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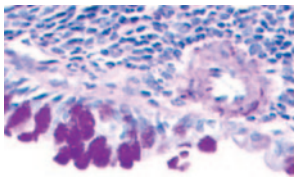
J Immunol 2005; 175:2767-2768; ;
doi: 10.4049/jimmunol.175.5.2767
http://www.jimmunol.org/content/175/5/2767

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.

IN THIS ISSUE

Smoking and asthma



Secondhand cigarette smoke is associated with an increase in allergic airway diseases, but the impact of mainstream or active tobacco smoke (MTS) on asthma is controversial. Robbins et al. (p. 2834) studied the effects of MTS in two murine models of experimental asthma. Mice exposed to cigarette smoke for 2–3 mo and sensitized to OVA in the presence of GM-CSF (MTS-GM/OVA) had splenocytes that produced higher levels of IL-4 and IL-5 in response to OVA and had serum levels of OVA-specific IgG2a 75% lower than sham-GM/OVA-exposed mice. The number and percentage of eosinophils and neutrophils in bronchoalveolar fluid (BAL) and the number of infiltrating eosinophils, dendritic cells, B cells, and $CD4^+$ T cells in lung tissue from MTS-GM/OVA mice were reduced compared with the sham-GM/OVA controls. Moderately enhanced levels of IL-5, IL-13, and eotaxin were measured in BAL from MTS-GM/OVA animals, which also exhibited decreased airway hypersensitivity to methacholine after OVA rechallenge compared with controls. In the second model, mice given ragweed pollen during the final week of MTS exposure had reduced numbers of BAL eosinophils, less airway mucus, increased production of IL-4, IL-5, and IL-13 by splenocytes, and lower allergen-specific IgG1 production compared with mice exposed only to ragweed pollen. The data suggest that MTS exposure increases Th2-associated cytokine production by splenocytes and, in contrast to secondhand cigarette smoke, attenuates eosinophilic inflammatory responses in lungs of mice challenged separately with two allergens.

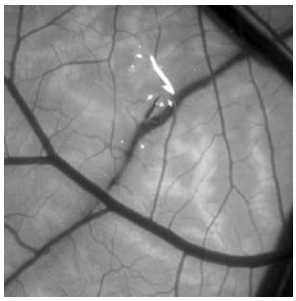
DCs and death from sepsis

Moldawer and colleagues recently demonstrated a loss of $CD11c^+$ dendritic cells (DCs) in spleen and lymph nodes in a mouse model of sepsis induced by cecal ligation and puncture. However, it is not known if DCs play a role in the septic response to microbes. In a study from the same laboratory, Scumpia et al. (p. 3282) selectively depleted DCs by injecting diphtheria toxin into mice transgenically expressing the diphtheria toxin receptor controlled by the CD11c promoter. Lymphoid and myeloid DC populations with a high expression of CD11c were depleted by 95 and 90%, respectively; plasmacytoid DCs, which express intermediate levels of CD11c, were reduced by 75%. Cecal ligation and puncture of DC-depleted transgenic mice resulted in 100% mortality compared with 45% mortality for wild-type controls treated with saline or diphtheria toxin. Blood bacteria levels and plasma concentrations of proinflammatory cytokines were comparable in the toxin-treated groups and were higher than in sham-operated controls. Only IL-18 levels were elevated in the treated transgenic animals. Bone marrow-derived DCs injected i.v. at the time of diphtheria toxin treatment reduced mortality among the transgenic mice from 100 to 65%. The authors demonstrate that $CD11c^+$ DCs play a critical role in preventing death in a mouse model of sepsis.

