The Journal of Immunology

In This Issue

J Immunol 2013; 191:523-524; ;
doi: 10.4049/jimmunol.1390038
http://www.jimmunol.org/content/191/2/523

Supplementary Material http://www.jimmunol.org/content/suppl/2013/07/03/191.2.523.DC1

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

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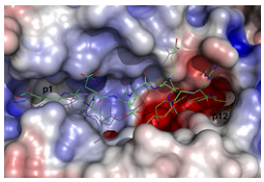
Selecting for Length



While Class I HLAs present peptides varying from eight to ten amino acids in length, how different HLA polymorphisms "select" these peptide lengths to initiate $CD8^+$ T cell responses has remained unclear. To clarify this, Rist et al. (p. 561) looked at the binding properties of the HLA-B*44 supertype, which includes the common alleles HLA-B*44:03 and HLA-B*18:01. The BLZF1 Ag of Epstein-Barr virus (EBV), used as a model Ag, is responsible for the switch in gene expression from latent to lytic forms of the virus, and has overlapping sequences of different lengths that conform to the HLA-B*44 supertype binding motif. Individuals with HLA-B*18:01 exclusively responded to an octamer, ^{173}SELEIKRY^{180}, whereas individuals carrying HLA-B*44:03 responded to an atypically large dodecamer peptide, ^{169}EECDSELEIKRY^{180}. HLA-B*18:01 binding to the octamer was found to be more stable than to the dodecamer. HLA-B*44:03 was only able to bind the dodecamer. Crystal structures of the viral peptide–HLA complexes revealed that the Ag binding clefts of HLA-B*18:01 and HLA-B*44:03 were specifically suited to binding shorter and longer peptides, respectively. Further analysis of >1000 naturally presented ligands by mass spectroscopy showed that HLA-B*18:01 presented shorter peptides compared with HLA-B*44:03. Thus, the authors demonstrate how polymorphisms within an HLA Class I supertype can add to the diversity of ligands selected for presentation and how $CD8^+$ T cell responses can be initiated against Ags of varied lengths.

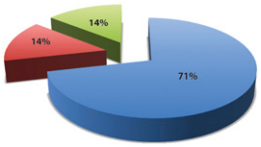
Complementing CD14 Blockade

Both complement and TLRs are necessary for innate immune function. However, inhibiting these players may be necessary to alleviate the consequences of sepsis. To build on previous work demonstrating that blocking the TLR coreceptor CD14 inhibited inflammation and thrombogenicity in porcine sepsis, Barratt-Due et al. (p. 819) investigated the effects of the C5 and leukotriene B4 inhibitor OmCI (coversin) and anti-CD14 in *Escherichia coli*–induced sepsis. In septic animals, treatment with OmCI blocked C5 activation and terminal complement complex formation, and lowered leukotriene B4 levels compared with controls. The authors also found that TNF-α, IL-6, granulocyte tissue factor, and thrombin-antithrombin complexes were all inhibited by OmCI treatment. With a combined treatment of anti-CD14 and OmCI, all of these markers of sepsis were significantly decreased ($p < 0.001$) or completely absent. OmCI and anti-CD14 combined therapy also abolished plasminogen activator inhibitor-1, IL-1β, and IL-8 production, and CD11b (wCD11R3) expression on granulocytes. Plasma concentrations of IL-10 increased under combined therapy and increases in heart rate and pulmonary artery pressure were delayed. Thus, the authors found that combining OmCI and anti-CD14 was a useful therapy in treating porcine sepsis, significantly abrogating inflammatory and thrombogenic aspects of the innate immune response.

Innate CD4 TCRs Regulate Selection

Innate $CD4^+$ T cells have an effector/memory-like phenotype, coexpress the transcription factor Promyelocytic leukemia zinc finger (PLZF) and the cytokine IL-4, and engage in important immunosuppressive functions in vivo. These cells undergo selection in the thymus, but unlike conventional $CD4^+$ T cells that are selected by thymic epithelial cells (TECs), MHC II–expressing thymocytes drive selection of innate $CD4^+$ T cells (T-CD4s). Because mice transgenic for MHC II–restricted OVA and cytochrome c-specific TCRs demonstrate poor T-CD4 selection by thymocytes, Zhu et al. (p. 737) hypothesized that T-CD4s may express a specific but diverse TCR repertoire that plays an instructive role in the T-CD4 selection process. To test this hypothesis, the authors generated a T-CD4–derived TCR Transgenic mouse (3T) and found that T-CD4 selection occurred efficiently when thymocytes (but not TECs) expressed MHC II. 3T thymocytes required SAP and PLZF for development and acquired PLZF and IL-4 expression at the double positive stage in a heterogeneous manner, suggesting that 3T T-CD4s acquire effector function soon after positive selection, but that TCR specificity alone was not sufficient to induce a uniform $PLZF^+IL\text{-}4^+$ innate $CD4^+$ T cell phenotype. These data indicate that TCR specificity regulates T-CD4 development, but other factors likely define T-CD4 programming.

