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THE JOURNAL OF IMMUNOLOGY

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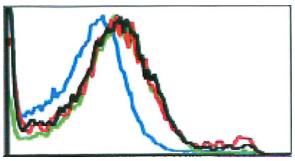
Periphery Shapes TCR Repertoire



Following thymic development, T cells enter the peripheral lymphoid compartment where they undergo further phenotypic and functional maturation before attaining the mature "naive" (MN) T cell stage. Whether the TCR repertoire of these recent thymic emigrants (RTEs) is fixed or undergoes further MHC-directed selection in the periphery is unknown. To address this issue, Houston Jr. and Fink (p. 7244) used a transgenic (Tg) mouse system, RAG2p-GFP Tg, to specifically express GFP on RTEs, thus facilitating their identification and isolation. Comparison of both $CD4^+$ and $CD8^+$ RTEs with comparable MN subsets revealed a skewing of longer CDR3 regions in RTEs, suggesting that MHC-driven modulation of the RTE TCR repertoire had occurred. Temporal analysis of maturing RTE TCR repertoires in competitive bone marrow (BM) chimeras, established from a mixture of syngeneic polyclonal TCR and TCR Tg BM cells, confirmed that the RTE TCR repertoire changed during the RTE to MN transition. Surprisingly, when RTE phenotypic and functional maturation were evaluated in mice that were either wholly or peripherally deficient in MHC II expression, both were found to be normal. These data show that the T cell repertoire is still under selective pressure after exiting the thymus, as peripheral MHC expression continues to shape the repertoire of maturing RTEs.

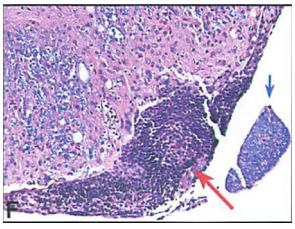
Th17 Cells Can't Resist CD39

T helper 17 cells, which play a negative role in the pathogenesis of multiple sclerosis (MS), appear to be resistant to suppression by $CD4^+CD25^+Foxp3^+$ natural T regulatory cells (nTregs). Recently CD39, an ectonucleotidase that hydrolyzes ATP, was found to be expressed on a subset of human nTregs. Fletcher et al. (p. 7602) compared the activity of $CD39^+$ and $CD39^-$ $Foxp3^+$ nTreg subsets on cocultured $CD4^+CD25^-$ responder T cells and found that both $CD39^+$ and $CD39^-$ nTregs suppressed responder T cell proliferation and IFN-γ production. $CD39^+$ nTregs, which were predominantly $FoxP3^+$, suppressed IL-17 production, whereas $CD39^-$ T cells enhanced the coculture IL-17 levels by producing IL-17. The frequency and suppressive function of nTregs from MS patients, excluded of recently activated cells, were analyzed. When compared with normal control individuals, $CD4^+CD25^+FoxP3^+CD39^+$ nTregs in MS patients were decreased in frequency and had diminished capacity to suppress IL-17 by responder cells. CD39 function appeared to be mediated by cell contact and its effects could be duplicated in suppression assays by the addition of adenosine, a product of CD39 and CD73 ectonucleotidase-mediated hydrolysis of ATP. These data indicate that $FoxP3^+CD39^+$ nTregs can suppress Th17 cells, and a decrease in their normal frequency could contribute to the pathogenesis of MS.

Spliced MASP Blocks Cascade

The lectin pathway of complement activation is triggered by the binding of soluble pattern recognition molecules (sPRMs), which include mannose-binding lectin (MBL) and ficolins, to certain sugar residues on pathogenic surfaces. This event activates two proenzymes complexed with each sPRM, the MBL-associated serine proteases (MASPs). MASPs in turn trigger the complement cascade. Previously, the only known physiological mechanism of inhibition of the lectin pathway was via the inhibition of complement factor C1, which also blocks the classical pathway of complement activation. The investigation of *MASP1* gene splice variants by Degn et al. (p. 7371) yielded MAp44, a novel, phylogentically conserved protein. MAp44 was formed by an alternative splicing product of the *MASP1/3* gene and the C-terminal addition of 17 unique amino acids. MAp44 was most highly expressed in the heart and formed Ca^{2+}-dependent complexes with sPRMs in the serum. In vitro experiments showed that MAp44 competed with MASP-2 and MASP-3 for binding to sPRMs, and binding of MAp44 to MBL down-regulated the complement factor C4-specific cleavage activity of MASP-2. Unlike the C1 inhibitor, MAp44 selectively inhibited the lectin pathway. Thus, MAp44 may be a new tool to block the complement pathway in pathological conditions where selective blockage of the lectin pathway would be advantageous.

