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This information is current as of October 30, 2017.

J Immunol 2004; 173:1499; doi: 10.4049/jimmunol.173.3.1499
http://www.jimmunol.org/content/173/3/1499

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Setting the stage

Over a half century ago, Landsteiner (1) demonstrated that Abs could be produced to nearly any substance (which he termed “hapten”) if it was attached to a proper (i.e., immunogenic) substance (the “carrier”). Carrying the torch, Benacerraf and Gell (2) demonstrated a major difference in discrimination between denatured vs native proteins in delayed-type hypersensitivity responses compared with Ab responses: while Abs specific for the hapten are highly conformation dependent, cellular responses to the carrier are largely conformation independent (3).

Benacerraf and colleagues then began to study the genetic underpinning of the biological phenomenon in guinea pigs. Using the hapten-carrier protein conjugate dinitrophenol-poly-L-lysine (DNP-PLL), they demonstrated the Ab response to DNP was under the control of a single dominant autosomal gene (4). Essentially, it was here that the term immune response (Ir) genes was introduced. Additional studies in other species and with other Ags solidified the finding of genetic control of responders and nonresponders in immune responses.

A star is born

McDevitt now began to make significant contributions to the “Ir” problem using a panel of simple branched copolymers synthesized by Sela, differing only in the side chain amino acids (5). Classical genetic crosses demonstrated that Ir genes were closely associated with the murine MHC called the H-2 complex (6). The defining moment came with McDevitt and Chinitz’s classic paper (7) examining the responses of inbred mice to the branched copolymers; Ab responsiveness of inbred mice to (T,G)-A-L, (H,G)-A-L, and (Phe,G)-A-L was based strictly on the H-2 genotype. This was an important conceptual advance; the MHC could now be seen as the master controller of Ab responses (8). These findings enabled act II of the play, which concluded with Zinkernagel and Doherty’s discovery of MHC restriction of killer T cell specificity (9).

In the study, McDevitt and Chinitz use 33 strains of inbred mice with 8 different H-2 alleles to map the responder phenotype. This is reasonably crude by today’s standards using gene-targeted knockouts and transgenics, but nevertheless effective. Using radio-iodinated or tritiated Ag binding assays, their results suggested that the Ab response to the three synthetic polypeptide Ags was either controlled by multiple loci all linked to the H-2 region or a single locus with five or more multiple alleles.

The availability of congenic mouse strains with recombinations in the H-2 complex (an approach pioneered by Snell, patiently breeding mice in the wilds of Maine) permitted McDevitt and colleagues to complete their double whammy and define the I region of the H-2 as the master controller of Ab responses (8). These findings enabled act II of the play, which concluded with Zinkernagel and Doherty’s discovery of MHC restriction of killer T cell specificity (9). This was as much as predicted by McDevitt and Chinitz’s concluding paragraph, which stated, “a cell’s own complement of surface Ags may predetermine in some way the type of exogenous Ags with which it may interact” (7).

Postscript

The McDevitt and Chinitz paper contributed an important and seminal finding by linkage of the immune response gene phenomena directly and unequivocally to the MHC. The 1980 Nobel Prize, awarded for “discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions,” easily could have included McDevitt. As science becomes an enterprise involving larger groups and more extensive collaborations, the difficulty in trying to award credit to a limited few crucial individuals will only increase.

References


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