The Journal of Immunology

IN THIS ISSUE

J Immunol 2008; 181:5811-5812; ;
doi: 10.4049/jimmunol.181.9.5811
http://www.jimmunol.org/content/181/9/5811

Supplementary Material **http://www.jimmunol.org/content/suppl/2008/10/17/181.9.5811.DC1**

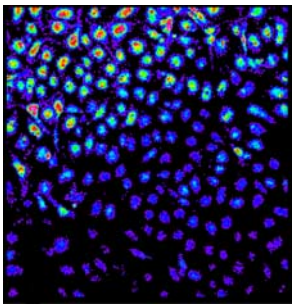
The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

THE JOURNAL OF IMMUNOLOGY

In This Issue

Keeping HIV Out of the Brain



Infection with HIV-1 leads to disruption of the blood-brain barrier (BBB) and infiltration of HIV-infected macrophages into the CNS. The HIV-1 envelope protein gp120 has been shown to damage the BBB by reducing tight junction (TJ) protein expression and increasing brain endothelial cell permeability through mechanisms that could involve chemokine receptor signaling and/or substance P (SP) activity. Previous studies showing that endocannabinoids can be neuroprotective led Lu et al. (p. 6406) to analyze whether cannabinoid agonists could protect against gp120-induced BBB disruption. Cocultures of human brain microvascular endothelial cells (HBMEC) and astrocytes were used as an in vitro BBB model. As predicted, HIV-1 gp120 induced SP expression, monocyte transmigration, and down-regulation of TJ proteins in this system. The cannabinoid receptor CB1 was expressed in these HBMEC, and addition of cannabinoid agonists inhibited gp120-mediated TJ protein down-regulation, thereby preserving TJ integrity. Cannabinoid agonists also inhibited gp120-induced SP secretion, monocyte transmigration, and HBMEC permeability and led to an association between CB1 and the TJ protein ZO-1. Finally, either an SP inhibitor or a cannabinoid agonist could inhibit BBB permeability alterations in a mouse model. These data suggest that cannabinoids may prevent the disruption of BBB integrity induced by HIV-1 envelope proteins and lead to the possibility that cannabinoids might protect against HIV-associated dementia.

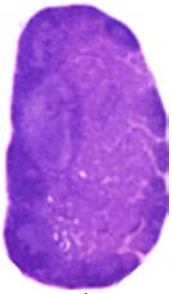
Keeping Stem Cells Quiet

Considering the almost limitless potential of stem cell function and the dangers of dysfunction, learning how hematopoietic stem cells (HSCs) replicate is of great interest. Yang et al. (p. 5885) used mice deficient in the transcription factor E47 to investigate how HSCs control their own replication and quiescence. The authors found that E47$^{-/-}$ mice had multipotent Lineage^{-}Sca^{high}cKit^{+} (LSK) cells that hyperproliferated due to a loss of cell cycle control. E47$^{-/-}$ animals treated with the mitotoxin 5-fluorouracil experienced 100% mortality within 15 days compared with 90% survival of wild-type mice undergoing the same treatment. Because the total LSK population contains both self-renewing HSCs and multipotential progenitors (MPPs) with very limited self-renewal, each of these groups was examined. E47$^{-/-}$ animals contained normal numbers of HSCs but a 60% reduction in the non-renewing MPPs, and those cells remaining had defects in up-regulating the cytokine tyrosine kinase receptor *flt3/flk2*, initiating V(D)J recombination, and cell cycle progression. The cell cycle inhibitor p21 was shown to be an E47 target gene in E47$^{-/-}$ LSKs, explaining the 50% decrease in p21 expression. LSK loss of cell cycle control explains the decrease in MPP population in E47$^{-/-}$ mice, as this cell group lacks self-renewal capabilities. Taken together, the data demonstrate the role E47 plays in controlling the development and function of hematopoietic progenitors.

