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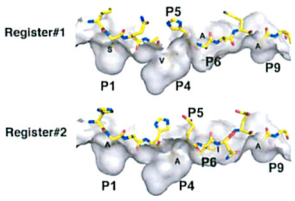
THE JOURNAL OF IMMUNOLOGY

In This Issue

Registering MHC II Tetramers



Tetramers consisting of peptide:MHC class I complexes (pMHCT-1) have been used extensively for the study of $CD8^+$ T cell responses. However, studies with peptide:MHC class II tetramers (pMHCT-2) have been far less successful. In hopes of developing functional pMHCT-2, Landais et al. (p. 7949) sought to identify why these tetramers often fail to stain Ag-specific $CD4^+$ T cells. To systematically address this question, the authors analyzed three characteristics of $I\text{-}A^d\text{-}OVA_{323–339}$ pMHCT-2 molecules: geometry, stability, and peptide display. Changing the tetramers' geometry or increasing their stability did not result in T cell staining. In contrast, $CD4^+$ T cells were extremely sensitive to the register in which the OVA peptide was displayed. Both DO11.10 and OT-2 cells could only be stained with tetramers expressing peptide in register 2. Altering the length and composition of the linker attaching the peptide to the MHC β-chain allowed staining optimization, presumably by encouraging peptide binding to the MHC in register 2. Immunization of BALB/c mice with whole OVA protein demonstrated that long peptides could be displayed in multiple registers in vivo, resulting in the selection of register-specific T cell populations. These data have useful implications for the effective design of pMHCT-2 and for the understanding of $CD4^+$ T cell activation.

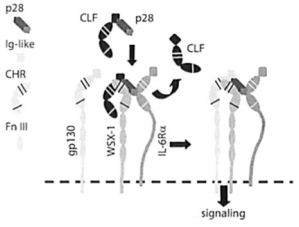
Cross-Priming Specialization

Dendritic cells (DCs), like most immune cells, consist of several functionally distinct subsets. Previous data have suggested that a fraction of murine $CD8\alpha^+$ DCs is particularly suited to cross-presentation, the MHC class I-mediated presentation of exogenous Ags to $CD8^+$ T cells. Using a mouse model that allowed the selective depletion of langerin (CD207)-expressing cells in vivo, Farrand et al. (p. 7732) asked whether $langerin^+CD8\alpha^+$ DCs were the DC subset responsible for cross-presentation. Indeed, $langerin^+CD8\alpha^+$ DCs were able to effectively shuttle soluble Ag to the cytosol and stimulate $CD8^+$ T cells. Depletion of this DC subset dramatically reduced this cross-presentation. In response to systemic activation via ligands for TLR2 or invariant NKT cells, $langerin^+CD8\alpha^+$ DCs up-regulated costimulatory molecules and effectively cross-primed CTL. This DC subset was also responsible for IL-12p40 production in response to these stimuli. Again, depletion of $langerin^+$ cells confirmed these observations by leading to the ablation of IL-12 release and a significant reduction in $CD8^+$ T cell responses following TLR2 or invariant NKT cell activation. This study defines a critical role for $langerin^+$, but not $langerin^-$, $CD8\alpha^+$ splenic DCs in cross-priming and IL-12 production. This advancement in our understanding of DC specialization may guide future vaccination strategies.

Sluggish Signaling

Signaling through TLRs is important for innate immune responses to pathogens. In a genetic screen using *N*-ethyl-*N*-nitrosourea mutagenesis to identify defects in TLR signaling, Xiao et al. (p. 7975) detected a mutation that they dubbed *Sluggish*. This mutation was found to affect splicing of the gene encoding tumor progression locus 2 (Tpl2)/MAP3K8, which is a kinase involved in many TLR signaling pathways. The *Sluggish* mutation caused the removal of exons encoding portions of the Tpl2 kinase domain and led to reduced TLR-induced ERK phosphorylation in vitro. Peritoneal macrophages from *Sluggish* homozygotes secreted little to no TNF-α in response to all TLR ligands tested and also showed impaired IL-6 secretion. Signaling through TLR7 and TLR9, but not other TLRs, led to reduced type I IFN production in peritoneal macrophages from *Sluggish* mice compared with those from wild-type mice. Despite this selectively impaired IFN production, *Sluggish* mice were able to effectively control viral infections. However, these mice were highly susceptible to group B streptococcus infection, and infected macrophages demonstrated profoundly impaired TNF-α and type I IFN production compared with those of wild-type mice. Interestingly, Tpl2 is therefore part of a signaling cascade required for the innate immune response to specific classes of pathogens.

