The Journal of Immunology

In This Issue

J Immunol 2013; 190:3013-3014; ;
doi: 10.4049/jimmunol.1390011
http://www.jimmunol.org/content/190/7/3013

Supplementary Material http://www.jimmunol.org/content/suppl/2013/03/22/190.7.3013.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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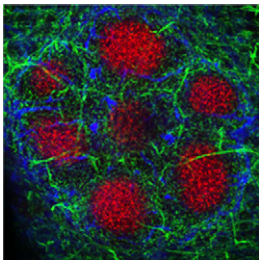
LTi Cells Lead the Way



Lymphoid tissue inducer (LTi) cells are key participants in the formation of peripheral lymphoid tissue (PLT) anlagen. Prior to Ag encounter, cellular compartmentalization into distinct zones occurs within PLT through a process that is not well understood. To determine whether LTi cells regulate this compartmentalization, Nakagawa et al. (p. 3309) analyzed neonatal Peyer's patch (PP) development. Cellular compartmentalization was found to occur during the first 7 days of life, and IL-7Rα$^+$ PP inducer (PPi) cells relocated within the PPs during this time. These PPi cells segregated into clusters corresponding to follicular zones (FZs) and then moved to the outer region of the FZs. PPi clustering occurred prior to lymphocyte redistribution within the PPs and was important for B cell accumulation in the FZs through a lymphotoxin-dependent process. Interestingly, the movement of PPi cells from the FZ to the outer zone required chemokine receptor switching. The PPi cells initially expressed CXCR5 but downregulated CXCR5 and upregulated CXCR4 during the neonatal period through independently regulated processes. This PPi cell relocation was necessary for T cell redistribution to the T cell zones in PPs. Thus, the authors have elucidated an important pathway in PLT organization, demonstrating that PPi cell movement regulates the development of lymphoid architecture in PPs.

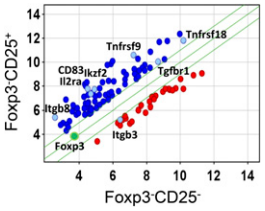
Remembering To Regulate

During the immune response to infection, regulatory T cell (Treg) actions can limit immunopathology and promote inflammatory resolution, but can also allow pathogen persistence. Because less is known about Treg activity during the memory response than the primary response, Brincks et al. (p. 3438) tracked Ag-specific CD4$^+$Foxp3$^+$ Tregs during primary and secondary responses to influenza. Influenza-specific Tregs were recruited to the lungs and lung-draining lymph node with accelerated kinetics during a secondary viral challenge, relative to the primary challenge. During the recall response to influenza, these "memory" Tregs controlled pulmonary inflammation, as revealed by dramatically augmented inflammatory responses in the lungs of Treg-depleted mice. Memory Tregs also reduced the magnitude of the memory CD8$^+$ T cell response to secondary influenza infection. In vitro experiments demonstrated that these cells regulated memory CD8$^+$ T cell proliferation in an Ag-specific manner, and their activity required Ag presentation via MHC class II. By characterizing a population of Ag-specific memory Tregs generated during viral infection, this study has implications for the future development of vaccine strategies and analysis of their success.

Navigating the iNKT SHP-1

Invariant NKT (iNKT) cells recognize lipid Ags in the context of CD1d. As lipid Ags from both bacterial and endogenous (self) origins can be targets of these innate lymphocytes, understanding the regulation of these cells is of critical importance. Although iNKT cell development is dependent on thymic CD1d expression, restriction of CD1d expression to the thymus results in a hyperresponsive and potentially autoimmune population of iNKT cells. Therefore, Napolitano et al. (p. 3299) postulated that a broader population of cells expressing CD1d was required to modulate the responsiveness of iNKT cells. The peripheral hyperresponsive iNKT cells in mice with thymus-restricted CD1d expression were found to express reduced levels of the tyrosine phosphatase SHP-1. A similar hyperresponsive iNKT cell population was found in mutant motheaten mice, which have defective SHP-1 expression due to a single nucleotide deletion in *Ptpn6*. When CD1d expression was restored to tissues outside the thymus, SHP-1 expression and iNKT cell reactivity were returned to normal. Radiation chimeras were used to demonstrate that CD1d$^+$ dendritic cells (DCs) increased iNKT cell SHP-1 expression and checked hyperresponsiveness after iNKT cell thymic emigration. Thus, DCs control SHP-1 levels and Ag reactivity of iNKT cells, promoting appropriate functioning of these important innate lymphocytes.

The Making of a Treg

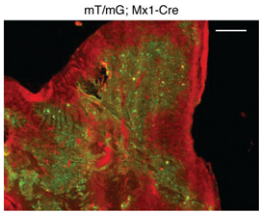


Regulatory T cells (Tregs) can be generally characterized by their ability to maintain immune homeostasis and their expression of *Foxp3*. For Tregs to maintain stable *Foxp3* expression, demethylation must occur at the eponymously named Treg-specific demethylated region (TSDR). The TSDR consists of a conserved, CpG-rich domain within the *Foxp3* locus. Although it is known that the majority of Tregs are generated in the thymus at the CD4 single positive stage, the timing of the *Foxp3* demethylation event has been unclear. Toker et al. (p. 3180) clarified this, determining that TSDR demethylation, and hence commitment to the Treg lineage, occurs during thymic development. The Treg gene expression profile was established via the engraving of lineage-specific epigenetic marks. In addition, the authors found that TSDR demethylation occurred through an active mechanism involving 5-hydroxymethylcytosines (5hmc) and the Tet (ten-eleven translocation) family of enyzmes. Interestingly, this is the first time the presence of 5hmc has been shown at a specific gene locus during T cell differentiation.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1390011

Thus, the authors have pinpointed when the initial TSDR demethylation event necessary for *Foxp3* stable expression occurs, and have determined that an active mechanism is required for this important epigenetic event.

