The Journal of Immunology

In This Issue

J Immunol 2012; 188:929-930; ;
doi: 10.4049/jimmunol.1190087
http://www.jimmunol.org/content/188/3/929

Supplementary Material http://www.jimmunol.org/content/suppl/2012/01/19/188.3.929.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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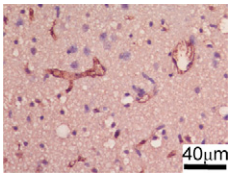
Abs Strike after Stroke



Ischemic stroke can lead to brain tissue injury through complement activation, but the involvement of self-reactive Abs that recognize epitopes specific to ischemic tissue in this process is not clear. Elvington et al. (p. 1460) observed that a novel mAb against phospholipids, as well as a previously characterized anti-annexin IV mAb (B4), contributed to complement-mediated injury in a model of murine cerebral ischemia and reperfusion injury (IRI). A phospholipid-specific IgM mAb (C2) derived from a mouse undergoing cerebral IRI was identified in a screen for neoepitopes specific to ischemic cells. Compared with wild-type (WT) mice, Ab-deficient *Rag1*$^{-/-}$ mice did not have any significant brain tissue injury or neurological damage following cerebral IRI. In contrast, treatment of *Rag1*$^{-/-}$ mice with mAbs C2 or B4 at the time of reperfusion resulted in damage associated with IRI as well as deposition of the C3 complement component similar to that observed in WT mice. Moreover, mAbs C2 and B4 bound to hypoxic, but not normoxic, endothelial cells. Treatment of WT or *Rag1*$^{-/-}$ mice with recombinant annexin IV prior to reperfusion with normal mouse sera significantly reduced cerebral IRI, suggesting that reactivity to a single epitope can drive complement-mediated damage. These results indicate that Abs specific to postischemic stroke neoepitopes are key mediators of cerebral IRI.

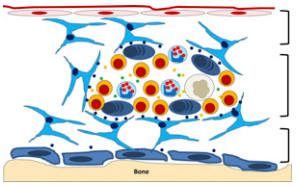
Early IL-10 Mollifies Lyme

Several mouse models have been tested in attempts to recapitulate the symptoms of Lyme disease-associated arthritis in humans infected with *Borrelia burgdorferi*, but an ideal model remains elusive. Sonderegger et al. (p. 1381) examined the effect of dysregulated cytokine production on arthritis in the joints of *B. burgdorferi*-infected C57BL/6 IL-10$^{-/-}$ (B6 IL-10$^{-/-}$) mice. Previous studies suggested that IL-10 produced in the joints of *B. burgdorferi*-infected mice reduced arthritis severity possibly by suppressing IFN-γ production. In this study, *B. burgdorferi*-infected B6 IL-10$^{-/-}$ mice, which develop severe arthritis, were treated with an IFN-γ–neutralizing Ab. These treated mice had reduced arthritis symptoms and lower levels of IFN-inducible gene transcripts in infected joints relative to control Ab-treated infected mice. Multiple cell types infiltrated arthritic joints in infected B6 IL-10$^{-/-}$ mice, although NK and CD4^{+} T cells were the primary IFN-γ–producing cells. These observations suggest that the absence of IL-10 results in unmodulated inflammatory gene expression, cell infiltration, and inflammatory cytokine production in the joints of *B. burgdorferi*-infected IL-10$^{-/-}$ mice. Thus, B6 IL-10$^{-/-}$ mice may serve as a powerful model for understanding the immunological causes of Lyme disease-associated arthritis.