Complex Cytokine Family Dynamics



Interleukin-27 is a heterodimeric cytokine composed of p28 and EBV-induced gene 3 (EBI3) that binds to an IL-27R composed of gp130 and WSX-1. Differences in the phenotypes of mice deficient in EBI3 vs WSX-1 have suggested that p28 might have EBI3-independent functions. In support of this idea, Crabé et al. (p. 7692) found that p28 could also form a secreted complex with cytokine-like factor 1 (CLF-1). Like IL-27, this complex was produced by dendritic cells and was able to stimulate NK cells. p28/CLF bound to a tripartite receptor made up of gp130, WSX-1, and IL-6Rα, leading to STAT1 and STAT3 phosphorylation and proliferation of receptor-transfected Ba/F3 cells. In primary $CD4^+$ and $CD8^+$ T cells, p28/CLF induced IL-6Rα-dependent STAT1 and STAT3 phosphorylation. This novel cytokine also inhibited $CD4^+$ T cell proliferation but stimulated Th17 differentiation and IL-10 production. This demonstration that p28/CLF and IL-6 can both act through the IL-6R has important therapeutic implications, because blocking Abs to IL-6Rα are being developed as treatments for multiple inflammatory and autoimmune diseases.

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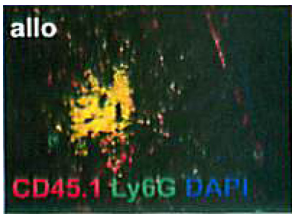
Innate Allogeneic Responses



Much is known about the adaptive immune response to allogeneic tissues, but less is understood about how the innate immune system might recognize allogeneic Ags. It has been observed that invertebrate organisms that lack T, B, and NK cells are still able to reject allogeneic tissues, leading Zecher et al. (p. 7810) to assess whether mammalian immune systems might also mount lymphocyte-independent alloimmune responses. $RAG^{-/-}$ mice were preimmunized or grafted with syngeneic or allogeneic $RAG^{-/-}$ cells and then challenged in the ear with syngeneic or allogeneic splenocytes. These lymphocyte-deficient mice generated an alloimmune response that required priming with allogeneic cells and showed characteristics of immune memory. The response was mediated by infiltrating monocytes/macrophages and neutrophils but did not involve NK cells. Alloimmunity could be adoptively transferred to naive $RAG^{-/-}$ mice by allograft-primed monocytes, supporting the existence of innate alloreactivity. Interestingly, the use of congenic mice that differed only at the MHC locus indicated that the innate alloresponse was dependent on non-MHC-linked determinants. Thus, mouse monocytes can mount responses to allogeneic nonself independently of NK cells and the MHC.

