The Journal of Immunology

In This Issue

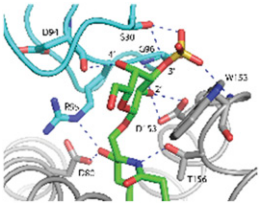
J Immunol 2017; 199:1-2; ;
doi: 10.4049/jimmunol.1790009
http://www.jimmunol.org/content/199/1/1

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

Sulfatide Plays Favorites with iNKT Cells

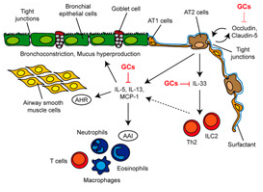


Invariant NKT (iNKT) cells are innate-like lymphocytes defined by their expression of a conserved TCRα-chain and the recognition of lipid Ags presented by CD1d. Because human and mouse iNKT cells generally display conserved recognition of lipid Ags such as α-galactosylceramide (αGalCer), it has been assumed their biology is equally similar. Investigating the hypothesis that the lipid-rich myelin sheath, which is the target of autoimmunity in multiple sclerosis (MS), may contain self-antigens recognized by iNKT cells, Stax et al. (p. 97) showed that myelin sulfatides with intact sulfate groups activated human iNKT cells when directly bound to CD1d. Surprisingly, iNKT cells from Vα-14 TCR transgenic mice, which express an invariant TCRα-chain with variable β-chains, showed no sulfatide reactivity when compared with αGalCer-stimulated controls. Additionally, coculture of different mouse or human iNKT hybridomas with either mouse or human APCs in the presence of αGalCer or sulfatide demonstrated that sulfatide could only be presented by human CD1d to human iNKT cells. To account for this difference between species, the authors modeled the interaction of sulfatide with human CD1d-TCR complexes and found that a human-specific Trp153 residue in CD1d elevates the galactose head of the sulfatide in a more energetically favorable orientation for TCR recognition than the corresponding mouse Gly155. Consistent with these observations, peripheral blood iNKT cells from healthy human donors recognized sulfatide carried by apolipoprotein E from the cerebral spinal fluid, which is the predominant lipid carrier in the CNS. Thus, this study identifies sulfatide as a self-lipid recognized by human iNKT cells and suggests that it may play a role in neuroinflammatory conditions such as MS. Furthermore, the unique recognition of sulfatide by human, but not mouse, iNKT cells underscores a significant divergence between human and mouse iNKT cell biology and indicates that the role of iNKT cells in mouse models of human diseases, such as experimental autoimmune encephalomyelitis and type 1 diabetes, may need to be re-evaluated.

Putting Complement in the Middle

TLR-induced maturation of dendritic cells (DCs) is important for the development of proinflammatory T cell immunity. Complement components C3a and C5a are produced during DC–T cell interactions, and resultant signaling through C3ar1 and C5ar1 also promotes effector T cell responses, leading Sheen et al. (p. 278) to hypothesize that complement signaling and TLR-mediated DC maturation are interconnected. Indeed, in vitro stimulation of DCs via TLR3, TLR4, or TLR9 in the presence of peptide Ag resulted in Ag-specific T cell activation through a process that required production of complement components and autocrine signaling through C3ar1 and C5ar1 in DCs. Analysis in a polyclonal system confirmed these data, demonstrating that treatment of wild-type (WT), but not *C3ar1*$^{-/-}$ *C5ar1*$^{-/-}$ or *C3/C5*$^{-/-}$, DCs with the TLR9 ligand CpG augmented T cell responses to DC-expressed alloantigens. Similar results were observed in vivo, where CpG failed to induce DC maturation and allogeneic T cell activity in *C3ar1*$^{-/-}$ *C5ar1*$^{-/-}$ mice, whereas CpG treatment of WT mice resulted in DC maturation, T cell activation, and induction of proinflammatory cytokine expression by DCs. Microarray analysis identified 1198 genes upregulated in WT DCs by CpG treatment, 51% of which were not upregulated in CpG-treated DCs from *C3ar1*$^{-/-}$ *C5ar1*$^{-/-}$ mice, further supporting the importance of the complement signaling pathway in TLR9-mediated effects. Although CpG is known to reverse the protective effects of CD40L blockade in cardiac allograft transplantation, *C3ar1*$^{-/-}$ *C5ar1*$^{-/-}$ transplant recipients survived significantly longer than WT following CpG treatment. Whereas donor-reactive CD8^{+} T cells expanded in WT CpG-treated graft recipients, these cells did not emerge in *C3ar1*$^{-/-}$ *C5ar1*$^{-/-}$ recipients, and bone marrow (BM) chimeric cardiac allograft recipients with *C3ar1*$^{-/-}$ *C5ar1*$^{-/-}$ BM survived significantly longer those with WT BM. Finally, CpG treatment of WT, but not *C3ar1*$^{-/-}$ *C5ar1*$^{-/-}$, mice increased the representation of ex-regulatory T cells, that is, regulatory T cells that have lost expression of Foxp3 and, as a consequence, allow graft rejection to proceed. Taken together, these data indicate that TLR stimulation of DCs promotes immune cell complement production that induces autocrine signaling through C3ar1 and C5ar1, a sequence of events that is necessary for efficient activation of effector T cell responses, with important implications for transplantation tolerance.

