The Journal of Immunology

IN THIS ISSUE

J Immunol 2009; 183:4829-4830; ;
doi: 10.4049/jimmunol.0990084
http://www.jimmunol.org/content/183/8/4829

Supplementary Material **http://www.jimmunol.org/content/suppl/2009/10/01/183.8.4829.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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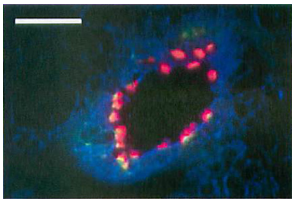
Promiscuous Genes Out of Bounds



Studies of the thymic architecture, which is comprised largely of pharyngeal endoderm (PE)-derived thymic epithelial cells (TEs), have been guided by certain assumptions about gene expression. For example, expression of the transcription factor Forkhead box N1 (FoxN1) is believed to be TE-restricted and absent in other PE-derived epithelial cells. Likewise, the otherwise organ-specific tissue restricted Ags (TRAs), such as parathyroid hormone, calcitonin, and thyroglobin, are thought to be unique markers for medullary thymic epithelial cells (MTECs). MTECs also express the Aire (AutoImmune REgulator) gene, which plays a role in the expression of a diverse range of self-Ags, including TRAs, and their subsequent role in the selection of T cells. Recent questions about thymic gene expression patterns led Dooley et al. (p. 5042) to assess the expression of TRAs and FoxN1 in the thymus and surrounding tissues. Comparison of their expression patterns with that of Aire and other markers, such as the keratin and claudin proteins, showed that TRAs and FoxN1 are expressed by diverse TE cell subsets and by extra-thymic epithelial tissue as well. Furthermore, TRA expression was, at least in part, Aire-independent, as TRA and Aire expression patterns did not always overlap. Together, these data indicate that TRA gene expression is more promiscuous than previously thought, as TRAs had multiple sources of cellular expression in—and out—of the murine thymus.

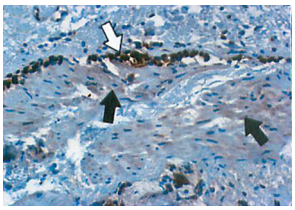
Sticking around with α-Glucan

The cell wall of the *Mycobacterium tuberculosis* (*MT*) bacillus is surrounded by a protective capsule comprised mainly of proteins and polysaccharides. The capsule constituents are first to contact host cells, but little is known about their role in host-pathogen interactions. To identify host receptors for the dominant capsular polysaccharide α-glucan, Geurtsen et al. (p. 5221) screened primary immune cells for their ability to bind *MT* α-glucan. The strongest interaction occurred between α-glucan and monocyte-derived dendritic cells (DCs). The screening of a panel of DC lectin receptors known to interact with mycobacteria revealed exclusive recognition by the C-type lectin DC-SIGN (DC-specific ICAM-3 grabbing non-integrin). The specificity of α-glucan for DC-SIGN was confirmed in vitro by its binding to a DC-SIGN-null cell line transfected with native DC-SIGN, but not to nontransfected cells. Furthermore, a DC-SIGN-specific blocking Ab abrogated binding of α-glucan to DCs. Finally, in contrast to a previous report that a fungal α-glucan stimulated TLR2, *MT*-expressed α-glucan is not a ligand for TLR2. These findings identify DC-SIGN, which is expressed by both macrophages and DCs, as a novel receptor for α-glucan.

Getting Loopy with Lef1

In chondrocytes, the cytokine IL-1β induces the expression of lymphoid enhancer-binding factor-1 (Lef1). In turn, Lef1 induces transcription of the COX2 and MMP13 genes. Yun et al. (p. 5129) sought to explain how Lef1 binding to the 3′ regions of these genes might regulate their transcription. In mouse chondrocytes, IL-1β stimulation also induced the transcription factors RelA and c-Jun to bind the 5′ ends of the COX2 and MMP13 genes, respectively. In nuclear extracts, Lef1 and its binding partner β-catenin physically associated with RelA and c-Jun. Coexpressed Lef1/β-catenin synergized with RelA and c-Jun, which enhanced IL-1β-dependent COX2 and MMP13 mRNA expression, respectively, as compared with either transcription factors or Lef1/β-catenin alone. The authors tested whether 3′ bound Lef1 mediated physical interactions with the 5′ ends of COX2 or MMP13 in response to IL-1β stimulation. Lef1 interacted with the RelA- and c-Jun-binding 5′ regions of the genomic COX2 and MMP13 loci, respectively, indicating the formation of gene loops. The siRNA-mediated knockdown of Lef1 decreased COX2 and MMP13 expression and diminished the efficiency of IL-β-dependent gene looping, while Lef1 overexpression had the opposite effects. These data reveal that IL-1β-dependent transcription of COX2 and MMP13 is regulated by Lef1-mediated gene looping.

