The Journal of Immunology

IN THIS ISSUE

J Immunol 2004; 173:7107-7108; ;
doi: 10.4049/jimmunol.173.12.7107
http://www.jimmunol.org/content/173/12/7107

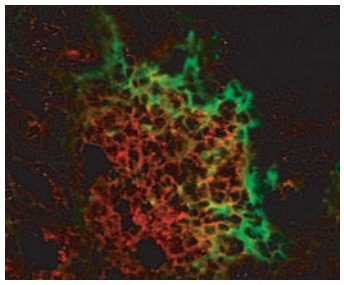
The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

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

THE JOURNAL OF IMMUNOLOGY

IN THIS ISSUE

Intestinal cryptopatch development



Development of Peyer's patches (PP) and isolated lymphoid follicles (ILF) in the small intestine requires interactions between lymphotoxin (LT) $\alpha_1\beta_2$ heterotrimers on inducer cells and LTβR on stromal cells. Similar interactions have not been demonstrated for cryptopatches (CP), a third type of lymphoid aggregate found in the small intestine. Taylor et al. (p. 7183) found by immunostaining with anti-c-*kit* Abs that crypts of small intestine from LT$\alpha^{-/-}$ mice lacked CP and by histological staining that LTβR$^{-/-}$ mice lacked lymphoid aggregates. However, mice deficient in NF-κB-inducing kinase had normal CP but no ILF. CD132 mice, which do not have peripheral lymph nodes or PP, rarely developed CP. Such mice also lacked splenic germinal centers after irradiation and reconstitution with T cell-depleted LT$\alpha^{-/-}$ bone marrow. In contrast, irradiated CD132 mice reconstituted with wild-type bone marrow developed CP and had normal-appearing spleens. LT$\alpha^{-/-}$ mice made chimeric with T cell-depleted wild-type bone marrow developed both CP and ILF. Irradiated CD132 mice that received a 1:1 mixture of T cell-depleted wild-type and LT$\alpha^{-/-}$ bone marrow developed CP and ILF consisting of cells from both donors. VCAM-1$^+$ cells were detected by immunostaining in the periphery of wild-type CP and in the CP and the B cell area of ILF of bone marrow-reconstituted CD132 mice. The authors suggest that cell interactions dependent on LTα and LTβR initiate CP development independent of NF-κB-inducing kinase and that novel VCAM-1$^+$ stromal cells are involved in CP and ILF development.

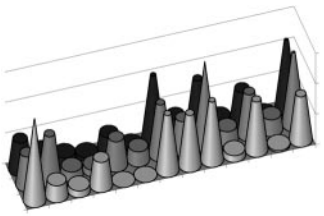
Inducing anergy

T lymphocytes that are stimulated through the TCR in the absence of CD28 costimulation become anergic and do not produce IL-2. However, the molecular factors that mediate anergy have not been identified. Harris et al. (p. 7331) used gene array screening to identify high level expression of early growth response gene-2 (Egr-2), a zinc-finger transcription factor, both in an Ag-challenged mouse CD4$^+$ T cell line anergized with immobilized anti-CD3 mAb and in fully activated T cells, but not in mock-stimulated controls. Only the anergic cells maintained high level Egr-2 mRNA expression for 5 days and Egr-2 protein expression for 9 days. Exposure of anergic cells to exogenous IL-2 up to 5 days poststimulation resulted in loss of Egr-2 protein. T cells in which the Egr-2 gene had been silenced by small interfering RNA (siRNA) before anergy induction had significantly lower levels of Egr-2 protein and had greater proliferation, IL-2 production, and ERK phosphorylation than anergic T cells that had not received siRNA. Electroporation of siRNA into T cells 5 days after anergy induction reduced Egr-2 protein levels but did not restore Ag responsiveness. The data indicate that Egr-2 contributes to the induction and maintenance of the anergic state in T lymphocytes and that addition of IL-2 abolishes anergy.