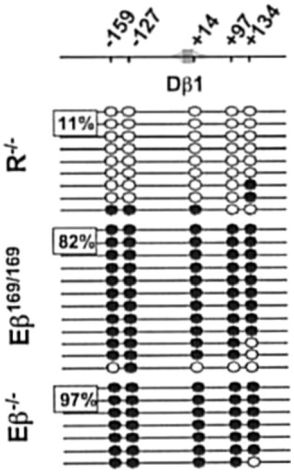
Tracking Responders

Responses of Ag-specific $CD8^+$ T cells can be effectively analyzed given knowledge of the cells' epitope specificity. However, responses to complex Ags such as viruses, bacteria, or transplanted organs are more difficult to assess. A complete understanding of T cell immunity and effective vaccine design in such real-world situations require a mechanism to track responding $CD8^+$ T cells. Rai et al. (p. 7672) found that up-regulation of CD11a and down-regulation of $CD8\alpha$ identified responding $CD8^+$ T cells following immunization with OVA-expressing, attenuated *Listeria monocytogenes*. These cell surface marker alterations were maintained during the establishment of T cell memory and were found to occur in response to Ag rather than inflammation. Enumeration of $CD11a^{high}CD8\alpha^{low}$ T cells could be used to determine the magnitude of $CD8^+$ T cell expansion in the blood and spleen following bacterial or viral infection and also allowed tracking of pathogen-specific $CD8^+$ T cells in nonlymphoid organs. In both bacterial and viral infections, the analysis of T cells expressing these markers in outbred mice revealed substantially more variability in the magnitude and kinetics of $CD8^+$ T cell responses compared with inbred mice. Despite this variability, the $CD11a^{high}CD8\alpha^{low}$ phenotype consistently identified responder T cells, suggesting that this phenotype could be useful for evaluating immune responses in situations relevant to humans. Thus, these markers allow the effective study of $CD8^+$ T cell responses without knowledge of the target Ags involved.

Manipulating MMP-9

Matrix metalloproteinase (MMP)-9 is involved in many inflammatory processes, but the regulation of its expression is not completely understood. Steenport et al. (p. 8119) asked whether other MMPs present in inflammatory or neoplastic conditions under which MMP-9 is up-regulated might affect its expression. Indeed, MMP-1 and MMP-3 were found to induce MMP-9 expression through a pathway requiring $MAPK^{erk1/2}$ activation, which induced cyclooxygenase-2 (Cox-2) expression. Cox-2 induced PGE_2 expression, and PGE_2 binding to the EP4 prostanoid receptor mediated MMP-9 expression. Inhibition of Cox-2, $MAPK^{erk1/2}$, EP4, or MMP activity attenuated MMP-9 expression, indicating the vital role of each component of the pathway in MMP-9 regulation. Analysis of the culture supernatants of MMP-1- or MMP-3-treated macrophages demonstrated the induction of TNF-α, which was found to be responsible for Cox-2 and MMP-9 induction. The ability of MMP-1 and MMP-3 to induce the Cox-2-dependent expression of MMP-9 reveals a connection between MMPs and prostanoids that the authors propose may be important in inflammatory diseases and cancer. The data also demonstrate that MMP-9 induction is targetable by inhibitors of any step of the pathway, providing possible avenues for therapeutic modulation.

Variety is the Spice of TCR Life



Transcriptional enhancers can affect a linked promoter in either a binary manner, by increasing the probability of its usage, or in a graded manner, by up-regulating the rate of transcription. The TCRβ gene enhancer (Eβ) is deeply involved in both triggering Dβ-Jβ recombination in early thymocytes and driving the expression of the assembled TCRβ gene in mature T cells. It is not known, however, whether Eβ acts in a binary or graded manner. To address this issue, Bonnet et al. (p. 7939) developed transgenic mice in which Eβ was replaced by a 169-bp Eβ core enhancer fragment ($E\beta^{169/169}$). Unlike in $E\beta^{-/-}$ mice, thymocytes in $E\beta^{169/169}$ mice were able to develop past the double-negative stage; however, $\alpha\beta$T cells were produced at reduced efficiency in these mice compared with wild type. $E\beta^{169/169}$ thymocytes demonstrated a block in the double-negative to double-positive transition that was associated with dysfunctional chromatin remodeling. These observations suggested that $E\beta^{169}$ acted in a binary mode in early thymocytes. However, mature $E\beta^{169/169}$ T cells showed heterogeneous expression of TCRβ and a biased Vβ repertoire, suggesting a graded mode of Eβ action. Taken together, these data suggest that an enhancer can have different modes of action at different stages of cellular development, and elucidation of the Eβ mechanisms of action may be important to the understanding of TCR rearrangement and allelic exclusion.

Summaries written by Jennifer Hartt Meyers, Ph.D.

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