The Journal of Immunology

In This Issue

J Immunol 2012; 189:5489-5490; ;
doi: 10.4049/jimmunol.1290077
http://www.jimmunol.org/content/189/12/5489

This information is current as of May 23, 2022.

Supplementary Material **http://www.jimmunol.org/content/suppl/2012/12/06/189.12.5489.DC1**

Why *The JI*? Submit online.

- **Rapid Reviews! 30 days*** from submission to initial decision
- **No Triage!** Every submission reviewed by practicing scientists
- **Fast Publication!** 4 weeks from acceptance to publication

**average*

Subscription Information about subscribing to *The Journal of Immunology* is online at: http://jimmunol.org/subscription

Permissions Submit copyright permission requests at: http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts Receive free email-alerts when new articles cite this article. Sign up at: http://jimmunol.org/alerts

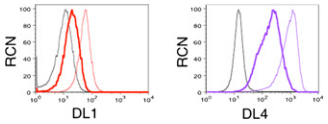
The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852
Copyright © 2012 by The American Association of Immunologists, Inc. All rights reserved.
Print ISSN: 0022-1767 Online ISSN: 1550-6606.

Downloaded from http://www.jimmunol.org/ by guest on May 23, 2022

THE JOURNAL OF IMMUNOLOGY

In This Issue

Dll4 Dominates Development

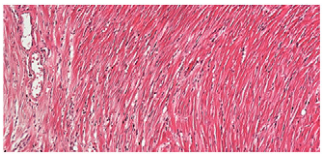


Immature thymocytes enter the thymus and undergo positive and negative selection in order to develop into mature T cells. A role for Notch signaling has been recognized during T cell development. In this issue, Shah et al. (p. 5797) used different constructs of the Notch1 ligands Delta-like (Dll) 1 and Dll4 to determine how endocytosis of these molecules affects their function during T cell development. They found that wild-type (WT) Dll4 interacted strongly with the E3 ubiquitin ligase Mind-bomb1 (Mib1), recycled back to the cell surface, and supported robust T cell development. In contrast, a chimeric Dll4 molecule in which the extracellular domain was fused to the transmembrane domain and cytoplasmic tail of CD25 was not recycled, did not interact with Mib1, and did not support T cell development or Notch target gene activation as efficiently as WT Dll4. Similarly, expression of a Dll4 molecule lacking its intracellular domain also correlated with reduced Notch target gene expression and T cell development. Both WT and modified Dll4 constructs supported more T cell development relative to similar Dll1 constructs, which is likely linked to biochemical analyses showing that Dll4 is excluded from lipid rafts, interacts more strongly with Mib1, and is associated with greater Notch1 uptake. Together these observations suggest that Dll4 recycling and its interaction with Mib1 contribute to the promotion of T cell development.

MicroRNA Modulator

Viral infection promotes a host of immune responses in dendritic cells (DCs), but what role DC microRNA (miRNA) plays has remained unclear. Rosenberger et al. (p. 5965) have now demonstrated that miR-451 is a miRNA that responds uniquely to influenza infection in primary DCs from lung and spleen. While several miRNAs underwent differential expression when DCs were exposed to the dsRNA agonist polyinosinic-polycytidylic acid, miR-451 underwent higher expression in response to influenza, an enveloped negative sense ssRNA virus. In primary murine DCs, both live and UV-inactivated influenza virus induced miR-451 expression. miR-451 also could be stimulated by treatment with IFN-β or IL-6 but not by polyinosinic-polycytidylic acid or LPS. It was determined that myeloid DCs preferentially upregulated miR-451 in response to influenza infection when compared with plasmacytoid DCs. By inhibiting miR-451 with antagomirs (locked nucleic acid-stabilized RNA oligonucleotide antisense to miR-451), Rosenberger et al. determined that DC costimulation was unchanged but that miR-451 was responsible for the downregulation of IL-6, TNF, CCL5/RANTES, and CCL3/MIP1α. The use of miR-451–deficient cells confirmed this finding. They also found miR-451 negatively regulates YWHAZ, an adaptor protein also known as KCIP-1 or 14-3-3 zeta, in DCs. YWHAZ was increased upon inhibition of miR-451, leading to decreased ZFP36/Tristetraprolin expression, a protein known to bind to and destabilize cytokine mRNAs. Thus, Rosenberger et al. postulate that miR-451 is induced by viral infection or by IL-6 and IFN-β to play a part in a negative regulatory loop. These data also provide evidence that miR-451 controls the DC secretion of IL-6, TNF, CCL5/RANTES, and CCL3/MIP1α through inhibition of a signaling pathway involving YWHAZ.

CDK2 Tips Away from Tolerance



Activation, differentiation, and function of naive T cells depend on signaling events triggered by engagement of the TCR and the CD28 costimulatory receptor. In the absence of costimulation, T cells become anergic and exhibit peripheral tolerance. This tolerant state is maintained in part by p27kip1, a protein known to inhibit the cyclin-dependent kinase (CDK) cascade activated during TCR and CD28 engagement. Previous studies have shown that CDK2 is the major target of p27kip1, and Chunder et al. (p. 5659) generated CDK2–deficient mice to better understand the role of CDK2 in T cell function and tolerance. $CD4^+$ T cells from CDK2–deficient mice showed no defects in activation, proliferation, or survival upon TCR activation with or without CD28 costimulation, but IL-2 and IFN-γ production were decreased relative to wild-type $CD4^+$ T cells. Transplantation of fully mismatched cardiac allografts into CDK2–deficient recipients in the presence of CD28 blockade yielded long-term acceptance of the allograft, whereas wild-type recipients had complete allograft rejection. Allografts in CDK2–deficient recipients showed significantly greater infiltration of $Foxp3^+$ regulatory T cells (Tregs), and these Tregs demonstrated enhanced suppressive function in vitro as well as in a mouse model of colitis. These observations define a role for CDK2 in promoting T cell differentiation and suppression of Treg activity that can be inhibited through upregulation of p27kip1.