Streptococcus pneumoniae virulence factor

Removal of *Streptococcus pneumoniae* occurs through phagocytosis of bacteria coated with C cleavage products or Ab. Pneumococci, in turn, use their surface protein A (PspA) to shield themselves from C deposition and to increase their virulence. Yet, the specific C receptors involved in host defense are not known. Ren et al. (p. 7506) found that mice deficient in factor D (lacking an alternative C pathway) infected with either PspA$^+$ or PspA$^-$ *S. pneumoniae* had lower survival rates than wild-type controls. Clearance of PspA$^-$ pneumococci was delayed and survival was reduced in mice lacking complement receptors 1 and 2 (CR1/2$^{-/-}$) compared with controls. In contrast, mice lacking CR3 or CR4 had higher death rates after infection with PspA$^+$ pneumococci, yet had reduced clearance but complete survival after infection with PspA$^-$ bacteria. Mice deficient in LFA-1 or CD18 cleared both forms of pneumococci faster and had slightly longer or equal survival times, respectively, than wild-type animals. Infection-resistant CD18$^{-/-}$ mice had higher levels of naturally occurring anti-pneumococcal Abs than controls, whereas susceptible CD1/2$^{-/-}$ mice had lower levels of anti-phosphocholine Abs. More C3, in the form of iC3b, was deposited on PspA$^-$ bacteria than on PspA$^+$ bacteria incubated with normal mouse or human serum. The authors conclude that PspA interferes with the alternative C pathway that uses CR1/2, CR3, and CR4 in host defense against *S. pneumoniae* infection.

Intestinal T cells in human infants

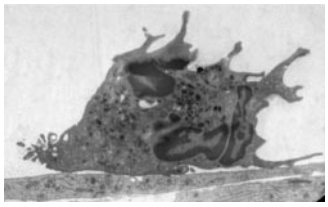


Although CD8$^+$ T cell maturation occurs among intestinal intraepithelial lymphocytes (IEL) in mice, little is known about T cell maturation in the human intestine. Williams et al. (p. 7190) examined by flow cytometry lymphocytes from intestine samples of patients ranging in age from 1 day to nearly 5 years. The percentage of IEL CD3$^+$ cells lacking expression of CD4 or CD8 dropped from 99% in a 6-day-old infant to 23% in a 12-mo-old child. CD3$^+$ cells coexpressing CD4 or CD8 (single positive (SP)) represented nearly 10% of IEL and lamina propria lymphocytes (LPL) from the small and large intestine; the percentage of SP increased with age. SP cells detected by immunohistochemistry were more numerous in LPL than in IEL in both small and large intestine of newborns. CD3$^-$ lymphocyte precursors were present at highest levels in patients younger than 9 mo. CD7$^+$ cells were more numerous than CD5$^+$ cells in LPL from small and large intestine; CD7$^+$ cells, but few CD5$^+$ cells, were found in IEL from

0022-1767/04/$02.00

either location. $CD5^+CD7^+$ cells were found in LPL but rarely in IEL. Transcripts for T early α transcript, TdT, and RAG were found by PCR in all cDNA samples prepared from intestines of infants 6 mo old or younger. TCR β-chain junctional sequences showed that the small intestine TCRBV6 and TCRBV12 repertoire was polyclonal, whereas the TCRBV4 repertoire was monoclonal at all ages; in contrast, the TCRBV6 and TCRBV4 repertoire was polyclonal in the large intestine. The findings indicate that large numbers of immature epithelial and mucosal T cells are present in the intestine at birth and differentiate to a polyclonal population during the first 12–18 mo of human development.