EAE Pathology Is Subject to Subsets



Experimental autoimmune encephalomyelitis (EAE) is a murine model for multiple sclerosis (MS). Like MS, the histopathology of EAE is heterogenous and features demyelination and a range of inflammatory pathologies within the CNS. EAE and MS induction are believed to be largely caused by myelin-reactive T cells, but identification of the T cell subset responsible has been elusive. To address this issue, Jäger et al. (p. 7169) tested different T cell subsets for their ability to transfer EAE from encephalitogenic myelin oligodendrocyte glycoprotein (MOG)-specific TCR-transgenic (2D2) mice into naive syngeneic wild-type (WT) recipient mice. Naive MOG-specific $CD4^+CD62L^{high}$ 2D2 T cells were differentiated ex vivo with polarizing cytokines into Th1, Th2, Th9, and Th17 cells, restimulated with anti-CD3 and anti-CD28, and then adoptively transferred into recipient WT mice. Histopathological analysis of recipient spinal cords indicated that all subsets except Th2 induced EAE independently of one another and manifested different pathological phenotypes. These findings suggest that variability in the populations of autoreactive

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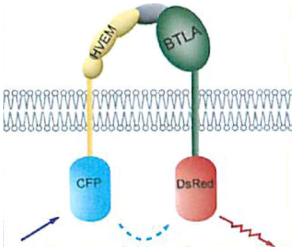
T cell subsets among MS patients contributes to the heterogenous presentation of MS pathologies.

HVEM Bound Up by BTLA



The TNFR family member herpes virus entry mediator (HVEM) can positively or negatively modulate T cell activation, depending upon its engaged ligand. Binding of HVEM to the TNF family ligand LIGHT on T cells induces positive signals, whereas the B and T lymphocyte attenuator (BTLA) induces inhibitory signaling pathways. Early studies showed that APC or endothelial cell-expressed HVEM engaged BTLA on T cells in *trans*. More recent data suggest that the HVEM-BTLA association may also occur in *cis*. Cheung et al. (p. 7286) analyzed naive human and mouse T cells and found coexpression of HVEM and BTLA at the cell surface. Coimmunoprecipitation studies revealed that HVEM and BTLA, whether ectopically or intrinsically expressed, formed a heterodimeric complex. Cell surface HVEM-BTLA *cis*-interactions were confirmed by fluorescence resonance energy transfer (FRET) analysis. *cis* binding of BTLA to HVEM blocked *trans*-interactions with BTLA. Surprisingly, HVEM was not activated in *cis* by BTLA binding even though the same region of HVEM was bound in *cis* and in *trans*. Similarly, LIGHT could still bind to HVEM complexed with BTLA, but LIGHT-induced signaling pathways were blocked. Thus, on naive human and mouse T cells, HVEM and BTLA form heterodimeric complexes that competitively inhibit HVEM activation by BTLA or other ligands in *trans*.