Protecting heart transplants

Graft survival in rats with allogeneic heart transplants is prolonged by treatment with α-melanocyte-stimulating hormone (α-MSH). However, the molecular mechanism by which this anti-inflammatory and immunomodulatory peptide exerts its effects is unknown. Colombo et al. (p. 3391) found less pathology in heart allografts from rats treated with the analog NDP-α-MSH than in those from rats given saline. Global gene expression profiles of 1267 genes determined by macroarray analysis on allografts harvested on days 1 and 4 after transplantation revealed two distinct gene clusters: genes overexpressed in treated allografts and reduced in untreated allografts and genes with the converse expression pattern. By day 4, a total of 172 genes that fell into five metabolic/regulatory pathways was modulated by peptide treatment, with up-regulated expression for genes involved in intracellular signaling cascades, protein phosphorylation, and glycolipid metabolism. Genes related to ribosome biogenesis and response to oxidative stress were down-regulated. Cluster analyses on the 172 genes identified three subsets with regard to expression patterns in response to NDP-α-MSH treatment. Expression patterns of 6 of the 172 genes were confirmed by real-time RT-PCR. This use of macroarray analysis reveals that improved graft survival and histology induced in rat heart transplants by NDP-α-MSH correlate with altered expression of gene clusters.

Myeloid DCs and angiogenesis



The resolution phase of the inflammatory response, facilitated by cytokines and chemokines released by dendritic cells (DCs), is characterized by enhanced angiogenesis. Yet, it is not clear that DCs play a direct role in angiogenesis. Riboldi et al. (p. 2788) matured human monocyte-derived DCs in vitro under one of two conditions. Classically activated DCs (CA-DCs) were obtained in the presence of LPS; alternatively activated DCs (AA-DCs) were obtained by a combination of LPS plus an anti-inflammatory molecule such as calcitriol, PGE_2, or IL-10. Expression of vascular endothelial growth factor (VEGF), but not fibroblast growth factor-2, was up-regulated in AA-DCs but not in CA-DCs as determined by RT-PCR and ELISA. IL-12 p40 expression was blocked in AA-DCs. Calcitriol stimulated VEGF production in the presence of

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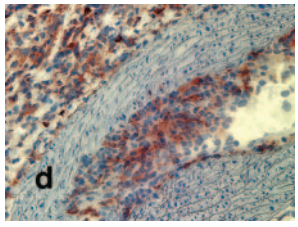
agonists other than LPS that induce DC maturation. Blood myeloid DCs, but not plasmacytoid or immature DCs, produced VEGF after treatment with LPS plus calcitriol or PGE_2. The response to calcitriol was concentration and time dependent. Supernatants from AA-DC contained two isoforms of VEGF and were able to induce ERK1/2 phosphorylation in endothelial cells transfected with VEGFR-2. An anti-VEGF Ab or a VEGFR-2 inhibitor blocked a potent angiogenic response induced by AA-DCs in an in vivo chicken embryo chorioallantoic membrane assay; CA-DCs were inactive in the in vivo assay. The data indicate that AA-myeloid DCs produce VEGF, which induces strong proangiogenic activities in vitro and in vivo.

NK cells and heart allograft rejection

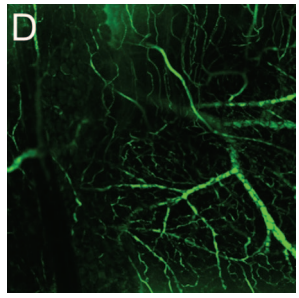


Cardiac allograft vasculopathy (CAV), which leads to progressive arteriosclerosis in a transplanted organ, occurs in >80% of human recipients by 5 years post-transplantation. Although T and B cells are known to contribute to CAV, contributions from cells of the innate immune system have not been documented. Uehara et al. (p. 3424) found advanced CAV in C57BL/6 (B6) hearts at 56 days after transplantation into (C57BL/6 × BALB/c)F_1 mice (F_1) that did not receive immunosuppressants. Cellular lesions containing NK cells, $CD8^+$ T cells, and macrophages were evident histologically at 21 days. Cytotoxicity of splenic NK cells from F_1 recipients of B6 hearts against target cells was greater than that of NK cells from F_1 recipients of F_1 hearts only up to 56 days after transplantation. T cells from F_1 recipients did not respond to B6 cells in MLR, and B6.RAG1$^{-/-}$ hearts failed to develop CAV when transplanted into F1.RAG1$^{-/-}$ recipients. CAV did develop in B6.RAG1$^{-/-}$ hearts transplanted into wild-type F_1 mice and in B6.RAG1$^{-/-}$ hearts in F1.RAG1$^{-/-}$ recipients adoptively transferred with naive F_1 $CD4^+$ T cells. Ab depletion of $CD4^+$ T cells plus NK cells in wild-type recipients prevented CAV development in transplanted F_1 hearts, whereas depletion of only $CD4^+$ T cells plus $CD8^+$ T cells did not. CAV developed in NKT cell-deficient F_1 recipients of wild-type B6 hearts. CAV did not develop in wild-type B6 hearts transplanted into F1.IFN$\gamma^{-/-}$ mice but did in B6.IFN$\gamma^{-/-}$ or B6.IFNγR$^{-/-}$ hearts transplanted into wild-type F_1 animals. The experiments demonstrate that NK cells interact with $CD4^+$ T cells to induce CAV during chronic rejection of heart transplants in a form of hybrid resistance mediated by host-derived IFN-γ.

