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THE JOURNAL OF IMMUNOLOGY

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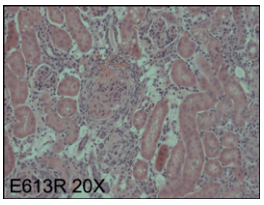
Autoimmunity through Negative Regulation



A single point mutation, E613R, in the cytoplasmic membrane-proximal wedge domain of CD45 causes a lupus-like autoimmune disease in susceptible mice. With this point mutation, the CD45 cytoplasmic domain no longer dimerizes and inhibits the phosphatase activity that regulates BCR signaling. To determine the mechanism by which a dysfunctional CD45 contributes to disease, Zikherman et al. (p. 2527) examined BCR signaling in mice with different CD45 expression levels. Interestingly, both B cells that overexpressed CD45 and E613R B cells displayed hyper-responsive B cell signaling. However, B cells with supraphysiologic levels of CD45 became anergic and only mice with the E613R mutation became frankly autoimmune. This difference was due to the E613R mutation changing the substrate specificity of CD45 for Lyn. Thus, autoimmunity in E613R mice was caused by blocking the action of the Lyn-specific negative regulatory pathway. By demonstrating that autoimmunity in these mice results from relaxing the negative regulation of BCR signaling rather than an overdrive of positive regulation, the authors have provided an important mechanistic insight into autoimmune disease.

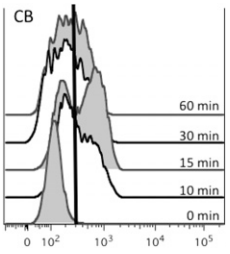
LAT Links *Listeria* and T Lymphocytes

Following an initial pathogenic infection, naive $CD8^+$ T cells undergo a three-phase response: expansion, contraction, and memory formation. The linker for activation of T cells (LAT), which links TCR activation to downstream signaling, is critical for thymocyte development and T cell activation. To examine the role of LAT in this three-phase response following *Listeria* infection, Ou-Yang et al. (p. 2938) used an OVA-specific LAT conditional knockout mouse (LATKO) to delete LAT in Ag-specific $CD8^+$ T cells at different stages of the immune response. T cell expansion was shown to be dependent upon LAT, since $CD8^+$ LATKO T cells adoptively transferred into wild-type (WT) mice prior to infection with *Listeria* failed to proliferate compared with WT T cells. $CD8^+$ LATKO T cells did not demonstrate an increase in programmed cell death, suggesting that the contraction phase is LAT independent. Deletion of LAT during the effector-to-memory transition led to an increase in the formation of long-lived memory precursor cells (MPECs) and central memory T cells (T_{CM}) compared with WT $CD8^+$ T cells. However, Ag stimulation through the TCR demonstrated a profound defect in effector cytokine production and calcium mobilization by LATKO memory $CD8^+$ T cells, and these memory cells failed to proliferate in response to a recall challenge with *Listeria*. The authors conclude that although LAT is dispensable for the contraction phase and memory maintenance of $CD8^+$ T cell responses to *Listeria*, it is essential for the recall memory response against these pathogens.

Persistence Pays Off

Memory cell persistence is important to long-lasting host protection from infection. Compared to their $CD8^+$ T cell counterparts, memory $CD4^+$ T cell populations persist for a shorter time. To better understand the development of $CD4^+$ T cell memory, Nelson et al. (p. 2828) examined the stability of pathogen-specific $CD4^+$ T cells during a sustained *Salmonella* infection. Using Nramp1-resistant ($Nramp1^R$) mice, which maintain a persistent intracellular infection after oral administration of *Salmonella*, the authors found that the number of $CD4^+$ T cells specific for *Salmonella* peptide:MHC class II (MHCII) ligands remained stable for a year. The stability of this $CD4^+$ T cell population was maintained by proliferation in secondary lymphoid organs containing bacteria and continuous presentation of the peptide:MHCII ligand. Phenotypically, these cells were Th1, upregulated PD-1, and became exhausted when exposed to systemic expression of *Salmonella* peptide:MHCII ligand. Taken together, these data indicate that pathogen-specific $CD4^+$ T cells can be maintained by Ag-driven proliferation of a small population of cells in discrete lymphoid sites.