IL-33 Takes Your Breath Away

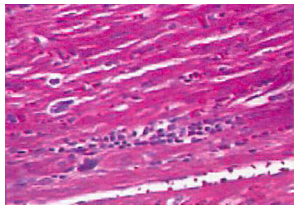


Interleukin-33, a member of the IL-1 cytokine family, is expressed in the lungs and drives a Th2 cell response. To determine whether the inflammatory milieu in bronchial asthma modulates IL-33 expression, Préfontaine et al. (p. 5094) obtained endobronchial biopsies from adults with or without mild, moderate, and severe asthma. Airway smooth muscle cells (ASMC) from asthmatic samples, regardless of severity of disease, expressed increased IL-33 mRNA levels compared with controls, which correlated with TNF-α expression. IL-33 protein was predominantly expressed by ASMC and epithelial and endothelial cells in asthmatic lungs but was absent in control samples. To test the effect of other cytokines on IL-33 expression, cultured biopsy-derived ASMC were treated with various cytokines. In contrast to the TGF-β and the Th2 cytokines IL-4 and IL-13, individual treatment with TNF-α or IFN-γ significantly up-regulated IL-33 mRNA and protein expression, and cotreatment revealed synergism. A subset of asthmatic subjects is nonresponsive to corticosteroid therapy; notably, pretreatment with the corticosteroid dexamethasone failed to inhibit TNF-α-driven IL-33 expression. Thus, IL-33 is expressed by ASMC in

www.jimmunol.org/cgi/doi/10.4049/jimmunol.0990084

asthmatic lungs and shows promise as a potential inflammatory marker for asthma.

Diabetes as a Matter of Expression



Susceptibility to type 1 diabetes (T1D), a T cell-mediated autoimmune disease (AID), is regulated by the genetic locus *Idd5.1* in nonobese diabetic (NOD) mice. Two candidate genes, ICOS and CTLA-4, have been mapped to this site. To investigate the role of CTLA-4 in T1D susceptibility, Araki et al. (p. 5146) generated novel *Idd5.1* congenic (cg) mice that differentially expressed the CTLA-4 isoform, ligand-independent CTLA-4 (liCTLA-4). When cg mice were compared with control NOD mice, which express little liCTLA-4, a negative correlation between liCTLA-4 expression and T1D susceptibility was revealed. Furthermore, NOD liCTLA-4 transgenic (tg) mice exhibited decreased frequency of diabetes onset that was nearly identical to that of NOD tg mice carrying the protective B10 *Idd5.1* locus. To test whether liCTLA-4 expression could compensate for the loss of full-length CTLA-4, liCTLA-4 tg mice were crossed with CTLA-$4^{-/-}$ mice and the resultant expression of liCTLA-4 partially rescued CTLA-$4^{-/-}$ mice from multiorgan AID and early lethality. Taken together, these data indicate that increased expression of liCTLA-4 correlates with decreased AID susceptibility and confers the protective effect mediated by the B10 *Idd5*.1 locus against T1D.

