The Journal of Immunology

In This Issue

J Immunol 2012; 188:4713-4714; ;
doi: 10.4049/jimmunol.1290016
http://www.jimmunol.org/content/188/10/4713

Supplementary Material **http://www.jimmunol.org/content/suppl/2012/05/03/188.10.4713.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.

THE JOURNAL OF IMMUNOLOGY

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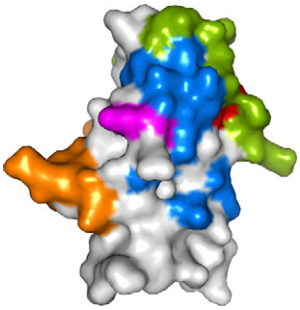
Anti-Dengue Discord



Dengue virus infection is increasingly common worldwide and can cause life-threatening dengue hemorrhagic fever. The identification of neutralizing Abs able to effectively interact with all four viral serotypes is an important goal of dengue vaccine development. Unfortunately, Abs that bind suboptimally to virions often enhance infection of FcR-bearing cells, urging caution in these studies. In this issue, Midgley et al. (p. 4971) characterize a mouse mAb, 2H12, that is specific for domain III of the dengue envelope protein (EDIII). 2H12 neutralized three of the four dengue serotypes (serotypes 1, 3, and 4) to a moderate degree and did not enhance infection of FcR-bearing monocytes despite suboptimal viral neutralization. The mAb had a similar binding avidity for recombinant EDIII proteins of all four serotypes, but demonstrated very different strengths of binding to whole virus particles. Analysis of crystal structures of 2H12 bound to EDIII proteins of dengue serotypes 1, 3, and 4 revealed very similar modes of Ab binding. The 2H12 binding epitope, which mainly consisted of the highly conserved AB loop of EDIII, was relatively inaccessible in mature dengue virions, suggesting a basis for the poorly neutralizing nature of this mAb. Temperature changes have been found to alter the conformation of the dengue virus, and a drop in temperature consistently reduced 2H12 binding. This structural insight into poorly neutralizing yet cross-reactive Abs has important implications for the development of a dengue vaccine.

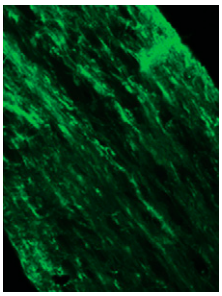
Innately Inducing IL-27

The complement activation product C5a is able to modulate both innate and adaptive immune activity by regulating the functions of a wide variety of cells. In this issue, Bosmann et al. (p. 5086) identify a specific role for C5a in the regulation of IL-27 production. IL-27 is produced by macrophages and dendritic cells during viral and bacterial infections and can act to keep T cell responses in check. Murine peritoneal macrophages released large quantities of the IL-27 subunit IL-27(p28) following stimulation with either the TLR4 agonist LPS or the TLR3 agonist polyinosinic-polycytidylic acid [poly (I:C)]. LPS-induced IL-27(p28) production was strongly inhibited by the addition of C5a via interactions with C5aR, but not C5L2. These results were upheld in vivo with the demonstration that IL-27(p28) levels were significantly higher in C5aR-deficient mice than wild-type mice after systemic LPS treatment. Interestingly, IL-27(p28) production was not affected by C5a following TLR3 stimulation, suggesting that C5a may have different effects on IL-27 production in bacterial versus viral infections. Mechanistic analysis revealed that C5a synergized with LPS, but not with poly (I:C), to activate the PI3K—Akt pathway, which inhibited IL-27(p28) expression. These data identify a pathway by which an innate factor can selectively regulate IL-27 expression and thereby influence the adaptive response to bacterial infection.

Nontraditional Th1

Over the past decade, it has become clear that $CD4^+$ T cell differentiation is much more complex than was suspected when Th1 and Th2 subsets were first identified. Varying cytokine conditions can induce the differentiation of subsets that include, but are not limited to, Th1, Th2, Th9, Th17, and regulatory T cells. Tofukuji et al. (p. 4846) have characterized a subtype of Th1 cells that developed when naive T cells were treated with IFN-γ in addition to the Th9-polarizing conditions using TGF-β and IL-4. Compared with Th9 conditions alone, IFN-γ addition upregulated IFN-γ production, inhibited IL-9 and IL-4 production, and induced both T-bet and eomesodermin (Eomes) expression in these cells. These IFN-γ/IL-4/TGF-β-induced Th1 cells stably expressed CD103 and demonstrated a distinct profile of cell surface marker and chemokine receptor expression relative to traditional Th1 cells. T-bet, but not Stat4, was required for the differentiation of $CD103^+$ Th1 cells and induced an open chromatin conformation at the *Ifnγ* and *Eomes* loci. Subsequently, Eomes activity was required for IFN-γ production in these cells. TGF-β activity suppressed Th2 differentiation and was important for the induction of Eomes and CD103. Although IL-4 signaling through Stat6 suppresses IL-12–mediated Th1 differentiation, it strongly enhanced the differentiation of $CD103^+$ Th1 cells and promoted Eomes, but not T-bet, expression. $CD103^+$ Th1 cells were observed in vivo among intestinal epithelial lymphocytes, but not in the spleen, and the presence of these cells was significantly decreased in mice lacking T-bet, Stat6, or IL-4. These data define an IL-12–independent pathway through which IFN-γ–producing Th cells can be generated.

