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Immunogenetics
Human immunogenetics
Editorial overview

Chester A Alper and Charles E Larsen

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Chester A Alper

The CBR Institute for Biomedical Research,
Harvard Medical School, Boston,
MA 02115, USA
e-mail: alper@cbr.med.harvard.edu

It was through an earlier interest in the genetics of the complement system that Chester Alper entered the field of immunogenetics in general. His current work concerns the role of genes in the MHC, lymphocytes and antigen-presenting cells in the control of immune function and autoimmune diseases.

Charles E Larsen

The CBR Institute for Biomedical Research,
Harvard Medical School, Boston,
MA 02115, USA
e-mail: larsen@cbr.med.harvard.edu

Charles Larsen trained as a protein chemist and has studied the biophysics of viral membrane fusion. His current interest is the cellular immunology and genetics of the human nonresponse to hepatitis B vaccine. This interest has broadened to include the relationship between MHC genetic structure and autoimmune phenomena.

Abbreviations

CEH	conserved extended haplotype
KIR	killer immunoglobulin-like receptor
MHC	major histocompatibility complex
NK	natural killer
T1D	type 1 diabetes
TAP	transporters of antigenic peptides

Human immunogenetics is a relatively young and expanding area of biomedicine. It embraces the conjunction of genetics and immunology, but it is also concerned with the very practical clinical matters of tissue transplantation (particularly of the bone marrow), cancer vaccines and autoimmune diseases. It is the study of the genetic control of innate and adaptive host defense against noxious microorganisms and the reactions to and control of inflammatory insults. Genetic control of the cells and soluble molecules that mediate these reactions also fall within its ken. In deciding which subjects to include in this section of *Current Opinion in Immunology*, the potentially wide range of areas to cover was both exhilarating and frustrating. In the end, our personal interests and the need for some relatedness between the subjects were determining factors.

Natural killer (NK) cells, a major subset of the innate immune system, are the subject of two reviews in this section. In the first, Moretta and Moretta [1], whose work was seminal in defining the field, describe the complex and rapidly evolving picture of the receptors that NK cells utilize to interact with their natural ligands, specific class I HLA molecules. They outline the genes that specify these receptors and their haplotypic organization as clusters within a number of genomic regions including, for a few, the major histocompatibility complex (MHC). As with the HLA genes of the MHC, the activating and inhibitory killer immunoglobulin-like receptor (KIR) genes form haplotypes that show remarkable diversity, reflected not only in nucleotide differences as alleles, but also in terms of the presence or absence of individual genes.

In a review of an exciting new area, Dupont and Hsu [2] describe recent work that promises to identify donors for hematopoietic stem cell transplantation of recipients with hematological malignancies who are not completely (or, possibly, even at all) matched for HLA. This approach is based on the very old observation of 'hybrid resistance', wherein the F1

offspring of two MHC-disparate strains of mice reject bone marrow from either parental strain. As the phenomenon is mediated by NK cells, and NK cell KIR receptors can induce NK cell activation in the absence of their HLA-class I ligands, the authors argue that one can use inferences from HLA typing to identify potential donors.

Whereas lowered expression of HLA class I surface molecule ligands trigger NK cell receptor-mediated NK cell activation, cytotoxic $CD8^+$ T cells of the adaptive immune system require MHC class I molecules to present antigenic peptides for effective killing. Defects in MHC class I molecules are common on malignant cells, presumably providing escape from $CD8^+$ T cell cytotoxicity. Nevertheless, there is no strict correlation between MHC class I expression, tumor growth and cytotoxic T cell lysis of tumor cells. Chang, Campoli and Ferrone [3] review the latest findings in this field. They point out the need for better methods for defining the relationship between specific tumor antigenic peptides in complexes with specific MHC class I antigens, particularly through the study of specimens ordinarily submitted to pathologists. The possible part played by immunomodulatory molecules, including HLA-G, is also considered.

The processing of endogenously generated antigenic peptides (and phagocytosed exogenous proteins) presented by MHC class I molecules is controlled by a pathway that includes the transporter associated with antigen processing (TAP) gene products, TAP1 and TAP2, as well as the endoplasmic reticulum TAP-associated protein tapasin, all of which are encoded within the MHC class II region. The immunogenetics of this subject is reviewed by McCluskey, Rossjohn and Purcell [4]. In the human, as with the MHC-encoded complement genes, there is considerable polymorphism, but no clear evidence for functional differences or independent disease associations with TAP alleles. Nevertheless, rare cases of deficiency of either TAP1 or TAP2 are associated with the activation of γδ T lymphocytes and necrotizing granulomatous lesions of the skin. TAP deficiency also results in increased susceptibility to infection, again similar to deficiencies of some complement proteins. It is of considerable interest that both viruses and certain tumor cells are able to evade immune destruction through inactivation of TAP function.

In our review, [5], we use the concept of conserved extended haplotypes (CEHs) to interpret older data and re-interpret the latest observations concerning the role of MHC susceptibility genes for type 1 diabetes (T1D) and related immune and autoimmune phenomena. The picture that emerges challenges a number of 'dogmas' and raises questions about the nature of non-MHC T1D susceptibility genes. In particular, the difficulties inherent in the fact that genetic markers for HLA-associated diseases and phenomena are parts of CEHs make definitive identification of responsible susceptibility genes extremely difficult. The problem is compounded by the likelihood that MHC susceptibility alleles at the T1D susceptibility locus are common. In aggregate, they have a frequency of a little over 0.5. Yet another confounding problem is the difficulty in separating disease markers (which may also be population markers) from pure population markers. Although it is beyond the scope of the present section on Immunogenetics, it is interesting to note that NK cells have recently been implicated in the pathogenesis of T1D in the NOD mouse model for that disease [6,7].

Hauptmann and Bahram [8] review the central MHC, an extraordinarily gene-dense region of the human genome. They point out the genetic polymorphism of the complement genes *C2*, *BF*, *C4A* and *C4B*. These genes form a single genetic unit or block [9] that rivals other haplotypic blocks of the classical HLA genes in the extent of their polymorphism. As, for the most part, this polymorphism is not accompanied by specific functional differences, which is true of antigenic peptide presentation to T cells by the HLA genes, it is difficult to enlist selection as an explanation for the extensive polymorphism. Rather, structural features, as yet undefined, of the MHC may be responsible, generating variant alleles at other nearby loci, some of which may then provide enhanced selective advantages. The relationship of central MHC genetic markers to disease is intriguing. As the authors point out, there is some evidence to suggest that some of the complement polymorphic markers may in fact contribute to certain autoimmune diseases, such as systemic lupus erythematosus, but this area requires considerably more work before conclusions can be drawn. The problem is that the human MHC genes are embedded within regions of genomic DNA fixity (at the population level) that may extend to three or four megabases or more [5].

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