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The TCR takes some immune responsibility

Ashley A. Viehmann Milam and

Department of Pathology and Immunology, Washington University

Paul M. Allen

Department of Pathology and Immunology, Washington University

Abstract

Van Braeckel-Budimmir et al. (2017) reveal that the pathogenic response of mice to a *Plasmodium berghei* infection is dominated by a V β 8.1 T cell response. Mice lacking V β 8.1 T cells fail to mount a pathogenic response, thus showing that the TCR locus can be an Immune Response (Ir) gene.

One of the seminal discoveries in modern immunology was that the ability to mount an immune response to an antigen is genetically controlled. Baruj Benacerraf and colleagues in 1963 showed that two inbred strains of guinea pigs differed in their ability to mount a T cell response to synthetic amino acid polymers (Levine et al., 1963). Strain 2 responded to the antigen poly L-lysine, whereas strain 13 did not. Conversely, Strain 2 did not respond to glutamic acid/tyrosine, while strain 13 did. This Ir (*immune response*) gene was identified as being autosomal dominant, but further genetic analysis in guinea pigs proved difficult.

Subsequently, Hugh McDevitt at Mill Hill in London with John Humphrey and Ita Askonas mapped the Ir gene to the MHC locus. Using synthetic co-polymers developed by Michael Sela, McDevitt initially observed that rabbits differed in their ability to respond to the co-polymers, but like the guinea pig, genetic analysis of this response proved difficult. Turning to MHC congenic mouse strains, McDevitt showed that the Ir genes mapped to the MHC locus (McDevitt and Sela, 1965). Up until this time, MHC molecules were the prerogative of transplantation biologists, and their real physiological role was not appreciated. McDevitt's discovery placed the MHC molecules into their appropriate framework-at the center of adaptive immune responses. Further mapping using intra-H-2 recombinant mouse strains mapped the Ir genes to a region between H-2K and H-2D, initially named the I region for Immune response, which we now call the MHC class II region (McDevitt, 2000).

The molecular mechanism of how Ir genes functioned was at the center of immunology research in the 1970s and many theories, entire meetings, and whole books were devoted to this subject (Katz and Benacerraf, 1976). Ir genes were identified for several small protein antigens such as cytochrome c, or hen egg-white lysozyme, but not when larger more complex antigens (such as KLH) were tested. A major breakthrough in the field of Ir genes was made by Unanue and colleagues, when they reported the first demonstration of a peptide binding to an MHC molecule (Babbitt et al., 1985). They showed that the HEL(46-61) peptide bound to I-A^k molecules from a responder strain, but not to I-A^d molecules from a non-responder strain. Thus, the basis for responder/non-responder “status” in mice was the

ability (or inability) of a peptide to bind to an MHC molecule, and subsequently be recognized by a TCR. It now also made sense why, for large protein antigens, responder/non-responder mouse strains could not be found: there were always one or more peptides that could bind to any particular MHC molecule, and stimulate the T cells. Ir genes were mostly a class II restricted phenomenon, but a few class I Ir genes were reported. As more and more class I- and class II-restricted epitopes were identified, another unexplained phenomenon arose: that of immunodominant responses against viruses and bacteria. For example, a dominant epitope in the class I-restricted response against LCMV is the gp33/H-2D^b epitope, comprising ~10 % of the responding CD8+ T cells (Wherry et al., 2003).

Infection of mice with *P. berghei* is an important model of severe malarial disease. Previous studies have reported that the development of experimental cerebral malaria (ECM) during *P. berghei* infection is absolutely dependent on pathogenic CD8+ T cells, in particular V β 8+ cells recognizing the immunodominant H-2D^b-restricted epitope GAP50₄₀₋₄₈, but, It had not been established why these T cells are pathogenic in ECM. In this issue, Van Braeckel-Budimir et al. established the basis for this pathogenic response (Van Braeckel-Budimir et al., 2017).

The authors first compared specific responses against GAP50₄₀₋₄₈ immunization to those of other *P. berghei*-derived epitopes. They found that, unlike responses to other epitopes, CD8+ T cells responding to GAP50₄₀₋₄₈ have a uniform and absolute usage of V β 8.1+. Using mutational analysis of the GAP50₄₀₋₄₈ peptide, they identified two key C-terminal residues that constituted “hotspots” for TCR recognition. A crystal structure of a prototypical TCR:peptide-MHC (pMHC) revealed that the TCR β chain overwhelmingly dictated interactions with the peptide, while the TCR α chain mostly interacted with the MHC molecule. Intriguingly, this suggested that the peptide itself, not the MHC in this case, was driving the preference for V β 8.1 usage. Structurally speaking, V β 8.1 and V β 8.2 TCR have been the most extensively studied TCRs. Evidence for a germline affinity between the TCR and MHC has been found for both V β 8.1 and V β 8.2 TCRs, in the form of conserved interaction motifs in the CDR2 β and framework TCR β chain (Feng et al., 2007). Strikingly, the GAP50₄₀₋₄₈-specific TCRs do not use the same conserved residues to bind H-2D^b, thereby challenging the concept of a germline encoded affinity between the TCR and MHC.

Focusing then on the naive repertoire that serves as the source of the ECM response to *P. berghei*, the authors used tetramer enrichment to estimate that there exists a pool of ~3000 GAP50₄₀₋₄₈-specific precursor cells per mouse; notably, this is the largest antigen-specific naive population ever described. This finding implied that thymic positive selection was a major contributor to the robust CD8+ T cell response to GAP50₄₀₋₄₈. To further support this idea, the authors found that levels of the immunomodulatory molecule CD5 are especially high on this population, indicating strong selection of these cells during thymic development. By then expressing the GAP50₄₀₋₄₈ epitope in *Listeria monocytogenes*, they showed that this rapidly expanding GAP50₄₀₋₄₈-specific precursor population conferred enhanced protection in the context of a bacterial infection.

