Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease.

Abstract:
Autoimmune diabetes mellitus in humans is characterized by immunological destruction of pancreatic beta islet cells. We investigated the circumstances under which CD8(+) T cells specific for pancreatic beta-islet antigens induce disease in mice expressing lymphocytic choriomeningitis virus (LCMV) glycoprotein (GP) as a transgene under the control of the rat insulin promoter. In contrast to infection with LCMV, immunization with LCMV-GP derived peptide did not induce autoimmune diabetes despite large numbers of autoreactive cytotoxic T cells. Only subsequent treatment with Toll-like receptor ligands elicited overt autoimmune disease. This difference was critically regulated by the peripheral target organ itself, which upregulated class I major histocompatibility complex (MHC) in response to systemic Toll-like receptor-triggered interferon-alpha production. These data identify the 'inflammatory status' of the target organ as a separate and limiting factor determining the development of autoimmune disease.