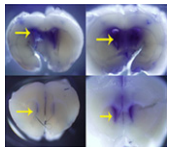
Baby Steps to Anergy



Complete activation of naive $CD4^+$ T cell responses to pathogens requires engagement of the αβ-TCR/CD3 complex and CD28. This leads to calcium release and phosphorylation of Erk in a MAPK cascade critical for activation of AP-1. Human neonates have a reduced and delayed $CD4^+$ T cell immune response to pathogens; however, the exact mechanism for this distinction is unclear. Palin et al. (p. 2682) compared calcium signaling in naive $CD4^+$ T cells from cord blood (CB) and adult peripheral blood (APB) and demonstrated an increase in signaling in CB T cells following CD3 cross-linking, reflecting retention of a thymocyte-like phenotype. Additionally, the percent of phosphorylated Erk^+ cells was higher in CB compared with APB $CD4^+$ T cells. Quantitative PCR showed elevated levels of microRNA (miR)-181a, which regulates calcium flux and Erk phosphorylation, in naive $CD4^+$ T cells from CB relative to APB, and overexpression of miR-181a in APB T cells significantly increased mean calcium flux. Transfection of an AP-1–dependent luciferase reporter gene demonstrated that CB T cells have significantly lower levels of AP-1 transcription and higher levels of Cbl-b induction following CD3 and CD28 stimulation compared with APB T cells, suggesting a tendency for CB

T cells to become anergic following activation. Thus, calcium signaling and AP-1 transcription are decoupled during the activation of CB $CD4^+$ T cells, providing a possible mechanism for the observed impairment in neonatal T cell immunity.

InterFeriNg with Encephalitis



Herpes simplex encephalitis (HSE), marked by enlargement of the lateral ventricles during HSV-1 infection, is a rapidly progressive disease with mortality rates of 30% in treated patients. Data suggest that IFN-γ is protective against the incidence of encephalitis; however, the events leading to the neuropathology and morbidity of HSE remain elusive. Conrady et al. (p. 2807) showed that type I IFN receptor α-chain–deficient ($CD118^{-/-}$) mice had a significantly increased HSV-1 viral burden in the cerebral cortex and lateral ventricular enlargement relative to wild-type (WT) mice. These $CD118^{-/-}$ mice had 100% mortality, whereas WT mice showed a delayed viral accumulation and 20% mortality. RT-PCR on CNS sections showed that HSV-1 entered the CNS through a neural route and selectively progressed to the ependymal cells. The authors' in vivo encephalitic model limited expression of HSV-1 Ag to the ependymal cells in the CNS of $CD118^{-/-}$ mice and demonstrated a loss of ciliated ependymal cells leading to reduced clearance of cerebrospinal fluid and a resulting expansion of the lateral ventricles. A therapeutic peptide, anti-secretory factor 16 (AF-16), used to reduce intracranial pressure without decreasing viral titer, significantly lowered mortality in HSV-infected WT mice but not $CD118^{-/-}$ mice. Organotypic brain slice cultures from $CD118^{-/-}$ mice infected with HSV-1 showed higher viral titers than WT brain slices, supporting a role for IFN-responsive cells. Depletion of microglia in these cultures further increased viral load, supporting a role for microglia in innate resistance to HSV-1. In conclusion, a functional type I IFN pathway in resident microglial cells is required for resistance to HSV-1–associated lateral ventricle enlargement.