Th17 Cells' Fear of Commitment

Much recent attention has focused on the differentiation and function of Th17 cells. Although IL-23 does not induce Th17 differentiation, this cytokine is required for the in vivo function of Th17 cells and has been proposed to enhance their proliferation and/or survival. Stritesky et al. (p. 5948) used a novel cytokine capture assay to address this idea and determine whether IL-23 mediates commitment to the Th17 lineage. IL-23 maintained the IL-17-secreting phenotype in long-term cultures but did not affect Th17 proliferation or survival. IL-1β synergized with IL-23 to maintain IL-17 secretion but did not do so by increasing IL-23R expression or by affecting IL-23 signaling. Preliminary experiments suggested that the addition of IL-1β might alter the responsiveness of the *Il17* locus through an as yet unidentified mechanism. Interestingly, when Th17 cells stimulated long term with IL-23 were switched to culture conditions promoting Th1 or Th2 differentiation, they were able to secrete IFN-γ or IL-4, respectively. In support of this phenotypic flexibility, signaling pathways active in Th1 and Th2 differentiation remained functional in Th17 cells. These data provide insights into the involvement of IL-23 in Th17 biology and suggest that the Th17 lineage, unlike Th1 and Th2 cells, may be transient and unstable.

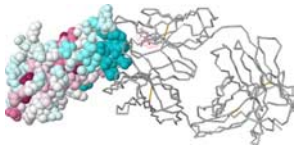
Directing an Autoimmune Dance



Recognition of B cell involvement in autoimmunity has been relatively recent. The transcription factor growth factor-independent-1 (Gfi-1) is a zinc finger protein that represses transcription and controls both immune and neuronal cell lineages. Rathinam et al. (p. 6222) have demonstrated how Gfi-1$^{-/-}$ mice develop autoimmunity in a B cell-dependent manner. The authors found that normal mice transplanted with Gfi-1$^{-/-}$ bone marrow developed ataxia and a dramatic "rotary dancing" phenotype that can be viewed in their supplemental material. Inflammatory infiltrates consisting of B cells, C9 deposition, glial fibrillary acidic protein (GFAP) expression, and large Ig deposits were found in the meninges of Gfi-1$^{-/-}$ mice. Examination of B cell populations within Gfi-1$^{-/-}$ mice compared with normal animals showed a

decrease in bone marrow B cells and an increase in the size of lymph nodes and spleens. The number of terminally differentiated CD138$^+$ B cells was also increased in Gfi-1$^{-/-}$ mice, and Gfi-1 was confirmed to be activated in CD138$^+$ B cells, most likely as a regulator of cell cycle control and differentiation. This was supported by the hyperproliferation and increased phosphorylation of Lyn and Erk observed in Gfi-1$^{-/-}$ peripheral B cells and by the identification of *Blimp-1* and *XBP-1* as downstream target genes of Gfi-1. Thus, the authors identify Gfi-1 as a "master regulator" in controlling autoimmunity.

CDR Redefined!



Using structural alignment analysis, Ofran et al. (p. 6230) have redefined what a CDR means, both by what the structure really consists of and how the term is defined. By painstakingly sorting through all available Ab-Ag complexes in the Protein Data Bank (PDB) they identified 140 structures that became candidates of their automated analysis. This analysis consisted of the following: 1) structurally aligning the candidate Abs; 2) marking the positions of Ag:Ab contact; and 3) identifying those aligned residues that contacted the Ag. They defined the CDR as the specific "residues on the antigenic interface" and identified that the epitopes bound by CDRs were in a linear rather than helical configuration. The four amino acids found to account for the majority of CDR sequences were tyrosine, serine, asparagine, and tryptophan, and the presence of some amino acids appeared to be entirely excluded from this region. Thus, this new refinement of the CDR sets the groundwork for identifying epitopes recognized by B cells, a process with obviously wide-ranging potential.

