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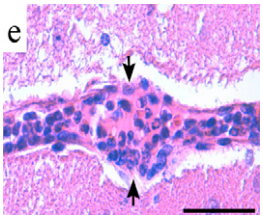
THE JOURNAL OF IMMUNOLOGY

In This Issue

Interfering with Cerebral Malaria



Cerebral malaria (CM) is a severe and generally fatal form of brain injury resulting from *Plasmodium falciparum* infection, and the immunological roles of $CD8^+$ T cells and type I IFN in the development of CM remain unclear. To evaluate the association of the IFN (α, β) receptor 1 (*IFNAR1*) gene with CM, Ball et al. (p. 5118) studied a cohort of Angolan children to identify *IFNAR1* variants, which led to the progression of CM from uncomplicated malaria. Two single nucleotide polymorphisms in the *IFNAR1* gene were associated with protection from CM. Using a mouse model of CM, experimental CM (ECM), in control or $Ifnar1^{-/-}$ mice, the authors demonstrated that loss of *Ifnar1* protected against disruption of the blood–brain barrier, a hallmark of ECM. This protection was not attributable to reduced parasite burden or impaired T cell migration to the brain. A decrease in *Tnf* and *Il10* mRNA expression in the brain of $Ifnar1^{-/-}$ mice relative to control mice suggested a reduction in the inflammatory response. Adoptive transfer experiments demonstrated that only control $CD8^+$ $Ifnar1^+$ splenocytes which were previously exposed to irradiated infected RBCs could restore ECM in $Ifnar1^{-/-}$ mice, suggesting that a deficiency in IFNAR1 signaling in $CD8^+$ T cells impairs the development of ECM. This report highlights the importance of IFNAR1 signaling in $CD8^+$ T cell–mediated protection against ECM.

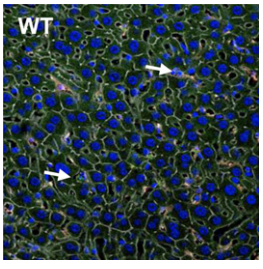
STINGing Mice, Not Men

A vascular disrupting agent (VDA), 5,6-dimethylxanthenone-4-acetic acid (DMXAA), has potent antitumor effects. In mice, this xanthenone derivative disrupts tumor blood supply, causes NK cell activation, and elicits cytokine release by tumor-associated macrophages. However, DMXAA has failed in clinical trials for cancer, and its mechanism of action has remained a bit of a mystery. In this issue, Conlon et al. (p. 5216) determined that DMXAA directly ligated STING to induce type I IFNs in mice, but not in humans. DMXAA ligation of murine STING induced signaling through TBK1 and IFN regulatory transcription factor 3 (IRF3). However, human STING did not ligate or cause signaling through DMXAA. Cyclic dinucleotides, bacterial second messengers known to bind to and signal through murine STING, were also found to have no effect on human STING. Thus, the authors have not only described how DMXAA signals through murine STING but have also shown the remarkable species specificity of this VDA, which may explain its failure in human clinical cancer trials.

Contagious Colitis

IL-22 is significantly upregulated in Crohn's disease and ulcerative colitis. It is known to regulate the production of antimicrobial molecules and play a role in protecting the gut epithelium during inflammation. Zenewicz et al. (p. 5306) hypothesized that the absence of IL-22 could lead to altered gut microbiota and play a significant role in the severity of colitis. Although IL-22-deficient ($IL\text{-}22^{-/-}$) mice do not demonstrate altered colon morphology in the absence of inflammation, they are more susceptible than wild-type (WT) mice to dextran sodium sulfate (DSS)–mediated colitis. When cohoused with $IL\text{-}22^{-/-}$ mice, DSS–treated WT mice developed decreased body mass and increased colitis severity relative to WT mice housed alone. Repetition of these experiments with a distinct colony of $IL\text{-}22^{-/-}$ mice led to similar results and suggested that the altered microbiota in $IL\text{-}22^{-/-}$ mice was transmissible. Pyrosequencing of the 16S rRNA gene V3 region showed that $IL\text{-}22^{-/-}$ mice had significantly different bacterial composition in their gut from WT mice housed alone. Interestingly, the gut microbiota of WT mice cohoused with $IL\text{-}22^{-/-}$ mice was indistinguishable from that of $IL\text{-}22^{-/-}$ mice, further demonstrating that this altered gut microbiota was transmissible. The antimicrobial peptides RegIIIβ and RegIIIγ, which are regulated by IL-22, were decreased in both $IL\text{-}22^{-/-}$ mice and WT mice cohoused with $IL\text{-}22^{-/-}$ mice, compared with WT mice housed alone. Thus, IL-22 regulates the composition of the colonic microbiota, leading to a transmissible susceptibility to inflammatory colitis.