Neuropathic Insight

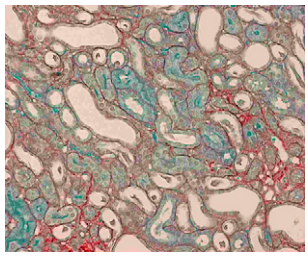


Chronic inflammatory demyelinating polyneuropathy (CIDP) has recently been associated with autoimmune polyendocrinopathy syndrome type 1 (APS1), which results from mutations in the autoimmune regulator (Aire) gene. The pathogenesis of CIDP is poorly understood; however, a strain of mice with hypomorphic Aire function ($NOD.Aire^{GW/+}$) has been found

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1290016

to spontaneously develop autoimmune peripheral neuropathy resembling CIDP. Su et al. (p. 4906) analyzed these mice, as well as patients with APS1, to further elucidate the mechanism(s) responsible for CIDP development. Infiltrating $CD4^+$ T cells were found in the sciatic nerves of NOD.$Aire^{GW/+}$ mice, and these cells tended to produce IFN-γ but neither IL-4 nor IL-17, indicating a Th1 effector response. Adoptive transfer experiments demonstrated that $CD4^+$ T cells from these mice were sufficient to transfer peripheral neuropathy to NOD.scid recipients. Myelin protein zero (P0) was identified as an autoantigen in NOD.$Aire^{GW/+}$ mice by characterizing autoantibody reactivity. Expression of P0 in NOD.$Aire^{GW/+}$ medullary thymic epithelial cells was significantly decreased relative to wild-type NOD mice, and NOD.$Aire^{GW/+}$ splenocytes demonstrated strong proliferation in response to P0 peptide, suggesting a defect in negative selection. Support for the clinical relevance of these data was provided by the detection of P0-specific autoantibodies in APS1 patients. The insight into CIDP pathogenesis provided by this study may aid future therapies for autoimmune peripheral neuropathy.

Hifs Have Their Day in the Kidney



Hypoxia is associated with renal fibrosis and chronic kidney disease progression. The transcription factors hypoxia-inducible factor (Hif)-1 and -2 are expressed in different cell types in the kidney and may have cell type-specific functions, as their activation can promote fibrosis but can also inhibit inflammation. To clarify the functions of Hifs in kidney inflammation, Kobayashi et al. (p. 5106) assessed the consequences of activating or deleting the Hif molecules. In a model of unilateral ureteral obstruction-induced kidney injury, global Hif activation suppressed inflammation, including macrophage infiltration, and reduced renal fibrosis relative to controls. Global deletion of the Hif molecules led to enhanced inflammation but, interestingly, did not appear to affect fibrosis. In this model, macrophage-specific Hif activation enhanced, and deletion impaired, macrophage infiltration into the obstructed kidney, but there was not an effect on fibrosis in either case. In macrophages, activating either Hif-1α or Hif-2α alone suggested that Hif-1α promoted macrophage polarization toward an M1 phenotype, whereas Hif-2α supported M2 polarization. Gene expression analysis of renal macrophages linked Hif activity to the suppression of inflammatory molecules, particularly the chemokine receptors CCR2 and CCR5. Similar alterations in gene expression were observed in chronically hypoxic kidneys, including downregulation of the CCR2 ligand CCL2 in proximal tubular epithelial cells. Hypoxia, leading to Hif activation, may thus be protective in chronic kidney disease.

Lyn-king DCs and NK Cells

The Lyn protein tyrosine kinase can positively or negatively regulate signal transduction by phosphorylating ITAMs or ITIMs, respectively. Although Lyn is important for B cell biology, its role in innate immunity is less clear. To address this question, Krebs et al. (p. 5094) investigated the involvement of Lyn in the in vivo response to LPS. Mice with a gain-of-function mutation in Lyn ($Lyn^{up/up}$ mice) were hyperresponsive to LPS, exhibiting significantly greater inflammation and morbidity than wild-type mice. LPS injection of $Lyn^{up/up}$ mice also induced the upregulation of proinflammatory cytokines, including IFN-γ production by NK cells, which was dependent on the presence of dendritic cells (DCs). In addition, both DCs and NK cells were required for the LPS-induced morbidity observed in $Lyn^{up/up}$ mice. Lyn activity in DCs, but not NK cells, was important for NK cell IFN-γ production. Following LPS stimulation, this Lyn activity also promoted the maturation of DCs and their upregulation of IL-12 and downregulation of IL-10. Mechanistically, Lyn inhibited LPS-induced DC signal transduction via the MAPK, PI3K, and NF-κB pathways and induced phosphorylation of SHIP-1 and SHP-1. SHIP-1 activation was particularly important for DC maturation and NK cell activation in response to LPS. This study reveals an important role for Lyn in DC:NK cell interactions following exposure to endotoxin.

Summaries written by Jennifer Hartt Meyers, Ph.D.