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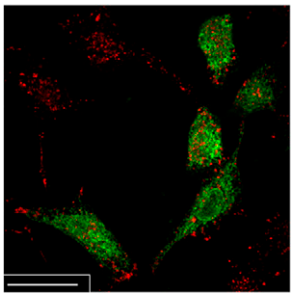
THE JOURNAL OF IMMUNOLOGY

In This Issue

Langerhans Lay Claim to HLA-DQ2



Two pairs of MHC class II genes are present in the *HLA-DQ* locus, the classical *HLA-DQA1/HLA-DQB1* and the relatively nonpolymorphic *HLA-DQA2/HLA-DQB2*. Although the latter genes are evolutionarily conserved, expression of *HLA-DQB2* has not been observed, and its potential biological role is therefore unclear. While comparing transcriptomes of dendritic cell (DC) subsets to investigate the immune function of Langerhans cells (LCs), Lenormand et al. (p. 3903) observed the expression of both *HLA-DQA2* and *HLA-DQB2* in LCs at both the mRNA and protein levels. Intriguingly, these genes were not expressed in myeloid DCs, plasmacytoid DCs, or CD1c$^+$ blood DCs. HLA-DQα2 and HLA-DQβ2 chains formed heterodimers which, upon association with invariant chain, trafficked from the endoplasmic reticulum (ER) to endosomal compartments. These heterodimers also associated with HLA-DM and could be found on the cell surface, where they were able to mediate the presentation of superantigens to T cells. Mixed heterodimers consisting of HLA-DQα2 and -DQβ1 could also form and exit the ER, whereas mixed HLA-DQα1/DQβ2 heterodimers could form but could not efficiently egress from the ER. This study identifies HLA-DQα2/β2 heterodimers as LC-specific MHC class II molecules that may have specialized roles in LC activity.

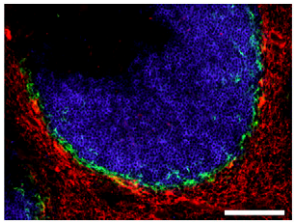
Lipid Lesson in the Lung

Lysophosphatidic acid (LPA) is a lipid that can affect various cellular processes, including activation and migration, upon extracellular engagement of LPA receptors. Several studies have indicated that LPA can inhibit inflammatory responses, and Emo et al. (p. 3784) now show that the LPA receptor Lpa2 negatively regulates dendritic cell (DC) activation and attenuates allergic airway inflammation. Lpa2 is a member of the Edg family of G protein-coupled receptors and is constitutively expressed on the surface of murine bone marrow-derived DCs. Compared with wild-type (WT) DCs, *lpa2*$^{-/-}$ DCs showed a hyperactive phenotype in both their ability to stimulate T cells and to secrete the proallergic cytokine IL-13. Transient expression of *lpa2* significantly reduced NF-κB activation upon LPS stimulation. WT mice that were given allergen-pulsed DCs from *lpa2*$^{-/-}$ mice developed significantly greater allergic airway inflammation upon aerosol Ag challenge compared with mice given allergen-pulsed WT DCs. In addition, *lpa2*$^{-/-}$ mice also developed significantly worse airway inflammation relative to WT mice in different models of allergic asthma. Together these results support a role for LPA signaling through *lpa2* as a mechanism to modulate excessive DC responses and airway inflammation.