The Bell Tolls for Sepsis Control



Sepsis results from an overwhelming host immune response to bacterial molecules such as LPS. These immune responses are mediated through pattern recognition receptors, including TLR4. Expressed on several cell types, including myeloid cells and hepatocytes, TLR4 contributes to the clearance of Gram-negative bacteria and the production of inflammatory responses. In this issue, Deng et al. (p. 5152) engineered mice with TLR4 deleted from myeloid cells (LysMTLR4KO) or hepatocytes (HCTLR4KO) to evaluate how TLR4 expression in specific cell types contributes to sepsis. Using the cecal ligation and puncture model (CLP) of sepsis, the authors found that myeloid TLR4 mediated phagocytosis and bacterial clearance. In the presence of antibiotics that cleared bacteria from the blood and peritoneum of septic animals, organ damage and cytokine production were driven by myeloid cells expressing TLR4. Hepatocyte expression of TLR4 promoted efficient LPS clearance; however, in the absence of TLR4, HCTLR4KO mice showed improved macrophage phagocytosis, better survival, and lower bacterial counts with

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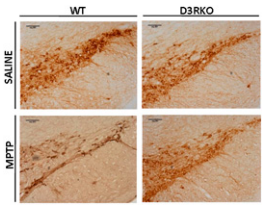
CLP compared with controls. Accordingly, in the presence of antibiotics during CLP, the ability of hepatocyte TLR4 to clear LPS was demonstrated to limit both septic inflammation and the resulting organ injury. These data establish that TLR4 functions vary depending on cell type expression and that future therapies for limiting sepsis can make use of these unique roles.

Protecting against Parkinson's



Parkinson's disease (PD) is characterized by the infiltration of inflammatory $CD4^+$ T cells into the substantia nigra, where they promote microglial activation and contribute to the degeneration of dopaminergic (DAnergic) neurons. Altered expression of the dopamine receptor D3 (D3R) is correlated with disease severity and is involved in IFN-γ production by $CD4^+$ T cells. To evaluate the role of D3R on $CD4^+$ T cells during neurodegeneration, González et al. (p. 5048) compared wild-type (WT) and D3R knockout (D3RKO) mice during 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD. Compared with MPTP-treated WT mice, MPTP-treated D3RKO mice were protected against a loss of DAnergic neurons and showed decreased microglial activation despite similar levels of $CD4^+$ T cell infiltration into the substantia nigra. Adoptive transfer experiments in RAG1 knockout mice, which are T and B cell deficient, demonstrated that D3R expression on $CD4^+$ T cells is essential for the destruction of DAnergic neurons. Furthermore, transfer of WT $CD4^+$ T cells into D3RKO mice led to MPTP-induced neural loss. T cell activation assays showed that stimulation of D3R increased IL-2 production, whereas the absence of D3R decreased IL-2 production and impaired T cell activation. Although D3R deficiency did not alter the capability of T cells to acquire a Th17 or regulatory T cell phenotype, loss of D3R significantly impaired T cell IFN-γ production and the acquisition of a Th1 phenotype. Taken together, the data demonstrate an essential role for D3R expression on $CD4^+$ T cells in the physiopathology of MPTP-induced PD.

Tim-3 Influences MS

Multiple sclerosis (MS) is believed to be caused by self-reactive myelin-specific $CD4^+$ and $CD8^+$ T cells that lead to demyelination and inflammation of the CNS. In experimental autoimmune encephalomyelitis (EAE), the murine model of MS, disease is also induced by effector myelin-specific T cells. Interestingly, signaling through T cell Ig mucin-3 (Tim-3), a cell surface molecule expressed on $CD4^+$ Th1 cells, can improve disease outcomes by eliminating pathogenic effector T cells. Tim-3 is also expressed on activated $CD8^+$ T cells, microglia, and dendritic cells, suggesting that it may play an important role in EAE. To determine a role for Tim-3, Lee and Goverman (p. 4991) manipulated Tim-3 signaling in EAE models with Th17, $CD4^+$ Th1, and $CD8^+$ T cells as antimyelin effector cells. When Tim-3 signaling was prevented in $CD4^+$ T cells, different patterns of inflammation in the CNS were found as a result of changes in the effects of Th1 and Th17 cells on disease; however, disease incidence was not different from that in wild-type mice. By contrast, a lack of Tim-3 signaling during $CD8^+$ T cell-mediated EAE caused increased disease. When Tim-3 signaling in dendritic cells and microglia, the innate immune cells involved in EAE, was disrupted, it had no effect on the outcome of disease. Thus, the role of Tim-3 in EAE is dependent on which effector T cells are responsible for disease, and Tim-3 particularly protects against disease that is mediated by $CD8^+$ T cells.

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