Neutrophil recruitment and transmigration

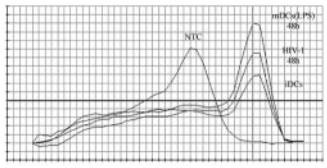


Neutrophils go to sites of inflammation, adhere to inflamed endothelial barriers, and migrate across the endothelium. However, mechanisms controlling these activities are poorly understood. Ariga et al. (p. 7531) used both pharmacological and genetic approaches to examine the impact of cAMP-degrading type 4 phosphodiesterases (PDE4s) on neutrophil recruitment to the lung in a mouse model of LPS-induced asthma. Four hours after exposure to LPS, mice deficient in PDE4B and PDE4D had neutrophil reductions of 31% and 48%, respectively, in bronchoalveolar lavage (BAL) but no significant decreases in numbers of circulating neutrophils or in chemokine levels in BAL compared with $PDE4A^{-/-}$ and wild-type mice. Treatment of $PDE4B^{-/-}$ or $PDE4D^{-/-}$ mice with a broad PDE4 inhibitor decreased neutrophil recruitment to levels observed with inhibitor-treated wild-type animals. CD18 expression was low in neutrophils recovered from BAL of $PDE4B^{-/-}$ and $PDE4D^{-/-}$ mice; mutant splenic neutrophils and PDE4 inhibitor-treated wild-type splenic neutrophils had reduced migration in an in vitro assay. Cinamon et al. (p. 7282) looked by real-time phase-contrast videomicroscopy at the ability of recruited and adherent neutrophils to cross HUVEC monolayers in vitro. The majority of neutrophils arrested on a TNF-α-activated monolayer transmigrated within minutes in the absence of chemoattractants or shear stress. Neutrophil adhesion, arrest, and transendothelial migration (TEM) in the presence of continuous physiological shear stress increased on resting HUVEC overlaid with the lipid chemoattractant platelet-activating factor (PAF); TEM was prevented by pre-exposure of the HUVEC to a PAF-R antagonist. Pre-exposure of the neutrophils to PAF or the antagonist had no effect. Neutrophil TEM through PAF-presenting moderately activated HUVEC was more rapid under shear flow, was partially dependent on integrins expressed on HUVEC, and was prevented by addition of IL-8. Electron microscopic analyses demonstrated neutrophil invaginations into nonactivated and moderately activated HUVEC surfaces and junctions in response to shear flow; no invaginations were seen in the absence of shear stress. Approximately 5% of these invaginations resulted in TEM. The picture that emerges from the two laboratories is that neutrophil expression of PDE4B and PDE4D cooperate to control migration to the inflamed lung. Subsequent TEM is dependent on integrin interactions, state of endothelial cell activation, and shear stress signals.

Peptidoglycan recognition

Organisms use host pattern recognition receptors to discriminate among, and defend against, invading microbes. However, the specific bacterial products recognized are not clearly defined. Stenbak et al. (p. 7339) used a combination of *Drosophila* cell culture and in vivo assays to analyze the specific structural components of peptidoglycans (PGs) recognized by a Toll-independent signaling cascade called the immune deficiency (Imd) pathway. Previously, the authors had shown that diaminopimelic acid (DAP)-containing PGs from Gram-negative and Gram-positive bacteria stimulated the Imd pathway via a specific PG recognition protein (PGRP). PGs from other Gram-positive bacteria in which lysine replaced DAP stimulated the Toll pathway but not the Imd pathway via a different PGRP. Reporter plasmids expressing pathway-specific antibacterial peptide genes confirmed those results in flies microinjected with purified PGs, and RT-PCR confirmed gene activation in a *Drosophila* cell line treated with PGs. By analyses of various digestion products and synthetic analogues, the authors determined that the minimal optimum motif for Imd pathway activation was a peptide containing *N*-acetylglucosamine plus *N*-acetylmuramic acid with a 1,6-anhydro bond that was connected to DAP by a 2-aa bridge. This PG motif is specific to Gram-negative bacteria. Modification of the sugar moieties, the anhydro bond, or the third amino acid (DAP) reduced Imd pathway induction.

HIV-induced DC maturation



Dendritic cells (DCs) are thought to carry HIV from mucosal tissues to $CD4^+$ T cells in lymphoid tissues. Yet the mechanisms by which the virus effects DC maturation and migration have not been delineated. Wilflingseder et al. (p. 7497) isolated immature DCs (iDCs) from healthy donors and exposed them to several strains of HIV. Cell sorting showed that maturation markers CD83 and CD86 on iDCs exposed for 2 days to virus or LPS were up-regulated compared with untreated controls; CCR7 mRNA expression also increased in the treated cells. ERK1/2 phosphorylation was induced in iDCs, but not in mature DCs, exposed to virus up to 4 h, but decreased when virus exposure was extended an additional 48 h; pretreatment of iDCs with p38 MAPK inhibitors enhanced ERK1/2 phosphorylation but kept DCs in the iDC state. Activation of p38 MAPK, a requirement for CCR7-dependent DC migration in chemotaxis assays in transwell experiments, was induced in both iDC and mature DC by HIV; DCs that migrated to the lower chamber infected unstimulated $CD4^+$ T cells. Incubation of iDCs with p38 MAPK inhibitors before HIV stimulation increased the ability of DCs to infect $CD4^+$ T cells in coculture. The authors conclude that differential MAPK signaling induced by HIV facilitates partial maturation of iDCs and their migration to lymphoid tissues.

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