Making Memory-Like T Cells

A subset of CD8 single positive (CD8SP) thymocytes, which has a similar phenotype to conventional CD8$^+$ memory T cells, has been characterized as memory-like CD8SP thymocytes. Development of these memory-like thymocytes requires expression of the promyelocytic leukemia zinc finger (PLZF) transcription factor, and Sharma et al. (p. 3859) examined the mechanism involved in the generation of these cells. The authors confirmed previous observations by showing that expression of β-catenin from the Lck promoter drives expansion of PLZF-expressing CD4$^+$αβ$^+$ thymocytes that produce IL-4. The proliferation and production of IL-4 by these cells promoted expansion of eomesodermin (Eomes)-expressing CD8SP thymocytes. In contrast, T cell factor (TCF)-1–deficient mice had significantly fewer PLZF-expressing thymocytes and Eomes-expressing CD8SP thymocytes. In addition to TCF-1 and β-catenin, expression of IL-4 and IL-4R were also required for the generation of memory-like CD8SP thymocytes. These memory-like thymocytes were able to migrate to the periphery and produce IFN-γ upon stimulation, suggesting that they were functional. Together these data indicate that IL-4 production by PLZF$^+$ thymocytes directs generation of memory-like CD8SP thymocytes by inducing expression of molecules that are critical to the development of their memory-like phenotype.

Antigenic Size Matters



For their activation and clonal selection, B cells must interact with Ags on follicular dendritic cells (FDCs). Various pathways have been proposed to account for the transport of Ag to the follicles; however, it remains unclear how Ag is presented to B cells during a primary response. Link et al. (p. 3724) expressed the coat protein of the bacteriophage Qβ as either a small dimeric protein or a large virus-like particle (VLP) to address the influence of antigenic size and structure on transport to the follicles in the absence of prior immunity. In naive mice, Qβ-VLPs were rapidly and efficiently transported to FDCs, where they accumulated over time. In contrast, Qβ-dimers were not deposited on FDCs unless specific anti-Qβ Abs were present to allow the formation of immune complexes. In agreement with these observations, Qβ-VLPs but not Qβ-dimers induced strong germinal center responses and the expansion of high numbers of Qβ-specific Ab-secreting cells. Transport of Qβ-VLPs involved their binding to noncognate B cells through a complement-dependent process that specifically required complement receptor expression on B cells. Natural IgM Abs were also

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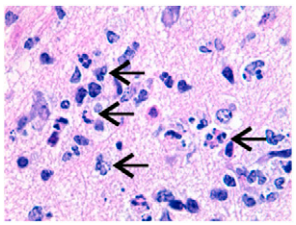
important for the transport of Qβ-VLPs to B cell follicles. Immunization with anti-Qβ IgG Abs led to the efficient transport of Qβ-dimers to FDCs but completely abrogated the interaction of Qβ-VLPs with FDCs. These data reveal a major influence of Ag size and structure on the initiation of a primary B cell response.

Tregs Choose Their Targets



Regulatory T cell (Treg)-mediated modulation of T cell activity has the potential to both positively and negatively impact the host by inhibiting autoimmunity and impairing antiviral immune responses. To address the function of Tregs during viral infection of the CNS, Cervantes-Barragán et al. (p. 3678) analyzed the effects of Treg depletion during mouse hepatitis virus (MHV) infection. Neurotropic MHV infection resulted in the infiltration of T cells, including Tregs, into the CNS. Specific depletion of Foxp3$^+$ Tregs during infection resulted in exacerbated inflammatory responses and an increased CNS infiltration of T cells that did not appear to be specific for MHV. Interestingly, Treg depletion had no significant effect on viral clearance or T cell-mediated antiviral immunity. Instead, Tregs were found to inhibit the MHV infection-induced activation, proliferation, and CNS infiltration of autoreactive CD4$^+$ T cells. These functions of Tregs were most pronounced in the CNS-draining lymph nodes and involved downregulation of the chemokine receptor CXCR3. Thus, in this system, Tregs selectively maintain immune privilege in the CNS by inhibiting autoimmune T cell responses without interfering with protective antiviral T cell responses.

