Protective Role of Complement C3 Against Cytokine-Mediated beta-Cell Apoptosis

Type 1 diabetes is a chronic autoimmune disease characterized by pancreatic islet inflammation and beta-cell destruction by proinflammatory cytokines and other mediators. Based on RNA sequencing and protein-protein interaction analyses of human islets exposed to proinflammatory cytokines, we identified complement C3 as a hub for some of the effects of cytokines. The proinflammatory cytokines interleukin-1 beta plus interferon-gamma increase C3 expression in rodent and human pancreatic beta-cells, and C3 is detected by histology in and around the islets of diabetic patients. Surprisingly, C3 silencing exacerbates apoptosis under both basal condition and following exposure to cytokines, and it increases chemokine expression upon cytokine treatment. C3 exerts its prosurvival effects via AKT activation and c-Jun N-terminal kinase inhibition. Exogenously added C3 also protects against cytokine-induced beta-cell death and partially rescues the deleterious effects of inhibition of endogenous C3. These data suggest that locally produced C3 is an important prosurvival mechanism in pancreatic beta-cells under a proinflammatory assault.
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