The Journal of Immunology

IN THIS ISSUE

J Immunol 2007; 178:1-2; ;
doi: 10.4049/jimmunol.178.1.1
http://www.jimmunol.org/content/178/1/1

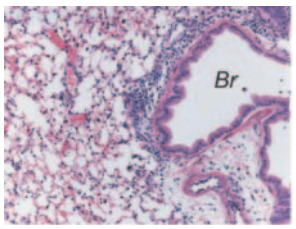
The Journal of Immunology is published twice each month by The American Association of Immunologists, Inc., 1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

THE JOURNAL OF IMMUNOLOGY

IN THIS ISSUE

Breathe Easier with Omega-3 Fatty Acids



Resolution of asthmatic airway inflammation is mediated in part by protectins and resolvins, newly identified families of lipid mediators generated from omega-3 fatty acids. Levels of docosahexaenoic acid (DHA), the precursor to protectin D1 (PDA), are decreased in respiratory tracts in airway inflammation, suggesting that omega-3 fatty acids may have beneficial effects on lung inflammation. Levy et al. (p. 496) measured higher levels of PD1 and its DHA precursor in exhaled breath condensates of normal vs asthmatic individuals. In an experimental animal model of allergic asthma, mice sensitized and aerosol-challenged with an allergen generated PD1 from endogenous and exogenous DHA. Lungs of sensitized animals given PD1 before allergen challenge had fewer infiltrating leukocytes, eosinophils, and lymphocytes, reduced levels of peptide, lipid, and cytokine proinflammatory mediators, and less methacholine-induced bronchial inflammation than vehicle-treated controls. Sensitized and challenged mice given PD1 also had reduced lung cellular infiltrates compared with controls given vehicle only. The authors present evidence for PD1 formation from its omega-3 fatty acid precursor DHA in human and mouse lungs and demonstrate the ability of PD1 to prevent and resolve allergic airway inflammation in sensitized mouse lungs.

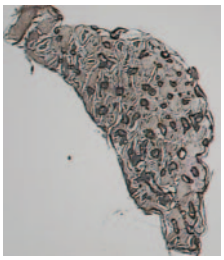
Motheaten T Cell-APC Conjugates

The $CD8^+$ T cells of motheaten mice, deficient in Src homology region 2 domain-containing protein tyrosine phosphatase-1 (SHP-1), have increased proliferation in response to Ag-pulsed APCs compared with wild-type mice. However, this hyperproliferative phenotype has not been characterized at the cellular level. On p. 330, Sathish et al. demonstrated a 2-fold greater increase in the number of CFSE-labeled motheaten T cells transgenic for a TCR specific for an influenza virus protein proliferating in response to virus Ag-pulsed APCs over controls. This was accompanied by a 2-fold greater down-regulation of cell surface TCRs on *SHP-1*$^{-/-}$ vs *SHP-1*$^{+/+}$ cells. Motheaten T cell-APC conjugate formation was twice that of control T cells, and anti-LFA-1 Ab blocked conjugate formation of motheaten or control T cells. Mutant and control cells adhered to plate-bound integrin ligands to an equivalent degree. Adoptively transferred motheaten $CD8^+$ T cells expanded to a greater extent in spleens of irradiated *RAG-1*$^{-/-}$ recipients than did *SHP-1*$^{+/+}$ cells. Cotransfer of Ag-pulsed dendritic cells followed 6 days later by challenge with CFSE-labeled Ag-pulsed splenocyte targets resulted in greater in vivo cytolysis of target cells by motheaten vs *SHP-1*$^{+/+}$ $CD8^+$ T cells. The authors conclude that SHP-1 negatively regulates the percentage of naive $CD8^+$ T cells that are activated by Ag-loaded APCs by decreasing engagement of TCRs.

