Ir Genes

Past, Present, and Future

Edited by

Carl W. Pierce, Susan E. Cullen, Judith A. Kapp, Benjamin D. Schwartz, and Donald C. Shreffler

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Preface

The Fifth Ir Gene Workshop was held at the Chase-Park Plaza Hotel, St. Louis, MO, August 28–31, 1982; 240 scientists participated in the Workshop. The manuscripts compiled in this book describe the state of the art concerning Ir genes. Although the notion of *Ir Genes: Past, Present, and Future* has not been addressed specifically by each author, the reader is certain to get this flavor from the contributions. In this Preface, we have tried to summarize some of the salient observations and discussions from the Workshop.

The multiple genes of the I region have been defined traditionally by serological analysis of intra-H-2 recombinant mice and the pattern of immune responses to certain antigens developed by these recombinant mice. The application of several new techniques, such as gene cloning and DNA sequencing, production of T and B cell hybridomas, and development of cloned T cell lines has changed this tradition and introduced a new phase into the analysis of the I region, Ia antigens, and Ir genes.

Serological and biochemical evidence now suggests more heterogeneity of Ia antigens than previously appreciated. Studies with monoclonal antibodies indicate that within a single strain of mouse multiple discrete α- and β-chains exist within the I-A and I-E subregion antigens. The existence of two or more epitopes per Ia molecule that are recognized by different monoclonal antibodies have been shown by several laboratories. Some heterogeneity is caused by the heterogeneity of carbohydrate groups, as shown by the observation that many different complex oligosaccharide structures are associated with the same Ia molecule, which suggests a possible functional role for carbohydrates. Anti-idiotype antibodies to monoclonal anti-Ia antibodies appear to offer promise for probing the nature of the T cell receptor for Ia determinants.

The I-J subregion has been identified by serologically defined markers recognized by monoclonal antibodies. Determinants encoded by the I-J subregion have been shown on functionally different subclasses of cells including: suppressor-inducer and suppressor-effector T cells, suppressor factors from these T cells, one helper T cell subset, and on a subclass of adherent antigen-presenting cells. The question of how many products are encoded by I-J subregion genes has not been resolved; cross-absorption studies suggested that more than one product exists. T cell-specific markers that map to the I-A and I-C subregions and low

molecular weight molecules found in cytoplasm, but not on cell membranes, that are encoded by a gene(s) in the K-I-A interval have also been described. Thus, the number of I region genes and their products continues to expand.

For the first time in an Ir Gene Workshop, data on the structure of genes encoding Ia antigens were presented. Human DRα and mouse I-Eα and I-Aβ genes have two exons encoding the two major domains of the chains, but differ in the detail of the exons determining the transmembrane and intracytoplasmic portions of these proteins. Amino acid sequences derived from DNA sequences indicate that DRα and I-Eα chains have one internal disulfide bond and the potential for two *N*-linked oligosacchride side chains. The molecular basis for the failure of $H\text{-}2^b$ and $H\text{-}2^s$ mice to produce I-Eα proteins appears to result from a faulty I-Eα gene with a deletion of 650 ± 50 base pairs within the promoter region and the first exon. One of the most intriguing questions is the mapping of the genes encoding the I-J subregion serological markers. The position of four genes, I-Aβ, I-Eβ, $I\text{-}E\beta_2$ (an I-Eβ-like gene) and I-Eα (from centromere) has been assigned in the $H\text{-}2^d$ complex by DNA hybridization. Part of the I-Eβ gene mapped to I-A and part mapped to I-E; an unsequenced region of no more than 3.5 kb separates the I-A from the I-E subregion and this unmapped region lies within the Eβ gene. Since the I-J serological markers map between I-A and I-E, the gene(s) encoding I-J determinants would have to map to this 3.5 kb region. Furthermore, no restriction enzyme polymorphisms of I region genes have been found between B10.A (3R) and B10.A (5R), one of the strain combinations that originally defined the I-J subregion. The paradox between the serological and functional data demonstrating an I-J gene product with the failure to find evidence for an I-J gene within the I region at the level of DNA awaits resolution.