Function of human M-ficolin

Two human serum lectins, L-ficolin and H-ficolin, associate with mannose-binding lectin-associated serine proteases (MASPs) and small mannose-binding lectin-associated protein (sMAP) to activate the lectin C pathway. It is not known if a third ficolin, M-ficolin, also is involved in the lectin C pathway. Liu et al. (p. 3150) molecularly cloned and purified human M-ficolin and produced an Ab against it. By immunohistochemistry, M-ficolin was detected in secretory vesicles and granules in the cytoplasm of peripheral blood neutrophils, monocytes, and lung type II alveolar epithelial cells. M-ficolin plus either MASP-1 or MASP-2 and sMAP were coimmunoprecipitated by anti-MASP-1 or anti-MASP-2 mAb from a mixture of M-ficolin and proMASPs. Activated forms of the MASPs and sMAP were produced after incubation of M-ficolin and proMASPs with *N*-acetylglucosamine (GlcNAc)-agarose plus Ca^{2+}. M-ficolin-MASP complexes activated C4 as measured by deposition of C4b onto GlcNAc-coated microplates. ^{125}I-labeled M-ficolin bound to GlcNAc-BSA, *N*-acetylgalactosamine-BSA, and sialyl-*N*-acetyllactosamine. Binding of M-ficolin to *Staphylococcus aureus* and the smooth-type strain of *Salmonella typhimurium* was demonstrated by flow cytometry. The results show that complexes of M-ficolin with MASPs and sMAP bind to specific carbohydrate ligands found in certain strains of bacteria to activate the lectin C pathway.

Regulating bradykinin formation



The peptide hormone bradykinin (BK), released from H-kininogen (HK) in several pathological conditions and bacterial infections, causes vasodilation, enhanced endothelial permeability, and vascular leakage in microcapillaries. The functional consequence of HK binding to glycosaminoglycans (GAGs) on endothelial cells is not known. Renné et al. (p. 3377) found that either of two GAGs, heparan sulfate or chondroitin sulfate, inhibited BK generation from HK in human plasma mediated either by enzyme FXIIa plus active plasma kallikrein (PKa) or by a mixture of neutrophil elastase and mast cell tryptase. Inhibition of BK release occurred with HK in solution or with HK attached to plate-bound GAGs. Four regions of HK that must be accessible for BK release were mapped using polyclonal Abs and mAbs and localized within two cell binding sites, the kinin domain and the PK binding site. Heparinase treatment of endothelial cell monolayers resulted in generation of BK from cell-bound radiolabeled HK. Increasing concentrations of two HK fragments, each containing one of the cell binding sites, reduced the fraction of uncleaved HK bound to the monolayers and increased the supernatant concentration of BK. A HK fragment lacking a cell binding site had no effect. In vivo confocal laser scanning micrographs of mouse intestine microcirculation showed increased leakage of FITC-dextran into surrounding tissue after topical application of FXIIa plus a HK fragment containing a cell binding site; similar treatment resulted in increased edema formation in mouse skin. The authors propose that BK generation at sites of tissue injury is regulated by HK binding to cell surface GAGs.

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