To demonstrate the *in vivo* significance of the GAP50₄₀₋₄₈ immunodominant response, the authors examined responses to *P. berghei* infection in C57/L mice, which are H-2^b-restricted,

but lack several TCR V β genes, including V β 8.1. Unlike their V β 8.1-replete B6 counterparts, the C57/L mice produced no detectable GAP50₄₀₋₄₈ responses. The C57/L mice did not succumb to ECM like B6 mice, but rather died from uncontrollable parasite burdens several weeks after infection. This remarkable finding shows that the absence of germline-encoded V β 8.1 results in not only a lack of the pathogenic response necessary for ECM development, but also the ability to control *P. berghei* infections (Preview Figure, left panel). This finding by Van Braeckel-Budimir et al., revealed that the TCR locus can be an Ir gene, and can determine if a T cell response against a pathogen will occur or not (Van Braeckel-Budimir et al., 2017). Thus, this novel demonstration shows that the T cell can also be responsible for an in vivo Ir gene response- a concept that had been previously proposed, but not supported by experiments (Preview Figure, right panel) (Katz and Benacerraf, 1976).

One implication of these studies is that there must exist a single peptide involved in positive selection of the V β 8.1 GAP50₄₀₋₄₈ T cells. The identification of this positively selecting peptide (and the explanation for this incredibly large naive precursor population) would form the basis of fascinating future studies. What is the significance of the finding that the TCR can be an Ir gene, in the context of human immune responses? The authors' findings raise the possibility that polymorphisms in the TCR loci could dictate whether an individual could respond (or not respond) to a vaccine challenge. Two recent reports describe a process of finding patterns in human T cell recognition of pMHC using tetramer enrichment, high-throughput TCR sequencing, and novel algorithms (Dash et al., 2017; Glanville et al., 2017). These studies could provide an approach to investigate the TCR Ir gene phenomenon in depth. Overall, these findings by Van Braeckel-Budimir et al. show how the TCR can take some of the responsibility away from the pMHC in determining whether an individual can respond to a pathogen.

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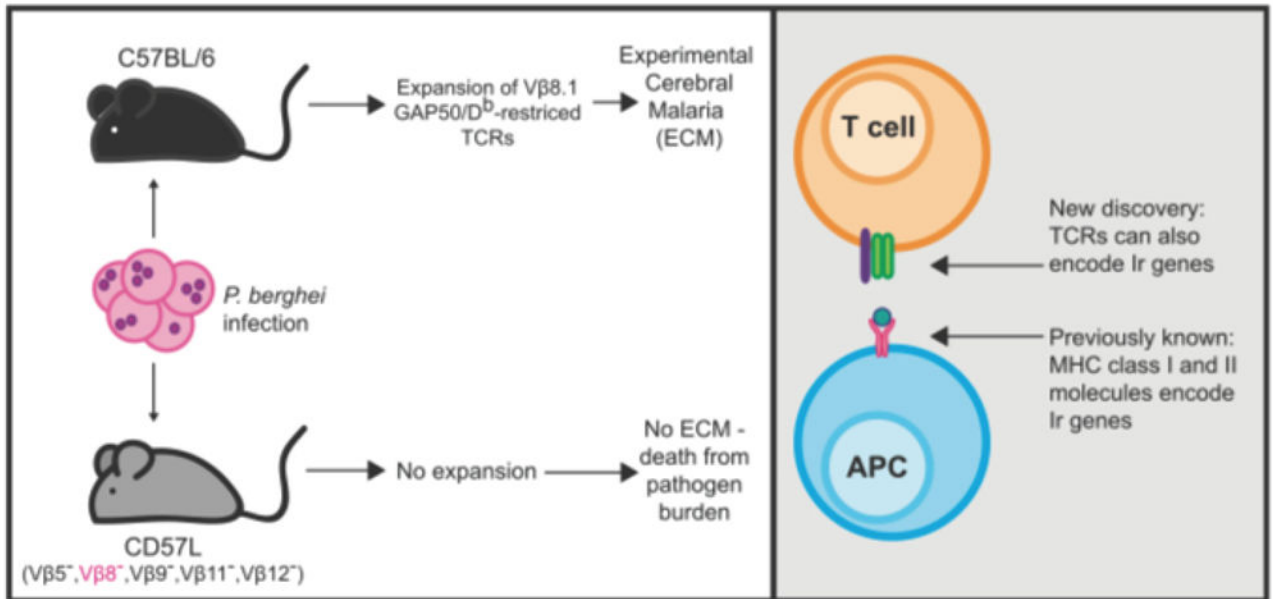


Figure. Mice must express Vβ8.1 to mount a pathogenic CD8+ T cell response against *P. berghei* infection

(Left) C57/BL6 mice mount a robust pathogenic CD8+ T cell response against *P. berghei* in a murine model of malaria, which ultimately leads to development of Experimental Cerebral Malaria (ECM). This response is overwhelmingly specific for an H-2D^b-restricted epitope that is derived from GAP50. In contrast, CD57L mice, which express H-2D^b but lack several TCR Vβ chains (including Vβ8), fail to control *P. berghei* infection and ultimately succumb to a large pathogen burden. (Right) Herein, the authors show that the capacity of C57/BL6 mice to mount this response lies in their germline expression of Vβ8.1. While it has been previously shown that MHC class I and II molecules can encode germline immune response (Ir) genes, Van Breackel-Budimir et al. for the first time show that TCR chains can also encode Ir genes.