In This Issue

J Immunol 2012; 189:2687-2688; ;
doi: 10.4049/jimmunol.1290053
http://www.jimmunol.org/content/189/6/2687

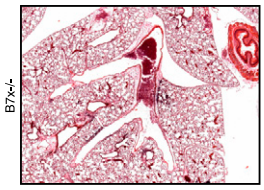
The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

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

THE JOURNAL OF IMMUNOLOGY

In This Issue

B7x Befriends Bacteria



The B7 family member B7x has not been extensively studied but is proposed to deliver coinhibitory signals to T cells in the periphery. Because mRNA encoding B7x is highly expressed in the lung, Hofmeyer et al. (p. 3054) chose a mouse model of pulmonary *Streptococcus pneumoniae* infection to investigate the function of B7x. Expression of the B7x protein was observed on the bronchial epithelium and in pancreatic β cells, but not in the spleen or lymph nodes. Compared with wild-type mice, B7x$^{-/-}$ mice exhibited significantly improved survival and bacterial clearance following pulmonary infection with *S. pneumoniae*. In contrast, there was no survival advantage for mice deficient in the related molecule B7-H3 during pulmonary infection, nor for the B7x$^{-/-}$ mice when infected systemically with *S. pneumoniae*. During pulmonary infection, B7x$^{-/-}$ mice had reduced lung inflammation relative to wild-type mice and produced lower levels of proinflammatory cytokines and chemokines. Control of infection in the B7x$^{-/-}$ mice was not linked to enhancement of natural Ab production or phagocytosis, but was associated with an increase in activated CD4^{+} and CD8^{+} T cells in the lungs compared with wild-type mice. B7x$^{-/-}$Rag1$^{-/-}$ mice, which lack T cells, were as susceptible to *S. pneumoniae* infection as wild-type mice, supporting the idea that the increase in activated T cells was responsible for protection in B7x$^{-/-}$ mice. These data suggest that B7x negatively regulates pulmonary T cell responses and may impair antibacterial immunity.

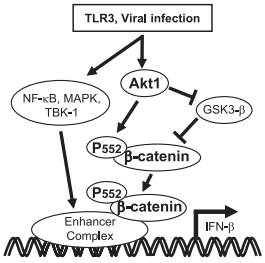
Transcriptional Trouble

HIV-1 preferentially replicates in activated CD4^{+} T cells that produce Th2 cytokines, but the mechanism driving this preference is not understood. Zhang et al. (p. 2746) hypothesized that Th2-specific transcription factors such as c-maf might drive HIV-1 replication. Single-cell level analysis of human CD4^{+} T cells in vitro confirmed that IL-4–producing cells preferentially promoted HIV-1 replication and long terminal repeat (LTR)-directed transcription. This preferential replication was not related to chemokine receptor expression, viral tropism, or differences in apoptosis between Th1 and Th2 cells. Instead, the transcription factor c-maf was found to specifically bind to the HIV-1 proximal LTR near the NF-κB and NFAT binding sites. These sites of the HIV-1 LTR were preferentially bound by NFAT2 and NF-κB p65, but not NFAT1 or NF-κB p50. Together with c-maf, NFAT2 and NF-κB p65 cooperatively enhanced transcription at both the IL-4 promoter and the HIV-1 LTR. Small interfering RNA-mediated depletion of c-maf impaired the transcription of both IL-4 and HIV-1 LTR. These results were upheld in primary CD4^{+} T cells by the observation that the three transcription factors cooperatively augmented HIV-1 expression. These data enhance our understanding of the mechanisms responsible for HIV-1 disease progression and present c-maf as a potential target for therapies aimed at slowing viral replication.

Semaphorin Supports Virus

Semaphorins are a large family of proteins active in both the immune and nervous systems. The broadly expressed semaphorin Sema7A is involved in nervous system development and regulates the activity of monocytes and T cells. Although DNA viruses encode immunomodulatory semaphorins similar to Sema7A, no such homologs have been identified in RNA viruses. To determine whether RNA viruses instead utilize host semaphorins, Sultana et al. (p. 3150) assessed whether Sema7A was involved in a mouse model of infection with the potentially fatal neurotropic flavirvirus West Nile virus (WNV). Expression of Sema7A was upregulated in both blood and brain following WNV infection. Relative to controls, Sema7A deficiency or Ab-mediated inhibition significantly increased survival following WNV infection. Improved survival was associated with reduced viral loads and neuroinvasion, decreased inflammatory cytokine production, and reductions in blood-brain barrier permeability. WNV infection of murine cortical neurons or human macrophages was reduced in cells in which Sema7A was absent or blocked, compared with control cells, indicating a role for Sema7A in both immune and nervous system infection. The mechanism of Sema7A-mediated promotion of WNV infection involved upregulation of TGF-β and the transcription factor Smad6. This identification of an important role for Sema7A in WNV pathogenesis suggests further investigation of this molecule as a potential therapeutic target.