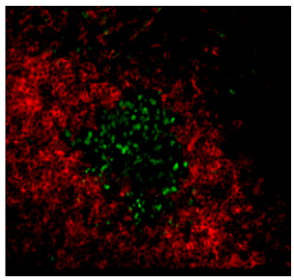
Memory Hangs in the Balance

A more thorough understanding of the factors involved in CD8$^+$ T cell memory generation could lead to enhanced vaccine efficacy. CD4$^+$ T cells induce the upregulation of CD70 on dendritic cells, and interaction of CD70 with CD27 may be important for primary and memory CD8$^+$ T cell responses. Dong et al. (p. 3829) hypothesized that this induction of CD27 costimulation explains the requirement for CD4$^+$ T cell help in CD8$^+$ T cell memory development. In immunized mice depleted of CD4$^+$ T cells, stimulation of CD27 on CD8$^+$ T cells rescued the development of CD8$^+$ T cell memory. Conversely, blockade of CD70 in the presence of CD4$^+$ T cells strongly impaired the CD8$^+$ T cell memory response. CD70/CD27-mediated costimulation during the primary CD8$^+$ T cell response was found to increase the number of IL-7R–expressing memory precursor effector cells while suppressing their expression of the IL-2 and IL-12 receptors. However, CD70 blockade did not significantly affect CD8$^+$ T cell memory development following an immunization regimen that did not stimulate inflammatory cytokines or in mice lacking IL-12. IL-12–deficient mice also showed no defect in CD8$^+$ T cell memory following CD4$^+$ T cell depletion. These data suggested that IL-12 impairs CD8$^+$ T cell memory, whereas CD27-mediated costimulation, supported by CD4$^+$ T cell help, prevents this impairment. Taken together, these data reveal important characteristics of the development of CD8$^+$ T cell memory that could be exploited for vaccine optimization.

IL-30 Ignition Switch

The p28 subunit of IL-27, termed IL-30, has different effects on cytokine signaling when it acts as an independent molecule than when it dimerizes with EBV-induced gene 3 to form IL-27. In this issue, Dibra et al. (p. 3709) examined the roles of different cell types and signaling pathways essential to coordinating IL-30 induction. Stimulation of splenocytes with anti-CD3/CD28 Abs in combination with the TLR9 ligand CpG oligodeoxynucleotide (ODN) promoted a significant increase in IL-30 expression, especially compared with treatment of cells with LPS or with either of these stimuli alone. These findings were supported in vivo by observations of high levels of IL-30 in the sera of mice immunized with OVA combined with CFA and CpG ODN but barely detectable IL-30 levels in mice immunized with OVA/CFA and control GpC ODN. APCs have been identified previously as a source of IL-30. This study showed robust expression of IL-30 from a mixture of macrophages and CD4$^+$ T cells stimulated with anti-CD3/CD28 Abs and CpG ODNs, although B cells and dendritic cells also contributed to IL-30 production. IL-30 induction triggered by interactions with these different cell types was dependent on CD40/CD154 signaling. Overall, these results provide novel mechanistic insight into IL-30 expression.

Kinase Conundrum



PI3K signaling is involved in many immunological responses, including B cell proliferation and Ab production. Previous studies have shown that disruption of p110δ PI3K signaling can induce activation-induced cytidine deaminase (AID) and an increase in Igε germline transcripts (εGLTs), thus promoting IgE class switch recombination (CSR). Zhang et al. (p. 3700) now observe that negative regulation of IgE CSR by p110δ is mediated by changes in BCL6 expression. The authors confirmed that disruption of p110δ, but not Akt, in B cells caused a selective shift toward transcription of εGLTs and IgE production. Interestingly, p110δ inhibition was also associated with a decrease in the expression of BCL6, a transcriptional repressor that can inhibit εGLT transcription. Long-term treatment of mice with a p110δ inhibitor also caused reduced expression of BCL6 in germinal center B cells. In contrast, overexpression of BCL6 in B cells with a blockade in p110δ signaling was associated with a decrease in εGLT levels and reduced IgE switching. These data provide evidence that p110δ signaling influences IgE class switching by modulating expression of BCL6 and present a unique perspective on how B cell functions can be influenced by PI3K signaling.