Glucocorticoids Find Their Target

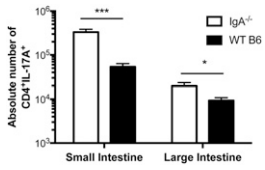


Asthma, a chronic lung disease characterized by airway inflammation, structural changes, and hyperresponsivness, involves a complex interplay between immune cells and airway epithelial cells that is not yet fully understood. Although glucocorticoids (GCs) such as dexamethasone (Dex) are often the treatment of choice for asthma, it is not yet known which cells are targeted to mediate their therapeutic effect. After confirming that an intact dimerization interface of the GC receptor (GR) is required for treatment of allergic

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1790009

airway inflammation (AAI) with Dex, Klaßen et al. (p. 48) investigated whether GCs target immune cells during AAI. Dex treatment of AAI in GR^{dim} mice harboring a point mutation in the GR DNA–binding domain that interferes with the dimerization interface showed the same impact on the levels of Ag-specific IgE, IgG1, and IgG2a and on T cell proliferation and IL-2 and IL-4 production as in treated wild type (GR^{wt}) controls. Furthermore, knockout of GR in T, B, myeloid, or dendritic cell populations had no impact on the Dex-sensitivity of AAI, indicating that GR expression in hematopoietic cells was dispensable for treatment of AAI with GCs. Furthermore, only bone marrow chimeras in which the non-hematopoietic compartment expressed a mutant GR were resistant to GC therapy following induction of AAI. Consistent with this, mice harboring mutant GRs in AT2 cells, a subtype of airway epithelial cells that present Ag and produce cytokines, were unresponsive to Dex therapy and this phenotype correlated with the inability of Dex to affect expression of GC-dependent genes including *IL-5*, *IL-13*, *IL-33*, and *MCP-1*, that are associated with asthma pathogenesis. Taken together, these data identify airway epithelial cells as target cells for GCs. This understanding may aid in the development of more specific therapies for the treatment of AAI.

Homing in on Homeostatic Th17 Cells



Th17 cells are the most abundant effector $CD4^+$ T cells in the intestine and are widely considered to be pathogenic due to their association with autoimmune disorders such as inflammatory bowel disease. In this issue, Zhao et al. (p. 312) examined the characteristics of homeostatic Th17 cells in the normal intestine. When compared with wild-type (WT) controls, IgA-deficient ($IgA^{-/-}$) mice showed a significantly expanded Th17 population in the small intestine that was further enhanced following immunization with cholera toxin (CT), a potent inducer of Th17 responses, despite the absence of intestinal inflammation. Intestinal microbiota from $IgA^{-/-}$ mice differed from those of WT mice, with higher proportions of *Firmicutes* and *Bacteroidetes*, phyla that are closely related to intestinal immune homeostasis, and of segmented filamentous bacteria (SFB), which induce Th17 responses. CT immunization of $IgA^{-/-}$ and WT littermates in which the intestinal microbiota was equalized eliminated the differences in intestinal Th17 responses, indicating that the elevated intestinal Th17 population in $IgA^{-/-}$ mice was due to their microbiota. Interestingly, CT immunization of altered Schaedler flora (ASF) colonized WT mice in the absence of SFB induced Th17 cells in the small intestine, indicating that bacteria belonging to ASF also have the potential to regulate Th17 responses following CT immunization. Furthermore, CT immunization of both SFB colonized ASF and germ-free mice significantly increased SFB-specific IL-17A production over that induced by CT in the absence of SFB colonization, indicating that CT immunization activates SFB-reactive Th17 cells. IL-17-producing cells from the small intestine of naive and CT-immunized $IgA^{-/-}$ IL-17A reporter mice share the same gene expression profile as shown by RNA-sequencing analysis. When compared with pathogenic Th17 cells induced with IL-6, IL-23, and IL-1β, homeostatic and CT-induced intestinal Th17 cells expressed lower levels of genes related to Th17 pathogenicity, such as *Tnf*, *Ifng*, *Il23a*, and *Gzmb*, and a four-fold increase in expression of genes involved in anti-inflammatory activities, such as *Ctla4, Icos,* and *Il-22*. In summary, this study identifies a nonpathogenic signature for homeostatic Th17 cells in the intestine and documents their regulation by commensal microbiota and sensitivity to CT exposure. Given that the ratio of homeostatic to pathogenic Th17 cells may be critical in preventing inflammation, this information should contribute to our understanding of whether these Th17 cells are of separate lineages and, if not, what may trigger their interconversion.