【招待講演】

Cytokines, Antigens and Regulation of Autoimmune Beta Cell Destruction in Non-Obese Diabetic (NOD) Mice

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Non-obese diabetic (NOD) mice, derived originally by Makino and colleagues in Japan, have served as the most useful animal model for understanding the pathogenesis of spontaneous insulin-dependent diabetes (IDD). Beta cell destruction in the NOD mouse is mediated by both CD4 and CD8 T cells, as recently confirmed by 'gene knockout' experiments, but the factors that drive and regulate beta cell autoreactivity are not well understood.

The insulinitis lesion resembles a delayed-type hypersensitivity immune response, the effect of interferon-gamma and interleukin-12 to accelerate and of anti-interferon-gamma antibodies to retard insulinitis and diabetes is evidence for a key pathogenic role for Th1 CD4 cells in beta cell destruction. In situ analysis of cytokine expression has confirmed the presence of Th1 cytokines (interferon-gamma, interleukin-2) in intra-islet T cells.

A number of candidate autoantigens have been identified in the NOD mouse, two of which, insulin and glutamic acid decarboxylase (GAD), elicit immune responses before the onset of clinical diabetes, as in humans at-risk for IDD. In a longitudinal study, the level of GAD antibodies in NOD mice was inversely related to the degree of insulinitis and the de-

velopment of clinical disease, whereas the detection of GAD-reactive T cells at 8 weeks of age was a marker of disease risk. Dominant GAD epitope regions have been identified which stimulate NOD CD4 T cells. To determine if recombinant insulin or GAD proteins or their synthetic peptides are involved in driving beta cell destruction *in vivo*, these antigens were given either intra-thymically (neonates), intravenously or subcutaneously (at 3-4 weeks), orally (daily from 3-4 weeks) or by aerosol (weekly from 3-4 weeks). Antigen-specific 'tolerance' was induced by all strategies, with significant reductions in the severity of insulinitis and diabetes. Moreover, tolerance was transferable. T cells from antigen-treated mice prevented the development of diabetes when co-transferred, with T cells from diabetic mice, into young, irradiated mice. The mechanisms underlying these therapeutic effects are being investigated but may be due, at least in part, to immune re-programming towards Th2 responses. These findings support the view that insulin and GAD are pathogenic autoantigens that contribute to beta cell destruction. They have implications for the prevention of IDD in humans.