cells

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Fas-mediated cell death may play an important role in the autoimmune destruction of β-cells in type 1 diabetes. β-Cells usually do not express Fas, but Fas expression is detected in β-cells from patients with recent-onset type 1 diabetes (1) and in cytokine-exposed mouse and human islets. Fas expression renders the β-cells susceptible to Fas ligand–induced apoptosis (2–4). It has been proposed that cytokine-induced Fas expression in human islets is mediated by nitric oxide (NO) production (4).

The aim of the present study was to investigate Fas regulation by cytokines in human, mouse, and rat β-cells. For this purpose, we analyzed Fas mRNA expression by reverse transcriptase–polymerase chain reaction in isolated human islets and fluorescence-activated cell sorter (FACS)-purified rat β-cells exposed to cytokines with or without N^G-monomethyl-L-arginine (L-MA), an inhibitor of inducible NO synthase (iNOS). Fas mRNA expression was also determined in islets isolated from wild-type and iNOS knockout mice. (A complete version of the present study will be published elsewhere [5].) In the second part of the study, regulation of Fas promoter activity was determined in FACS-purified rat β-cells.

In human islets, Fas mRNA expression was induced by interferon-γ (IFN-γ), a cytokine that did not induce iNOS expression. A combination of IFN-γ and interleukin-1β (IL-1β) induced both iNOS and Fas expression, but L-MA did not prevent Fas mRNA expression. In purified rat β-cells, Fas expression was induced by IL-1β alone and was not prevented by L-MA. Islets isolated from wild-type or iNOS$^{-/-}$ mice similarly expressed Fas mRNA after exposure to a mixture of three cytokines (IL-1β + IFN-γ + tumor necrosis factor-α). These results indicate that cytokine induction of Fas expression is NO-independent in human, mouse, and rat pancreatic cells.

Transfection of rat Fas promoter–luciferase reporter constructs into purified rat β-cells showed that IL-1β induction of promoter activity is mediated by a region between nucleotides –223 and –54 that contains putative binding sites for the transcription factors NF-κB, CCAAT/enhancer binding protein, and Ets. The individual contributions of these transcription factors for Fas expression is presently under study.

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FACS, fluorescence-activated cell sorter; IL-1β, interleukin-1β; INF-γ, interferon-γ; iNOS, inducible NO synthase; L-MA, N^G-monomethyl-L-arginine; NO, nitric oxide.