T Cells on the LAM

T cell responses to *Mycobacterium tuberculosis* are initiated in the draining pulmonary lymph nodes. However, activated T cells take longer to migrate to the infected lung in *M. tuberculosis* infection compared with other pulmonary pathogens. Previous work on the mycobacterial cell wall molecule glycophospholipid, mannose-capped lipoarabinomannan (ManLAM) showed the ability to induce human T cells from peripheral blood to undergo chemotaxis. In addition, chemokine receptor cross-desensitization has been shown to be an important component of the process in

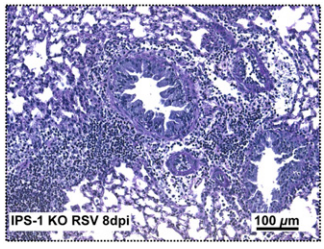
Copyright © 2012 by The American Association of Immunologists, Inc. 0022-1767/12/$16.00

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1290077

Downloaded from http://www.jimmunol.org/ by guest on May 23, 2022

which lymphocytes are recruited to sites of inflammation. These observations led Richmond et al. (p. 5886) to examine whether cross-desensitization occurred with ManLAM. As activated T cells exit the lymph node due to a sphingosine-1-phosphate (S1P) gradient, Richmond et al. examined the ability of ManLAM to regulate S1P-induced T cell migration. They found that exposure to ManLAM inhibited S1P-induced migration of both human and murine T cells. Murine $CCR5^+$ Th1 cells were recruited into the draining pulmonary lymph nodes by intratracheal administration of ManLAM. Further insight into how *M. tuberculosis* infection might cause immunomodulation was derived from ManLAM pretreatment, which was only able to inhibit the S1P-induced migration of Th1 cells but not Th2 cells in vitro. ManLAM treatment inhibited S1P-stimulated AKT phosphorylation in T cells, and the PI3K/AKT inhibitor Ly294002 blocked S1P-directed migration in Th1 cells. The ERK inhibitor U0126 was found to inhibit Th2 cells from migration along the S1P gradient, indicating that Th2 cells employed a signaling pathway that was unaffected by ManLAM pretreatment. Thus, Richmond et al. present a cohesive explanation of how ManLAM "hijacks" activated Th1 cells into residing in the draining lymph node and delays an effective immune response against the mycobacterial pathogen.

Multilateral Virus Fighter



Respiratory syncytial virus (RSV) infection can trigger severe respiratory complications in infants and lead to long-term airway complications, including asthma. Viral RNA can be detected by cytosolic RNA helicases, which interact with the IFN-β promoter stimulator (IPS-1) adaptor protein. Demoor et al. (p. 5942) explored how IPS-1–dependent responses in a mouse model of RSV influenced immunity. IPS-1 knockout (KO) mice infected with RSV showed poorer inflammation resolution and a higher viral load in the lung tissue relative to wild-type (WT) mice, as well as diminished inflammatory responses by alveolar epithelial cells, $CD11b^+$ dendritic cells (DCs), and pulmonary macrophages. They found that infected IPS-1 KO mice had increased activation and infiltration of IFN-γ–producing $CD4^+$ and $CD8^+$ T cells in lymph nodes compared with WT controls, and increased recruitment of monocytes, neutrophils, and DCs to the lung. RSV–infected $CD103^+$ DCs from IPS-1 KO mice showed increased inflammatory cytokine and chemokine responses relative to WT $CD103^+$ DCs. In bone marrow chimeras, the absence of IPS-1 from both immune and nonimmune cell compartments corresponded with severe lung pathology during RSV infection, although restoration of IPS-1 in either of these compartments promoted viral clearance. Together these observations affirm that IPS-1 has multiple nonredundent roles during RSV infection that influence viral replication and inflammation.

Searching for Tubercular Ags

Intracellular pathogens like *Mycobacterium tuberculosis* provide unique challenges to immunologists studying its pathogenesis or trying to find target Ags for vaccines. In addition, *M. tuberculosis* has become adept at adapting to host conditions, for instance, becoming latent in oxygen-limited conditions, termed the enduring hypoxic response. Accordingly, Gideon et al. (p. 5867) used a variety of bioinformatic methods and empirical data to identify potential transcripts that were upregulated when *M. tuberculosis* was exposed to prolonged hypoxia. Generally speaking, genes were identified that were highly induced after seven days of hypoxia, transcript abundance was considered, and literature searches were conducted to choose potential target genes. The MHC class II peptide binding prediction server (ProPred) was also used, and results were adjusted for the Xhosa population–specific allele frequency to further analyze potential Ags. Of the 26 candidate genes that were chosen from these combined approaches, 23 of the associated proteins induced IFN-γ from PBMCs from active or latent tuberculosis patients. Three immunodominant Ags (Acr-1, CFP-10, and ESAT-6) were used as references in IFN-γ and IL-2 ELISPOT assays. Five unique immunodominant peptides were identified as generating dominant IFN-γ responses from active or latent patient PBMCs. Of note was that there was little stage-specific (active or latent) recognition of Ags, opening up new possibilities for viewing *M. tuberculosis* immune responses and identifying vaccine candidates.

Downloaded from http://www.jimmunol.org/ by guest on May 23, 2022