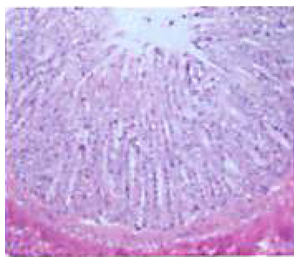
STAT1 Recruitment Up in PAH

Patients with pulmonary arterial hypertension (PAH) typically present with deficient levels of the eicosanoid prostacyclin (PGI_2), which is believed to naturally exert therapeutic effects on PAH by dilating vascular pulmonary beds and suppressing vascular inflammation. PGI_2 appears to mediate its anti-inflammatory effects by down-modulating the expression of various inflammatory cytokines, including MCP-1. To better understand the anti-inflammatory properties of PGI_2, Strassheim et al. (p 6981) focused on the transcriptional control of IL-6- and IFN-γ-mediated production of MCP-1 and other cytokines in monocytes. Treatment with the PGI_2 analog iloprost significantly decreased IL-6- and IFN-γ-mediated MCP-1 production through inhibition of STAT1 activation. In a dose-dependent manner, iloprost directly inhibited phosphorylation of the S727 residue in the STAT1 transactivation domain, thereby disrupting recruitment of the histone acetyltransferase and coactivator CBP/p300 to STAT1. Furthermore, iloprost inhibited JAK2 activation, which reduced STAT1-Y701 phosphorylation levels and the subsequent activation and nuclear recruitment of STAT1. These data indicate that PGI_2 suppresses vascular inflammation by limiting the production of MCP-1 and other detrimental cytokines via inhibition of STAT1 activation and nuclear recruitment.

$CD8^-$ cDCs Fly with Blimp-1

B lymphocyte-induced maturation protein-1 (Blimp-1) is a transcriptional repressor and a critical player in the lives of B cells, T cells, and macrophages. To assess its role in the dendritic cell (DC) lineage, Chan et al. (p. 7039) conditionally knocked out the gene encoding Blimp-1, *Prdm1*, in the pan-hematopoietic lineage (CKO). Analysis of hematopoietic cells revealed a greater frequency of $CD11c^{high}$ cells in CKO mice compared with control mice, which suggested a role for Blimp-1 in DC development. Pre-conventional DCs (pre-cDC), from which both the $CD8^+$ and $CD8^-$ cDC populations arise, had similar frequencies in CKO and control mice, but both $CD4^+$ and $CD4^-$ $CD8^-$ cDC precursor frequencies were significantly increased in CKO mice. Because the survival and proliferative rates of $CD8^+$ and $CD8^-$ cDCs were similar, the greater frequency of CKO $CD8^-$ cDC precursors appeared to be due to the increased number of steady-state $CD8^-$ cDCs. Consistent with these findings, Blimp-1 mRNA levels in control $CD8^-$ cDCs were higher than in other DC populations. Interestingly, stimulation of $CD11c^{high}$ cDCs with TNF-α and a variety of TLR ligands revealed that Blimp-1-deficient cDCs matured poorly relative to control cDCs. These data indicate that whereas Blimp-1 expression negatively modulates $CD8^-$ cDC numbers, it enhances their subsequent maturation.

T Cells Held Up by Sialomucins



The cell surface-expressed sialomucin CD43, which is highly glycosylated with sialylated *O*-linked glycans, inhibits in vitro homotypic adhesion and proliferation of T cells and their migration into secondary lymphoid organs. The role of another sialomucin expressed on T cells, P-selectin glycoprotein ligand-1 (PSGL-1), is not known. Because CD43 can act as an anti-adhesive or pro-adhesive selectin ligand, depending on the cell type, Matsumoto et al. (p. 7204) investigated whether PSGL-1 had positive or negative regulatory roles in T cell adhesion. Activated T cells from both PSGL-1- and CD43-deficient mice exhibited increased adhesion and proliferation in comparison with wild-type cells, responses that were further enhanced for T cells from CD43/PSGL-1-double knock out (DKO) mice. Reexpression of either CD43 or PSGL-1 reversed these enhancements in DKO $CD4^+$ T cells. Studies using chimeric constructs with CD8 and either PSGL-1 or CD43 revealed that the intracellular domains of these sialomucins were necessary for anti-proliferative but not anti-adhesive effects. Furthermore, PSGL-1 deficiency exacerbated the development of inflammation in a murine model of T cell-mediated inflammatory bowel syndrome. These results indicate that PSGL-1 plays a negative role in T cell adhesion and proliferation and may negatively regulate T cell responses in vivo.

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