Akt-ivating IFN

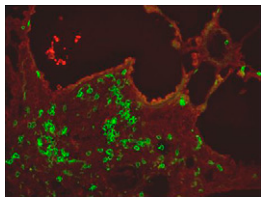


Expression of IFN-β, an important antiviral cytokine that influences numerous aspects of immunity, is tightly regulated by multiple signaling pathways and transcription factors. The signaling molecules GSK3-β, Akt, and β-catenin have been shown to participate in this regulation, but the specific mechanisms involved are not yet clear. Gantner et al. (p. 3104) have identified an important role for one of the isoforms of Akt, Akt1, in IFN-β transcription following TLR3 activation. In response to the TLR3 ligand polyinosinic:polycytidylic acid, Akt1 deficiency resulted in a reduction in IFN-β production and decreased transcription of IFN-β-stimulated

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1290053

genes, compared with cells from wild-type mice. Akt1$^{-/-}$ mice were also less able to control infection with herpes simplex virus 1 than were wild-type mice. Akt1 played a non-redundant role in Akt signaling following TLR3 stimulation but was not involved in signaling involving IRF3, NF-κB, or MAPK. Instead, Akt1 acted by phosphorylating the transcriptional activator β-catenin on Ser^{552} and was necessary and sufficient for this phosphorylation, which was required for optimal IFN-β transcription. These data reveal a mechanism by which Akt1 contributes to the proper regulation of IFN-β expression, which is critical to antiviral defense.

Regulating Recall Responses



During chronic infections, regulatory T cells (Tregs) can protect the host by preventing excessive immunopathology but can also support pathogen persistence. To address the behavior of pathogen-specific Tregs during acute viral infections, Sanchez et al. (p. 2805) investigated their actions in two different murine infections. Influenza hemagglutinin (HA)-specific Tregs were activated and expanded following acute infection with vaccinia virus expressing HA. Upon resolution of infection, the Ag-specific Treg population contracted and formed a stable memory population with an effector memory phenotype. These memory Tregs rapidly expanded following secondary viral challenge and were able to suppress the recall response of non-Treg CD4$^+$ T cells during the secondary infection. Tregs behaved similarly in the influenza model of acute infection. In both models, memory Tregs acted to reduce immunopathology during the secondary response. These memory Tregs secreted high levels of IL-10, which was required for their suppressive actions. Taken together, these data demonstrate the establishment of pathogen-specific memory Tregs following acute infection and suggest that these cells serve to prevent the tissue damage that can occur in the presence of a strong recall response.

Repertoire Revelations

The benefits of generating a diverse Ab repertoire must be balanced with the risks of autoreactivity during B cell development. To better understand the development of the germline Ig repertoire, Larimore et al. (p. 3221) used Illumina deep sequencing to analyze both productive and nonproductive IgH rearrangements in human naive peripheral B cells. From each of four healthy individuals, they collected an average of 1.76 million IgH CDR3-containing sequences. Comparison of out-of-frame rearrangements carried in naive B cells, which were not subject to selection, with the functional IgH sequences that survived selection allowed the authors to draw several conclusions regarding repertoire development. It was calculated that at least 69% of productive IgH rearrangements in pro-B cells are selected against during development, and that CDR3 regions are more likely to be selected against if they are longer, contain tandem D gene segments, or contain hydrophobic D segments. However, IgH sequences containing long CDR3 regions and/or tandem D genes were observed in the mature repertoire, suggesting that this selective preference is not absolute. Selection bias was also observed in the usage of D gene segments and their reading frames. All of these results were consistent among the four individuals analyzed. The potential of this data for use in rational vaccine design was demonstrated by the identification of candidate IgH precursors for the anti-HIV broadly neutralizing Ab 4E10. Collectively, the data generated in this study provide a powerful means by which to assess the IgH repertoire.