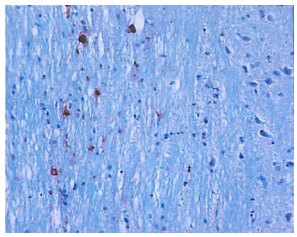
Sweet on Dermatophytes

The dendritic cell-associated heparin sulfate proteoglycan-dependent integrin ligand (DC-HIL) inhibits activated T cells via binding to a saccharide on syndecan-4 (SD-4). To determine whether DC-HIL also binds saccharide ligands on microbial pathogens, Chung et al. (p. 5190) screened various pathogens, including several types of bacteria and the yeast *Candida albicans*, and found that DC-HIL bound exclusively to the dermatophytes (DPs) *Trichophyton rubrum* and *Microsporum audouinii*. The addition of heparin or the removal of saccharide residues abrogated DC-HIL binding to DPs. Preincubation with various fungal saccharides weakly to moderately inhibited binding, suggesting only structural similarities to the DC-HIL ligand. Tyrosine phosphorylation of the ITAM-like signaling motif on DC-HIL was induced by DP binding, Ab-mediated cross-linking of DC-HIL on DCs, or by treatment with immobilized SD-4-Fc. Cross-linking of DC-HIL or stimulation with dried *T. rubrum* upregulated various genes, including TNF-α and IL-1β. Cross-linking of DC-HIL also induced the activation/maturation markers CD80 and CD86 to be expressed and potentiated the stimulation of OVA-specific $CD4^+$ and $CD8^+$ T cells by OVA-loaded DCs. These data reveal that DC-HIL is a receptor for a DP-expressed saccharide and that this interaction can augment the T cell-stimulatory capacity of DCs.

Quelling Viral Acute Lung Injury

Respiratory viruses, such as H5N1 influenza and SARS, can cause acute lung injury (ALI), which is characterized by pulmonary edema, capillary leakage, and hypoxemia. Excessive neutrophil recruitment is implicated in the pathogenesis of ALI and is mediated by the expression of IL-17 receptor A (IL-17RA). To identify a pathway by which neutrophil infiltration could be regulated, Crowe et al. (p. 5301) employed an acute H1N1 influenza mouse model. Two days postinfection, mRNAs encoding IL-17A and IL-17F (produced primarily by $\gamma\delta$ T cells) were detectable and persisted through 7 days postinfection. As compared with wild-type lungs, IL-$17RA^{-/-}$ lungs showed reduced neutrophil immigration, whereas macrophage and viral Ag-specific $CD8^+$ T cell levels remained unchanged. The lungs of IL-$17RA^{-/-}$ mice had decreased inflammatory cytokine levels, relatively mild inflammation, and exhibited lower levels of ALI that correlated with higher survival rates. Surprisingly, IL-$17RA^{-/-}$ mice appeared to tolerate increased viral burden. Oxidized phospholipids (OPLs), often formed by neutrophil-generated myeloperoxidase (MPO), are implicated in ALI development. IL-$17RA^{-/-}$ lungs showed decreased MPO activity, which correlated with significantly decreased levels of OPLs. Thus, IL-17RA, essential for neutrophil recruitment but dispensable for the T cell response and viral clearance, shows promise as a new therapeutic target for influenza-induced ALI.

New Recruits to the CNS



In cases of murine hepatitis virus (MHV)-induced chronic infections of the CNS, viral Ag-specific T cells persist at the sites of infection. Whether T cell numbers are maintained by proliferating in situ Ag-specific T cells or by peripheral T cells migrating into the CNS is unknown. During the course of MHV-induced chronic infection Zhao et al. (p. 5163) found that the frequency of dominant viral epitope (DVE)-specific $CD4^+$ and $CD8^+$ T cells decreased, whereas the frequency of subdominant viral epitope-specific T cells rose. The $CD4^+$ T cell epitope shift was not due to trafficking between the CNS and periphery, but rather appeared to be due to enhanced survival. However, BrdU treatment revealed that a low level of homeostatic and/or Ag-driven proliferation had also occurred. After the adoptive transfer of donor splenic $CD8^+$ T cells from acute and chronic phase mice into infection-matched wild-type congenic recipients, DVE-specific donor T cells were detected in recipient CNS, spleen, and LNs. These results, confirmed by a bone marrow-reconstitution model, indicated that naive T cells were recruited into the CNS as well. Thus, the T cell population in chronically infected CNS is dually maintained by the immigration of peripheral T cells and by low-level proliferation of the acute phase-derived, Ag-specific T cells.

Summaries written by Meredith G. Safford, Ph.D.