SLAMming Lupus

Members of the signaling lymphocyte activation molecule (SLAM) receptor family have recently been characterized as costimulatory molecules that help promote T cell activation. Single nucleotide polymorphisms in the gene locus that includes the *SLAM* cluster have been linked to systemic lupus erythematosus (SLE). In this issue, Chatterjee et al. (p. 1206) examined the expression of SLAM receptors on SLE T cells and how they influenced IL-17 production. SLAMF3 and SLAMF6 were both significantly upregulated on CD4^{+} T cells from SLE patients relative to healthy controls. IL-17 production increased significantly in Th17-polarized SLE CD4^{+} T cells upon costimulation through CD3 and SLAMF3 or SLAMF6, and IL-17 production correlated with disease severity in the donors of SLE CD4^{+} T cells. Costimulation of naive or memory CD4^{+} T cells with anti-CD3 and either anti-SLAMF3 or anti-SLAMF6 resulted in prolonged and greater production of IL-17, compared with anti-CD28 plus anti-CD3 costimulation. In addition, the adaptor molecule SLAM-associated protein was required for IL-17 production following costimulation via either SLAM receptor. Thus, SLAMF3 and SLAMF6 may be key costimulatory molecules that influence IL-17 production in SLE and may contribute to other autoimmune disorders in a similar manner.

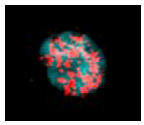
Plasma Cell Safe Haven



Plasma cells (PCs) in the bone marrow (BM) can survive and produce Abs for long periods, but the complex network of cellular and molecular elements that support their survival is not well understood. Belnoue et al. (p. 1283) adoptively transferred Blimp-1$^{GFP/+}$ PCs into wild-type (WT) and various knockout mice to assess which factors are essential to BM survival. Blimp-1$^{GFP/+}$ PCs colocalized most frequently with Ly-6C^{+} neutrophils, Ly-6C^{+} monocytes, MBP^{+} eosinophils, and megakaryocytes, which were considered to serve as "nursery" cells in the BM of WT mice. The TNF-like ligand APRIL was essential to survival of Blimp-1$^{GFP/+}$ PCs, and monocytes were the primary source of APRIL in the BM. However, APRIL was not required for colocalization of PCs with "nursery" cells. Instead, expression levels of the homing and adhesion molecules CXCR4, VLA-4, LFA-1, and CD93 by PCs, monocytes, eosinophils, and megakaryocytes correlated directly with colocalization and retention of PCs in the BM. Thus, homing and adhesion

molecule expression patterns appear to contribute to determining the BM niche critical for PC survival.

Clamping down with cAMP



Both human and mouse regulatory T cells (Tregs) have suppressive functions, but the common mechanisms mediating suppression are not well understood. Klein et al. (p. 1091) found that the cAMP pathway in human Tregs is pivotal to regulating suppression. In vitro stimulation of $CD4^+CD25^+Foxp3^+$ Tregs caused a rapid and sustained increase in cAMP levels, whereas cAMP levels changed very little upon stimulation of $CD4^+CD25^-$ conventional T cells. Treatment of human Tregs with an adenylate cyclase inhibitor to repress cAMP production significantly reduced the suppressive actions of Tregs relative to untreated Tregs. Human Tregs ectopically expressing a phosphodiesterase that degrades cAMP also showed significantly lower suppressive activity than did untreated Tregs. cAMP repression by adenylate cyclase inhibition reversed the anergic state of Tregs and was accompanied by nuclear translocation of NFATc1. In addition, human Tregs with repressed cAMP production showed significantly reduced suppressive function upon transfer into humanized mice. These findings indicate that cAMP generation in activated human Tregs is a key component of suppressive activity.