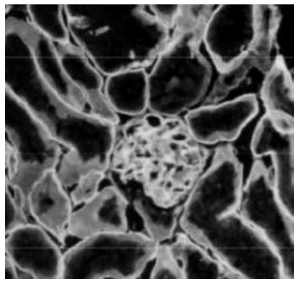
Ly49H in Host Pathogenesis

The NK cell activating receptor, Ly49H, is coded by *Cmv1* and was originally identified as a resistance locus to murine cytomegalovirus (MCMV). Ly49H is known to specifically recognize the m157 viral protein that is expressed at the surface of MCMV-infected cells. To test the role that Ly49H played in MCMV pathogenesis, Fodil-Cornu et al. (p. 6394) generated Ly49H-deficient mice from the normally resistant C57BL/6 background. In MCMV-infected mice the results were dramatic, with 100-fold higher viral levels in the spleens of Ly49H$^{-/-}$ mice and enhanced production of IFNα/β, IFN-γ, and IL-12 at 36 h after infection compared with wild type. Phenotypic analysis of the spleen indicated a massive loss of CD8$^+$ T cells 72 h after infection in MCMV-infected Ly49H$^{-/-}$ mice. As resistance to *Leishmania major* and Ectromelia virus (ECTV) infections have previously been mapped to the NK gene complex, the responses of Ly49H$^{-/-}$ mice to these pathogens were also investigated. Loss of Ly49H showed no effect on *L. major* infection, but mice lacking Ly49H were additionally resistant to ECTV, strongly suggesting a yet to be identified ligand for Ly49H on ECTV-infected cells. Thus, these results verify the essential role of Ly49H in protecting the mouse from MCMV, as well as providing intriguing clues to novel innate immune mechanisms against pathogens.

IL-17, Not Just for T Cells Anymore

In asthma, the cellular origin of IL-17 has not yet been identified despite the important role it plays in disease pathogenesis. Song et al. (p. 6117) have now determined that alveolar macrophages (AMs) and not T lymphocytes or NKT cells are the source of this proinflammatory cytokine. In a mouse model of asthma consisting of OVA challenge, resident AMs increased their expression of IL-17. There was no increase in the IL-17 expression of the interstitial macrophage population, and the increase in IL-17$^+$ AMs was not due to chemotaxis. Instead, AMs could be induced to express IL-17 by supernatants derived from mast cells that had been serially stimulated with anti-OVA IgE and OVA. The role of IL-17$^+$ AMs in producing inflammatory pathogenesis was confirmed by depletion of AMs in the asthma model, as well as by the use of a neutralizing Ab against IL-17. Both of these treatments reduced the number of inflammatory mediators and cells in the bronchial alveolar lavage fluid. As IL-10 is a Th2 cytokine known to suppress the production of IL-17, an examination of patients with asthma was undertaken to determine their relative levels of these cytokines. Not surprisingly, the bronchoalveolar lavage fluid of these individuals showed increased levels of IL-17 and decreased levels of IL-10. Taken together, the data identify AMs as the predominant producers of IL-17 in asthma subject to stimulation by mast cell products.

Goodpasture's Syndrome and Central Tolerance



Patients with Goodpasture's syndrome (GPS) develop autoantibodies to the noncollagenous domain 1 (NC1) of the α3 chain of type IV collagen (α3(IV)NC1) found in basement membranes. The deposition of autoantibodies on the basement membranes causes the patients to display crescentic glomerulonephritis, kidney failure, and severe alveolitis as symptoms. One current hypothesis credits GPS to a loss of peripheral tolerance. However, Zhang et al. (p. 6092) have developed a new murine model that challenges this and attributes the development of GPS to a loss of central tolerance. By developing a mouse transgenic for the Ig that recognizes α3(IV)NC1, they created a model of GPS. α3(IV)NC1 mice had fewer splenic B cells compared with normal littermates, had tolerant collagen-reactive cells, and showed editing of the L chain. α3(IV)NC1 mice were then crossed with Rag-deficient mice, and the resulting phenotype was one of central B cell deletion. The development of B cells reactive to α3(IV)NC1 was halted in the bone marrow because receptor editing could not occur, as this process is dependent on the missing recombinase. Thus, the authors have developed a new model for the investigation of GPS and are leading the way by challenging the hypothesis that predicts how this autoimmune syndrome develops.

Summaries written by Kira R. Gantt, Ph.D.