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MECHANISMS OF DEVELOPMENT OF INSULITIS WITH ABNORMAL GLUCOSE TOLERANCE IN REOVIRUS TYPE 2-INFECTED MICE

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Diabetes mellitus (DM) and its complications are now increasing in human and animals. There are two major types of DM; insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus. IDDM is considered to be a disease mediated by an autoimmune process, resulting in the selective destruction of beta cells in the pancreatic islets. In human, viruses may be one of the causative agents of IDDM. For example, coxsackie B4, mumps, cytomegalo, varicella, and rubella viruses may cause IDDM. The mechanisms of virus-induced diabetes are hypothesized as follows: The host antigens and/or virus-induced altered host antigens may be released from the damaged beta cells by direct viral multiplication. The antigens are then processed by macrophages and presented to helper T (Th) cells in association with the class II major histocompatibility antigen (MHC) molecule. Th cells secrete interleukins that activate other Th cells, B lymphocytes and cytotoxic T (Tc) cells. The activated Tc cells recognize the host antigens coupled with the class I MHC molecule on the beta cell. Macrophages, Th and Tc cells act synergistically in the destruction of beta cells, leading to the clinical onset of IDDM. The exact pathomechanisms of virus-induced diabetes, however, are largely unknown.

Generally immunosuppresive agents such as corticosteroids, cyclophosphamide, antilymphocyte serum etc, are applied for the treatment of autoimmune diseases. These appear to be extremely active and powerful immunosuppressants. However, these agents evoke and/or enhance exogenous infections and have undesirable side effects.

One approach to the solution of these problems is to suppress the response to a single auto-antigen, or constellation of auto-antigens, while leaving all other immune responses intact. Other approaches are to eliminate locally produced harmful molecules and/or to normalize abnormal host immune system. Thus, we are focussing on molecules and/or immunocompetent cells associated with the development of insulitis in mice induced by reovirus type 2. In brief, adhesion molecules participate in the many stages of various immune and inflammatory responses. Furthermore, it is now well recognized that induction of cell-mediated vs humoral immune responses correlates with the development of Th1 and Th2 subset, respectively, which can determine

resistance vs susceptibility to disease. Also numerous evidence suggests that reactive oxygen species are responsible for local tissue injury. In considering concepts described above, we are investigating the mechanisms of reovirus type 2- induced insulitis with abnormal glucose tolerance in suckling mice.

In summary, intercellular adhesion molecule-1 and lymphocyte function-associated antigen-1 may participate in islet cell damage. The development of insulitis may be mediated by Th1 cell-associated cytokines, such as interleukin-2 and interferon-γ. Reactive oxygen species especially hydrogen peroxide may be involved in the destruction of pancreatic islet cells. The role of these molecules on the development of insulitis will be discussed.

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