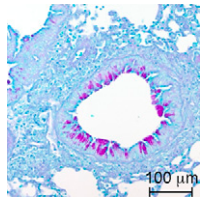
Receptor Mutation Matters

FcγRIIc is an activating NK cell receptor encoded by the *FCGR2C* gene, which has been characterized as a product of an unequal crossover between the gene that encodes the activating FcγRIIa (*FCGR2A*) and the gene that encodes the inhibitory FcγRIIb (*FCGR2B*). Previous work identified a single nucleotide polymorphism in FcγRIIc that results in either expression of the gene (*FCGR2C*-ORF) or no expression owing to the presence of a stop codon (*FCGR2C*-Stop). van der Heijden et al. (p. 1318) characterized two other variations of FcγRIIb/c expression that influence immune responses. FcγRIIc expression was not detected in NK cells from several individuals genotyped as *FCGR2C*-ORF, and further analysis revealed a novel point mutation that introduced a stop codon. Conversely, some individuals with the *FCGR2C*-Stop genotype had detectable expression of FcγRIIb, which was expected to be absent. Sequence analysis exposed a previously unidentified deletion within the *FCGR* locus between *FCGR2C* and *FCGR3B*. This deletion most likely disrupted an inhibitory element and allowed expression of FcγRIIb. Ab-dependent cellular cytotoxicity studies confirmed that FcγRIIb on NK cells from individuals with the "nonclassical" *FCGR2C*-Stop genotype was functional and could inhibit FcγRIIIa-mediated cell killing. Together these data indicate that FcγR expression in NK cells is more variable than previously appreciated.

Plasmodium Protection

Much of the immunopathology associated with malaria infection is due to the proinflammatory cytokine response. IL-10 has been identified as a key anti-inflammatory molecule that mutes proinflammatory responses in mice with a blood stage infection of the malaria parasite *Plasmodium chabaudi chabaudi* AS. Previous studies have shown that $IL10^{-/-}$ mice develop more severe pathology relative to wild-type mice infected with *P. chabaudi*. Freitas do Rosário et al. (p. 1178) now show that IFN-γ^+ Th1 cells are the major IL-10–producing cells during infection. The severity of *P. chabaudi* infection in mice with a T cell-specific deletion of IL-10 was similar to that observed in $IL10^{-/-}$ mice. $Foxp3^+$ Tregs also produced IL-10, but further experiments confirmed that IL-10 from $Foxp3^-$ IFN-γ^+ Th1 cells was essential for controlling inflammation during the acute blood stage infection. In addition, optimal amplification of IL-10 responses required intact IL-27 signaling. These findings provide insight into the critical source of IL-10 during blood stage malaria infection, and this knowledge may be useful to improve the development of immunomodulatory therapies and vaccines for protection against severe malaria immunopathology.

Under the Influence of IL-33



IL-33 has been identified as a cytokine that promotes Th2 responses in allergic airways, but the mechanisms contributing to these responses are not clearly defined. Bartemes et al. (p. 1503) characterized a unique lymphoid cell type that responds to IL-33 and promotes allergic airway inflammation. Intranasal administration of IL-33 to wild-type or $Rag1^{-/-}$ mice induced a significant increase in airway inflammation, eosinophil infiltration, and secretion of the Th2-type cytokines IL-5 and IL-13 relative to untreated mice, even in the absence of adaptive immunity. Further scrutiny revealed a novel lymphoid-like cell type in the mouse lung that produced abundant amounts of IL-5 and IL-13 in response to IL-33. This lymphoid-like cell lacked expression of lineage-specific markers but expressed the IL-33 receptor ST2, as well as CD25, CD44, IL-7Rα, Thy1.2, ICOS, and Sca-1 ($Lin^-CD25^+CD44^{hi}$ lymphoid cells). IL-7R signaling was required for development of $Lin^-CD25^+CD44^{hi}$ lymphoid cells in lungs. Airway exposure to the fungus *Alternaria alternata* induced Th2-type cytokine responses and airway inflammation via lung-resident $Lin^-CD25^+CD44^{hi}$ lymphoid cells, but these Th2-type responses were significantly diminished in ST2-deficient mice. These results reveal that IL-33–mediated allergic airway responses can be attributed to $Lin^-CD25^+CD44^{hi}$ lymphoid cells, thus providing a new perspective on how Th2-like responses develop in the upper respiratory system.

Summaries written by Christiana N. Fogg, Ph.D.