DAFfy Interactions with C3 Convertase

Decay accelerating factor (DAF) prevents host cell damage by binding and inactivating the C3 convertase of the alternative pathway of C. However, it is not known how the short consensus repeat domains (SCRs) of DAF interact with convertase components. Harris et al. (p. 352) found that intact DAF (DAF1234) prevented C-mediated lysis of sheep RBCs, whereas deletion mutants containing only SCR domain 3 (DAF3), domains 2–3 (DAF23), or domains 3–4 (DAF34) did not prevent lysis. Surface plasmon resonance studies demonstrated binding of DAF1234 and DAF34 to the C3b component of convertase and DAF1234 and DAF23 to the Bb component; no binding of DAF to properdin was detected. Chip-immobilized properdin-C3 convertase (C3bBb) was sensitive to decay by DAF1234. Immobilized C3bBb was rapidly decayed by DAF1234 or by DAF34 at a high concentration; DAF23 bound but did not decay the complex, and DAF3 did not bind. The surface plasmon resonance results were confirmed by interaction of bound C3 convertase with wild-type and deletion DAF mutants in a microtiter plate assay. The authors use several sensitive methods to demonstrate DAF SCR2 binding to Bb of convertase and SCR4 binding to C3b and propose that SCR3 provides the correct orientation and presentation of SCR2 and SCR4 to their binding partners to mediate convertase decay.

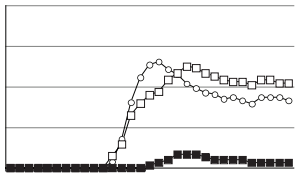
B Cells in Inflammatory Myopathies



Although two inflammatory myopathies (inclusion body myositis and polymyositis) are considered to be $CD8^+$ T cell-mediated autoimmune diseases, detection of plasma cells in muscle tissues from patients suggests that Ab-mediated autoimmunity might be involved. In an examination of muscle tissues from 12 patients with inclusion body myositis, polymyositis, or dermatomyositis (a third inflammatory myopathy), Bradshaw et al. (p. 547) detected Ig V_H sequences indicating class switching from IgM to either IgG or IgA. Muscle tissues had 11–30 V_H mutations compared with 0–5 mutations in blood samples from patients and normal individuals. Ig sequences were rarely detected in muscle tissues from nonneuromuscular disease control patients, and only IgM sequences were detected in blood samples. Groups of clonal variants that mostly differed by single amino acid replacements as a result of single nucleotide point mutations

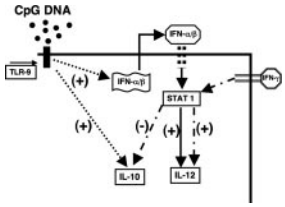
were identified in 85% of the inflammatory myopathy muscle samples. Insertions and deletions of three bases within or adjacent to a CDR also were detected. Ig V_H sequence analyses on laser capture microdissection samples from separate areas of tissue sections from the same patient confirmed the presence of plasma cells and clonal expansion of B cells in inclusion body myositis and dermatomyositis. Analyses of CDR regions of individual clones suggested both Ag-driven mutation and the existence of mutational hotspots. These results from several experimental approaches suggest that affinity maturation of B cells is Ag-driven in the muscle tissue of patients with inflammatory myopathies.

TGF-β Induces Peripheral Foxp3$^+$ Tregs



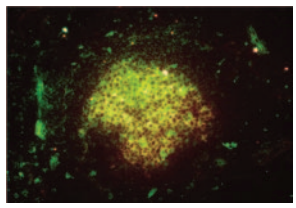
Although T cells expressing TGF-β are important in regulating peripheral immune responses in several autoimmune diseases, the role of TGF-β-producing Th3 cells in induction of CD4$^+$ regulatory T cells (Tregs) is not well defined. Carrier et al. (p. 179) found that naive T cells from mice transgenic for TGF-β1 under control of the IL-2 promoter had reduced proliferation and IL-2, IFN-γ, IL-13, and IL-10 production but increased transient TGF-β production in response to anti-CD3 Ab stimulation in the presence of syngeneic APCs compared with nontransgenic littermates. Myelin oligodendrocyte (MOG)-primed T cells from mice carrying transgenes for the TFG-β construct and for a MOG peptide-specific TCR were hyporesponsive when challenged in vitro with MOG peptide plus syngeneic APCs and suppressed proliferation of MOG peptide-specific TCR responder cells. Anti-TGF-β Ab abrogated anergy and suppressive properties of the double-transgenic cells. *Foxp3* mRNA expression was induced in naive splenic doubly transgenic CD25$^-$ and CD25$^+$ T cells stimulated by MOG peptide plus syngeneic APCs in vitro; both subsets of cells were anergic and suppressive but had no increase in surface markers associated with Tregs. Experimental autoimmune encephalomyelitis was drastically reduced in wild-type mice that were transferred with MOG peptide-primed double transgenic cells before or after MOG peptide immunization. Thus, transient TGF-β expression by Ag-specific TCR-stimulated Th3 cells induces differentiation of peripheral Foxp3$^+$ Tregs that protect against Ag-induced autoimmune disease in mice.

