Blocking type I interferon signaling rescues lymphocytes from oxidative stress, exhaustion, and apoptosis in a streptozotocin induced mouse model of type I diabetes.

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Abstract:

Elevated levels of type I interferon (IFN) during type 1 diabetes mellitus (T1D) are associated with a defective immune response. In the present study, we investigated whether blocking type I IFN signaling during streptozotocin- (STZ-) induced T1D in mice improves lymphocyte proliferation and escape from continuous apoptosis. Three groups of mice were examined: diabetic mice, type I IFN signaling-incompetent diabetic mice, and control nondiabetic mice. We first found that diabetes induction was accompanied by an elevation in the plasma levels of reactive oxygen species (ROS), hydroperoxide, malondialdehyde (MDN), and the proinflammatory cytokines IL-1α, IL-1β, IL-6, and CXCL10. Blocking type 1 IFN signaling in diabetic mice significantly decreased the levels of oxidative stress and proinflammatory cytokines. In addition, lymphocytes from diabetic mice exhibited a marked reduction in their proliferative capacity, increased apoptosis, upregulation of the exhaustion marker PD-1, and aberrant phosphorylation of STAT1, STAT2, AKT and IκB-α. Interestingly, following the blocking of type I IFN signaling in diabetic mice, the lymphocytes exhibited restored proliferative capacity, decreased apoptosis, normal expression of PD-1, and normal phosphorylation of STAT1, STAT2, AKT and IκB-α. Our data suggest that elevated levels of type I IFN during T1D trigger lymphocyte exhaustion and a defective lymphocyte-mediated immune response.

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