The major portion of the Workshop focused on the cellular site and mechanism of Ir gene expression and restrictions on cell interactions mediated by Ia antigens. One model of the site of expression of Ir genes places defect in the T cell receptor repertoire, such that T cells are unable to recognize antigens under Ir gene control in the context of self-MHC antigens, whereas the antigen can be recognized in the context of allo-MHC components under conditions in which alloreactivity has been abolished. An alternative model to explain Ir gene function, the determinant selection hypothesis, proposes that unresponsiveness is caused by the failure of antigen-presenting cells from nonresponder animals to display foreign antigenic determinants in the proper array with self-MHC determinants. Although "defects in the T cell repertoire" and "determinant selection" models explain certain experimental observations, neither model adequately explains all instances of Ir gene control. In immune responses to some antigens, responder and nonresponder animals can develop antigen-specific helper and suppressor T cells. Unresponsiveness results from an imbalance in the regulatory T cells such that suppressor cells are preferentially stimulated and preempt stimulation of helper T cells.

The functional role of Ia antigens in regulating cell–cell interactions was addressed at several levels. Restriction of B cell responsiveness mediated by Ia antigens was examined using chimeras; B cells appear to learn to cooperate with Ia-bearing cells, suggesting that restriction on B cell–macrophage interactions are phenotypic characteristics acquired by the B cell. T cell clones are being used as a

model system to analyze fine specificity of the epitope recognized by the T cell receptor and to map the I-A determinants that serve as restriction elements for antigen presentation. Alloreactive T cell clones that recognize unique F_1 hybrid Ia antigens can be divided into subgroups by determining the ability of various monoclonal antibodies specific for Ia antigens to inhibit activation of these clones. Since inhibition of activation of these clones presumably reflects competition between the T cell receptor and the antibody for the Ia antigen, understanding the nature of the determinant recognized by monoclonal antibodies may indirectly reveal the nature of the antigenic determinant recognized by T cells.

Another approach to understanding Ia restrictions in cell interactions is the isolation of the T cell receptors and/or regulatory T cell factors from a variety of different T cell hybridomas. A soluble factor specific for (T,G)-A-L with helper T cell replacing activity apparently consists of two antigen-binding proteins: one with a 67,000 mw and one with a 14,000–17,000 mw. Monoclonal suppressor factors specific for GAT and GT that are single polypeptide chains bearing an antigen-binding site and I-J determinants can induce second order suppressor T cells that produce specific suppressor factors. These factors resemble the carrier-specific factors described by Tada and Taniguchi; they are I-J-restricted factors composed of two chains: an antigen binding polypeptide and an $I\text{-}J^+$ polypeptide. The two chains of the carrier specific suppressor factor are encoded by separable mRNA species; 11s mRNA encodes a 25–29 kd, $I\text{-}J^+$ peptide, whereas 13s and 18s mRNA encoded the antigen binding, $I\text{-}J^-$, 31–34 kd proteins. The serology of Ia antigens expressed on T cell augmenting factors and suppressor factors have been compared using monoclonal anti-I-A and anti-I-J antibodies; epitopes unique for the augmenting or suppressor factors as well as epitopes shared by these functionally distinct factors have been identified.

At this point, one could ask whether a consensus regarding the mechanism of Ir gene expression and Ia restrictions had been reached. Although new experiments were presented, many of the arguments have been with us since the First Ir Gene Workshop in 1974, raising the question of whether one of these hypotheses could be eliminated by an unambiguous experiment. Some clearly felt these experiments had already been done and that the results supported their own point of view. Others felt that the definitive experiment had not been done, but no one offered the design for such an experiment. Thus, despite the refinement that has been achieved through the use of monoclonal antibodies, T cell clones, and T cell hybridomas, many questions remain to be answered. Possibly some of these answers will be available at the Sixth Ir Gene Workshop schedueld for 1985.

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