IFN-γ Suppresses IL-10 in DCs



Cancer immunotherapy exploits the Th1 response induced by IL-12 derived from CpG-stimulated dendritic cells (DCs). However, the impact of IFN-γ produced by Th1 cells on DC cytokine production has not been established. Flores et al. (p. 211) measured higher IL-12 secretion and mRNA production in immature and mature mouse DCs stimulated with LPS or CpG in vitro; the levels were greatly increased by addition of IFN-γ. At the same time, the LPS- or CpG-stimulated production of IL-10 was suppressed by IFN-γ in a dose-dependent manner. *IL-12* mRNA was detected 8 h after activation, whereas *IL-10* mRNA did not appear until 24 h. Synthesis of *IL-12* mRNA was increased and appeared earlier in the presence of IFN-γ, but IFN-γ prevented *IL-10* mRNA production even in the presence of anti-IL-12 mAb. A delay of $\geq$2 h in IFN-γ addition after CpG treatment of DCs resulted in reduced production of IL-12 and increased IL-10 production. DCs pretreated with IFN-γ never produced IL-10 in response to CpG and had reduced IL-12 levels if stimulated $\geq$4 h after pretreatment. IL-12 production in response to CpG with or without IFN-γ was significantly lower in *STAT1*$^{-/-}$ vs wild-type DCs; IL-10 production was the same in stimulated STAT1-deficient cells with or without IFN-γ. Anti-IFN-β mAbs reduced CpG-induced IL-12 production but had no effect on IL-10 production. The authors propose that the ability of IFN-γ to enhance IL-12 production by CpG-activated DCs is mediated through STAT1-dependent suppression of IL-10 synthesis.

Maintaining Memory (B Cells)



Although long-lived plasma cells continue to produce Ag-specific Abs, the role of the immunizing Ag in maintenance of the humoral response is not known. Gatto et al. (p. 67) found that the initial Ag-specific IgG response in mice injected with noninfectious virus-like particles (VLPs) derived from a bacteriophage peaked at 3–4 wk but decayed at later time points with a half-life of 80 days. High numbers of VLP-specific IgG-secreting Ab-forming cells (AFCs) were detected in spleen and bone marrow and, along with VLP-specific isotype-switched B cells and germinal centers (GCs) in spleen, decayed with time. Flow cytometric measurements of splenic B cells and bone marrow plasma cells labeled early or late with BrdU indicated that nearly all VLP-specific B cells had divided by 10–20 days postimmunization. Splenic B cells declined rapidly within a few days but remained a constant percentage of the total B cell population thereafter, whereas the bone marrow plasma cells declined more slowly with a half-life of 80 days. Animals depleted of splenic VLP-Ag/follicular dendritic cells by injection with a lymphotoxin β receptor-Ig fusion protein (LTβR-Ig) on days 9 and 11 after immunization had reduced numbers of GCs, isotype-switched Ag-specific B cells, and IgG AFCs and less B cell proliferation. LTβR-Ig injection later (on days 39/41) decreased the frequency of GC B cells but had no impact on generation and/or maintenance of splenic memory B cells or bone marrow plasma cells; very late LTβR-Ig injection (on days 100/102) had no impact on any parameters in spleen or bone marrow. The results establish that the half-life of 80 days for plasma cells determines the lifetime of the Ab response and that follicular dendritic cell-associated Ag drives the GC reaction early in the response to immunization but is not required for late Ab production.

Summaries written by Dorothy L. Buchhagen, Ph.D.