The Role of Genetics in Autoimmune Disease

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It is an obviously overwhelming conceptual problem to address the genetic control of autoimmune disease; such control could function at so many different points in the pathogenesis of any autoimmune disease, and have such pleiotropic effects, that it is far beyond a single talk. Rather than provide a broad overview, I have decided to focus on the genetic control of the immune response and comment, as an example, about one disease that has been extensively studied with regard to genetic control: namely, insulin dependent diabetes (IDD), or type 1 diabetes.

A great deal of attention has focused on the major histocompatibility complex (HLA in humans) as playing a critical role in susceptibility and possibly development of autoimmunity. Although this is a most important area, and one that I shall comment on further, I want to emphasize that there are almost certainly multiple genes that segregate independently of HLA that determine susceptibility to disease. Two examples will suffice. First, it was shown many years ago that there were at least ten independently segregating genes that regulate the magnitude of an immune response. The major histocompatibility complex (MHC) is only one of these. Second, the classical work of Frank Lilly and his colleagues demonstrated the importance of the major histocompatibility complex in mice (H-2) in susceptibility to virally induced disease. Yet, Lilly also showed quite clearly that different alleles of H-2 influenced the severity/magnitude of the disease process and the genes segregating independently of H-2 determined whether an individual was susceptible or not. Thus, as we emphasize HLA, it is very important to keep in mind that these background genes exist.

The HLA complex encodes two classes of antigen: the class I antigens (HLA-A, -B, and -C), and the class II antigens (DR, DQ, and DP). Most diseases have shown their strongest association with the class II antigens. Class II antigens are thought to be important in regulating immunity because they present peptides of foreign antigens that may be involved in the immune process to the immune system. Given the known crystallographic structure of an HLA class I antigen, with a suggested structure of class II antigen, exciting models have been presented that relate the molecular interactions between the T-cell receptor and the two alpha helices of the class II antigen with the peptide in the groove between those alpha helices.

Associations between certain HLA class II genes and disease, thus, may relate to the ability of those class II molecules to present a disease-causing peptide (molecule) to the immune system in such a way that an autoimmune disease process will ensue. There are, however, at least two further levels of complexity that must be considered. First, there is some, albeit limited, evidence that the different families of class II dimers (e.g., DR versus DQ) function differentially in activating or suppressing the immune system; preferential presentation by one or the other type of dimer might thus regulate immunity against a given peptide. Second, HLA genes appear to be involved not only in the presentation of antigen but in other processes that play a role in the regulation of immunity. Among these, individuals carrying different HLA haplotypes appear to produce different levels of various cytokines, such as interleukin 1 (IL-1). Not only does IL-1 influence the strength of the immune response but, in addition, has a direct effect on islets in the case of IDD. The basic information that is available with regard to HLA in terms of its role in regulating immunity will be related to possible genetic factors in the development of autoimmune disease.

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