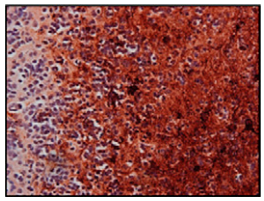
Malaria in the Crosshairs



One of the biggest challenges when developing a vaccine to a complex human pathogen, such as malaria, is determining which Ags to target. Richards et al. (p. 795) attempted to address this challenge by analyzing potential Ags that the malarial parasite *Plasmodium falciparum* expresses during its extracellular blood (merozoite) phase. Ninety-one recombinant proteins, chosen because of their expression on the merozoite surface or parasite invasion organelles, were analyzed for their ability to elicit Ab reactivity in malaria-infected individuals. As a result of this analysis, 46 Ag-specific Abs were identified and followed in a longitudinal cohort of 206 New Guinean children (aged 5–14 years). Individuals were examined to determine at what age Ab responses

could be measured and which Ab profiles correlated with protective immunity. Older children with active parasitemia had higher levels of antimalarial Abs. Interestingly, the presence of Ab responses to two erythrocyte invasion proteins, rhoptry and microneme, had the strongest correlation with protective immunity. Additionally, a number of the newly identified Ags appeared to have a greater correlation with protection than many malaria vaccine candidate Ags currently under investigation. The authors found that some combinations of Ab responses were more closely associated with protective immunity than were single Ag-specific Ab responses. Thus, the authors successfully identified a number of target Ags that were strongly correlated with protective immunity, identifying excellent candidates for future antimalarial vaccines and biomarkers of effective malarial surveillance.

SARM Deficit Shields CNS from Harm



The highly conserved Toll/IL-1R (TIR) domain-containing adaptor family members signal downstream of TLRs and are components of pathways essential to type-1 IFN production and NF-κB activation in innate immune responses. However, the function of one family member, sterile alpha and TIR domain–containing 1 (SARM), is not well characterized. SARM is expressed in the CNS and mediates axonal destruction in the brain. Previous work also demonstrated a role for SARM in innate immunity in *C. elegans*, prompting Hou et al. (p. 875) to determine whether SARM is involved in innate immune responses in mammals. To do this, the authors challenged $SARM^{-/-}$ mice with myriad bacterial and viral pathogens and examined the resulting immune responses. They found that $SARM^{-/-}$ mice had normal responses to most pathogens, but, unlike WT mice, were protected from death after CNS infection with vesicular stomatitis virus (VSV). Using mixed bone marrow chimeras, the authors determined that $SARM^{-/-}$ nonhematopoietic cells, possibly neurons, had reduced levels of inflammatory cytokine production in the brain, and that there was reduced CNS injury after VSV infection. These results suggested that *SARM* deficiency in these cells afforded mice protection from neuropathology. Thus, SARM may positively regulate inflammatory cytokine production by nonhematopoietic cells in the brain during innate immune responses and inhibition of this process could reduce the extent of CNS injury that occurs during neural pathogen challenge.

Orchestrating Tolerance with p38α

A subset of dendritic cells (DCs) expressing CD103 helps maintain immune tolerance in the intestine by promoting the differentiation of induced regulatory T cells (iTregs) and the expression of lymphocyte gut-homing receptors. Signaling in DCs via the MAPK p38α has been found to support inflammatory T cell differentiation. Huang et al. (p. 650) investigated whether p38α also plays a role in DC-mediated tolerance by analyzing mice specifically lacking this kinase in DCs ($p38\alpha^{\Delta DC}$). Oral tolerance and the development of iTregs, but not thymus-derived natural Tregs, were impaired in $p38\alpha^{\Delta DC}$ mice. This defect in iTreg generation was specifically linked to p38α-dependent production of TGF-β2 by $CD103^+$ DCs from the mesenteric lymph nodes (MLNs). In addition to inducing iTreg differentiation, signaling via p38α in $CD103^+$ DCs also downregulated Th1 differentiation in a TGF-β2–dependent manner. In contrast, T cells from mice bearing a T cell–specific deletion of p38α showed no changes in iTreg or Th1 differentiation. Relative to WT DCs, $p38\alpha^{\Delta DC}$ $CD103^+$ MLN DCs had lower expression of retinaldehyde dehydrogenase (Aldh1a2), which reduced DC retinoic acid synthesis and led to impaired expression of gut-homing receptors in T cells. Taken together, these data reveal that p38α in $CD103^+$ MLN DCs both controls the balance of iTreg/Th1 differentiation via TGF-β2 expression and regulates T cell trafficking via Aldh1a2 expression.