Editorial

Interferon gamma (IFN-γ) and molecules with similar overlapping functions are important for immune responses to pathogens. Many lines of evidence suggest that they are also critical for the initiation and maintenance of pathogenic autoimmune responses such as that which causes insulin-dependent diabetes mellitus (IDDM). In predisposed individuals, IFN-γ and related molecules such as interleukin-12 (IL-12) are elicited. Targeted expression of IFN-γ induces several of the pathologies associated with IDDM including immune activation, inflammation, autoreactivity, and tissue destruction (1). In the spontaneous animal model of diabetes, the nonobese diabetic (NOD) mouse, the modulation of endogenous IFN-γ expression correlates with disease onset. Additionally, neutralizing antibodies to IFN-γ block disease transfer. Another cytokine molecule with overlapping functions, IL-12, is also expressed prior to the onset of disease in the NOD mouse. Recent work has demonstrated that treatment of NOD mice with IL-12 accelerates and exacerbates disease development. It is not known how or why, in genetically predisposed individuals, these cytokine molecules are elicited. Recent interesting and important work published in this issue of *The Journal* has implicated the disregulation of a comparatively new molecule in the cytokine arena, interferon-gamma inducing factor (IGIF), as mediating the overproduction of these potentially destructive inflammatory mediators in disease susceptible individuals (2).

This newly discovered molecule IGIF (now designated interleukin-18) was originally isolated from the liver where it has been shown to have potent IFN-γ inducing activity (3). IGIF actually has more potent IFN-γ inducing capabilities than the cytokine IL-12 and apparently utilizes a distinct signal transduction pathway for its elicitation. Studies thus far imply that IGIF has a T helper 1 type pattern of induction of cytokine elicitation since it increases IFN-γ production, but decreases IL-10 production. Interestingly no effect on IL-4 expression was observed (4). The induction of Th1 type cytokines is generally thought to be necessary for cell mediated autoimmune diseases such as IDDM. Indeed the presence of IGIF has been demonstrated to be critical for damage to occur in a murine model for bacteria induced liver damage. In the current issue of JCI, the first report correlating this molecule with autoimmune diabetes is indeed provocative. In this study, the expression pattern of IGIF was determined in IDDM susceptible NOD mice as well as diabetes resistant strains. Additionally, genetic linkage analysis was performed. The results point to a critical importance for IGIF in spontaneous diabetes in the NOD mouse. In this study the authors report that levels of IGIF rise very rapidly after cyclophosphamide treatment and precede induction of IFN-γ. Strikingly, the cyclophosphamide inducibility of IGIF was not seen in the non-diabetes prone strain studied by these authors. This indicates a fundamental difference in activation state and IFN-γ inducing function in macrophages of NOD mice and the diabetes resistant strain. Interestingly, the authors demonstrated that IGIF gene maps to an interval of chromosome 9 where a diabetes susceptibility gene from the NOD mouse (Idd2) has been located.

The action and identity of diabetes susceptibility genes represents an important area for consideration of disease mechanism in both animals and humans. Of course, the rodent populations are more accessible experimentally. In intercrosses between the disease susceptible NOD mouse and the disease resistant C57BL/10 strain, it has been revealed that genetic differences exist that contribute to the likelihood that any individual will develop disease. Years of analysis of genetic crosses between the NOD mouse and the C57BL/10 mouse have revealed at least ten of these traits and their location of the chromosome has been mapped and termed Idd loci (5). With the exception of the MHC, which is universally required, the other genes appear to have an additive effect on the likelihood of any individual mouse succumbing to the disease. Importantly, when different inbred strains were analyzed in this manner distinct sets of genetic differences were revealed, each contributing to disease susceptibility and resistance. This complexity illustrates an important truth regarding genetic susceptibility to diabetes: that predisposition is a very exquisite interaction of comparative "defects" conferred by susceptibility loci and "ability to overcome them" in resistance loci. Within any individual intercross mouse (and in humans) these will vary, at least to some extent. The Idd2 locus is one of these susceptibility locations on the NOD chromosome. It has been revealed in backcrosses with the C57Bl/10 mouse and also more recently in crosses with a second strain, NON, increasing its significance. While the exact length of the interval is unknown, the Idd2 locus could be presumed to encompass the coding regions for many genes. Thus, it will certainly be important to determine whether a difference exists in the NOD IGIF allele compared with the non-disease susceptible BALB/c mouse, studied in the current report. In this case there may be a difference in the regulatory region of the gene since its expression was upregulated in NOD mice following cyclophosphamide treatment but was not upregulated in BALB/c mice, implying a regulatory, not a structural, polymorphism.

The pathway toward disease in genetically predisposed individuals with different combinations of susceptibility genes is predicted to be at least subtly distinct. The reported dysregulation of the IGIF molecule in NOD mice may be one way to cause a pathogenic Th1 response that could lead to autoimmunity. However, there is probably more than one molecular pathway to disease, even within the overwhelmingly genetically susceptible NOD mouse. Indeed, while IFN-γ overexpression leads to inflammatory autoimmune disease and treatment of NOD mice with neutralizing antibody to IFN-γ eliminates disease, it was recently demonstrated that the genetic inactivation of the IFN-γ gene from NOD mice does not

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prevent the diabetes from ultimately occurring (6). This paradox illustrates the redundancy within the NOD autoaggressive system, and in general for the cytokines involved in regulating cell mediated immunity. For determination of disease-causing potential it is far more significant that an elicited molecule can mediate disease, than the antithetical situation where the mediator has never been there at all. In the current study both IL-12 and IL-18 show overlapping function in their ability to induce expression of IFN-γ; and all three molecules share specific immune stimulatory properties in common. The NOD mouse maximizes these pathogenic redundancies, since not all Idd loci mapped are required for disease. We can still look for a central mechanism within these distinct pathways, since molecules of similar function form a cascade with a finite number of possibilities.

The net result of the genetic interactions is elicitation of molecules like IGIF and pathogenic immune stimulation. Macrophage activation and release of interferon-gamma leads to expression of costimulatory molecules and priming of islet antigen specific T cells (1). This T cell activation fuels the specific loss of pancreatic beta cells. Important work such as that described in the current issue of JCI on IGIF furthers the identification of molecules that provide the molecular basis for initiation of disease and allow for the development of therapeutic strategies of increased range and efficacy.

Nora Sarvetnick
Departments of Immunology and Neuropharmacology
The Scripps Research Institute

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