Managing mTEC Maturation



Type I IFNs are important mediators of innate immunity that were also recently implicated in thymic selection. Here, Otero et al. (p. 3289) identified a key role for type I IFN in the establishment of central tolerance. Compared with wild-type mice, those deficient in STAT1 or IFNAR1 had reduced numbers of autoimmune regulator (AIRE)-positive medullary thymic epithelial cells (mTECs) presenting self Ag. AIRE expression in mTECs was stimulated by IFN-β, which was in turn upregulated in thymic stromal cells by receptor activator for NF-κB (RANK) signaling. Analysis of a transgenic reporter mouse strain revealed constitutive IFN signaling in the thymic medulla in the absence of infection. AIRE-negative immature mTECs appeared to be the major thymic source of IFN-β production. The transcription factor IFN regulatory factor 7 (IRF7) was required for IFN-β upregulation in mTECs following RANK ligand (RANKL) stimulation. This IFN-β expression was necessary for the maturation of mTECs into cells able to present self-Ags and mediate the establishment of central tolerance. In addition to demonstrating the importance of IFN-β in mTEC maturation and thymic selection, these data urge caution in the interpretation of experiments using STAT1 or IFN-deficient mice for the study of adaptive immune responses.

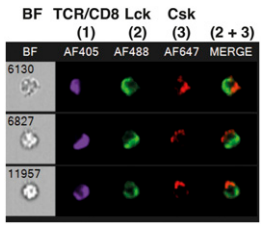
Interfering with HIV

Immature monocyte-derived dendritic cells (MDDCs) can be infected by HIV-1 and, upon maturation, can migrate and transfer virus to T cells. Apolipoprotein B mRNA–editing, enzyme-catalytic, polypeptide-like 3 (APOBEC3, or A3) family members are cytidine deaminases that are expressed in MDDCs and act to restrict HIV-1 replication. Because A3 proteins can be induced by type I IFN, Mohanram et al. (p. 3346) compared the effects of TNF-α and IFN-α, which can both induce MDDC maturation, on A3 expression and HIV-1 restriction. TNF-α induced MDDC maturation in vitro in a dose-dependent manner, whereas only high concentrations of pegylated (PEG) IFN-α2b induced maturation. Conversely, PEG-IFN-α2b reduced HIV-1 replication in MDDCs in a dose-dependent manner, whereas only high concentrations of TNF-α could do so. PEG-IFN-α2b, but not TNF-α, also significantly reduced viral transfer from MDDCs to autologous T cells. Analysis of A3 expression in MDDCs following HIV-1 exposure revealed that even low concentrations of PEG-IFN-α2b induced significant upregulation of A3A, A3G, and A3F, which could effectively mediate HIV-1 hypermutation. However, TNF-α did not induce A3 expression at any concentration tested. Taken together, the data indicate that low-dose IFN-α can induce A3 expression and viral restriction without causing MDDC maturation and migration, suggesting further investigation of this mechanism for clinical application.

Th17-Inducing Macrophages

Although Th17 cells can be beneficial in maintaining antimicrobial immunity, they also drive detrimental autoimmune responses. To determine more precisely how autoimmune Th17 cells develop, Simons et al. (p. 3134) used the transgenic arthritic mouse TS1xHACII. These mice become arthritic through autoreactive $CD4^+$ T cells recognizing the ubiquitously expressed hemagglutinin protein (HA) of influenza virus as a self Ag. The authors found that lymph nodes in these mice contained increased numbers of inflammatory macrophages (iMO). These iMO promoted $CD4^+$ Th17 differentiation in the context of a regional inflammatory response in the paw-draining lymph nodes. Importantly, these Th17-trophic iMO were activated before the development of arthritis. Adoptive transfer experiments demonstrated that iMO activation was dependent on the presence of autoreactive $CD4^+$ T cells, and that iMO recruitment to the lymph node required IFN-γ. These data establish that autoreactive $CD4^+$ T cells recognizing a systemic self Ag cause the recruitment of Th17-trophic iMO to lymph nodes, a regional event that leads to the development of arthritis.

Sequestering Csk



The Ag-specific recall response in $CD8^+$ T cells is more efficient than the initial response, but the molecular mechanisms responsible for this increased Ag sensitivity are not clear. The Src-family kinase Lck, which is important for determining the T cell activation threshold, directly associates with CD8. Lck is inhibited by the tyrosine kinase Csk, and Csk recruitment to the plasma membrane is promoted by the Src-family kinase Fyn. In this issue, Borger et al. (p. 3089) used confocal microscopy and imaging flow cytometry to assess whether the distribution of Lck, Csk, and Fyn following TCR stimulation controlled the different activation kinetics of naive and Ag-experienced $CD8^+$ T cells. Lck redistributed to the site of TCR/CD8 activation in both naive and Ag-experienced cells, but was more efficiently recruited in Ag-experienced cells. In naive T cells, the majority of Csk colocalized with Lck at the TCR. However, in Ag-experienced cells, less Csk was found associated with Lck. Instead, Csk was observed at a discrete cytoplasmic site distal to the TCR. In both cell types, Fyn closely associated with Csk, but Csk redistribution in Ag-experienced cells was independent of Fyn. This study suggests that specific compartmentalization of signaling molecules upon TCR stimulation may regulate the different activation thresholds of naive and memory $CD8^+$ T cells.