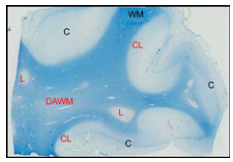
Tuberculosis as Transcript Regulator

The pathogenic *Mycobacterium tuberculosis* enhances its survival by altering the gene expression and IFN-γ response of host macrophages. Salamon et al. (p. 2747) examined how this pathogen affected the mRNA transcripts of STAT1 and IRF-1, IFN-γ responsive transcription factors, in *M. tuberculosis*–infected cells. The authors examined steps involved in the postinitiation processes of mRNA biogenesis to determine if these were responsible for changes in STAT1 and IRF-1 expression levels. These mRNA postinitiation steps can include 3′ end cleavage, 5′ end capping, elongation, polyadenylation, and splicing of message. Transcriptome analysis of infected cells treated with and without IFN-γ revealed that *M. tuberculosis* infection negatively regulated postinitiation mRNA biogenesis. Patient samples were then examined to determine the clinical relevance of this effect. The authors found that postinitiation mRNA biogenesis steps are suppressed in both latent and active tuberculosis disease, although to a differing extent. Thus, *M. tuberculosis* suppresses macrophage responses through its action on the postinitiation mRNA biogenesis events of key regulators of IFN-γ signaling.

Taking the STING out of *Listeria*

MPYS (also known as STING) is thought to be a critical participant in the host response to *Listeria monocytogenes*. Although MPYS has been shown to be an essential component of host defense against DNA virus infections, its in vivo role in defense against nonviral pathogens is unknown. Jin et al. (p. 2835) observed an increase in bacterial burden in the liver but not the spleen of *Listeria*-infected MPYS-deficient ($MPYS^{-/-}$) mice compared with wild-type (WT) mice. No differences were observed in serum IFN-γ, IL-1β, and TNF levels or in the number of B, T, or NK cells in the livers of $MPYS^{-/-}$ mice relative to WT mice. MPYS is predominantly expressed on $CD45^+$ liver cells, of which ~ 50% are $Ly6C^{hi}$ monocytes newly immigrated from the bone marrow during *Listeria* infection. Compared with WT mice, $MPYS^{-/-}$ mice displayed a significant reduction in the number of $Ly6C^{hi}$ monocytes in the liver and the bloodstream during *Listeria* infection. Diminished production of the CCR2 ligands, MCP-1 and MCP-3, which control emigration of $Ly6C^{hi}$ monocytes, led to their impaired emigration from the bone marrow to the liver in $MPYS^{-/-}$ mice. Adoptive transfer of WT $Ly6C^{hi}$ monocytes into *Listeria*-infected $MPYS^{-/-}$ mice increased the number of $Ly6C^{hi}$ monocytes recruited to the liver and significantly decreased the bacterial burden. Taken together, these data demonstrate a role for MPYS in the recruitment of $Ly6C^{hi}$ monocytes to the liver, which is essential for bacterial clearance during *Listeria* infection.

More Ways To Kill Brain Cells



Multiple sclerosis (MS) is an inflammatory disorder characterized by the infiltration of immune cells into the CNS and the destruction of oligodendrocytes and myelin membranes. Although myelin-specific $CD4^+$ T cells expressing CD56 are cytotoxic toward oligodendrocytes, a previous study showed that an anti-CD56 blocking Ab did not inhibit their cytotoxicity, suggesting the involvement of additional cytotoxic effector molecules. To identify these molecules, Zaguia et al. (p. 2510) analyzed myelin basic protein (MBP)-specific $CD4^+$ T cell lines and PHA-activated $CD4^+$ T cells for NK-associated markers. The majority of $CD56^+CD4^+$ T cells (85%) expressed NKG2C and had elevated levels of cytotoxic molecules, including FasL, granzyme B, and perforin. Treatment of oligodendrocytes with proinflammatory cytokines increased the expression of HLA-E, the cognate ligand of NKG2C, and blocking this interaction inhibited $CD4^+$ T cell–mediated killing of oligodendrocytes. To evaluate the physiological relevance, the authors examined the expression of NKG2C on PBMCs from MS patients and healthy donors by flow cytometry. Increased levels of NKG2C were seen on $CD4^+$ T cells from MS patients relative to healthy controls, and patient T cells also expressed higher levels of FasL, granzyme B, and perforin. Additionally, immune cells expressing NKG2C and oligodendrocytes expressing HLA-E were observed in situ in postmortem CNS tissue. Taken together, these data demonstrate a novel mechanism by which $CD4^+$ T cells contribute to tissue injury in MS.