The Journal of Immunology

IN THIS ISSUE

J Immunol 2003; 170:5807-5808; ;
doi: 10.4049/jimmunol.170.12.5807
http://www.jimmunol.org/content/170/12/5807

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

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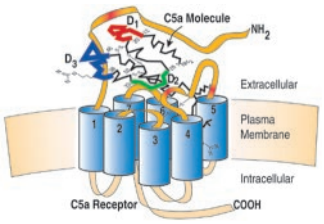
Three-point contact



The human complement activation product, C5a, plays a central role in host defense and inflammation. Site-directed mutagenesis studies of C5a previously implicated two regions in binding to the C5aR. Huber-Lang et al. (p. 6115) have further defined the regions of C5a/C5aR interactions. The investigators synthesized peptides derived from the amino (A) and carboxyl (C) termini, the middle (M) region, and from the each of the three loops (D1, D2, D3) of the C5a molecule as visualized by nuclear magnetic resonance and sequence analyses. Peptides with scrambled C and D2 sequences were used as controls. All peptides except D3 and the scrambled peptides significantly reduced binding of C5a to blood neutrophils in competition experiments. Preincubation with peptides M, C, D1, and D2 reduced neutrophil chemotactic responses to C5a but not to an unrelated chemotactic peptide. A, D3, and the scrambled peptides did not inhibit the chemotactic response of neutrophils to C5a. Pre-exposure of neutrophils to peptides A, M, C, D1, or D2, but not to D3 or the scrambled peptides, significantly reduced PMA-induced generation of H_2O_2. The data are consistent with a three-site binding model for C5a/C5aR interaction that includes discontinuous interacting sites and a newly recognized binding site (D2). The sites defined by the model represent possible targets for the development of C5aR-antagonists for intervention in the inflammatory response.

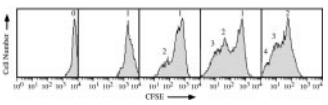
Notch1

Notch1 signaling promotes T cell commitment and inhibits B cell development of common lymphoid progenitors in the thymus. Yun and Bevan (p. 5834) used overexpression of two transcriptional targets of Notch1 signaling to define its role at different stages of T cell development. Notch regulated ankyrin repeat protein (Nrarp) was retrovirally transduced into AKR1010 thymoma cells in vitro. Overexpression of Nrarp blocked Notch1-induced up-regulation of CD3 and inhibited Notch1-induced activation of the transcription factor CBF-1 and CBF-1-activated genes. In addition, the transduced cells lost their Notch1-mediated resistance to glucocorticoid-induced apoptosis. Nrarp transduction into hematopoeitic stem cell precursors subsequently injected into lethally irradiated mice blocked the DN1 to DN2 and the DN2 to DN3 transitions in thymocyte development. Overexpression of Deltex-1, another transcriptional target of Notch1 signaling, also blocked T lineage commitment but did not inhibit CBF-1 activation or DN transitions through the DN2 stage. The data suggest that there are two Notch1 signaling pathways in T cell development that are differentially regulated by Nrarp and Deltex-1.

Anti-phosphocholine Abs

Phosphocholine (PC) is an antigenic determinant on microbial pathogens as well as on cells undergoing apoptosis and on neo-Ags formed in autoimmunity. Shaw et al. (p. 6151) examined the extent to which anti-PC Abs were cross-reactive in the innate and adaptive immune responses. The investigators set up a panel of six naturally occurring group I anti-PC Abs and two group II T cell-dependent anti-PC Abs generated in response to PC-protein conjugates. Most of the group I Abs bound to pneumococcal cell wall polysaccharide, PC-keyhole limpet hemocyanin (KLH), a PC-containing oxidation-specific epitope in atherosclerotic vascular lesions, and copper oxidized low-density lipoprotein (LDL). Binding was inhibited by PC-Cl salt, PC-KLH, or oxidized LDL. The group II Abs exhibited the same specificities except for recognition of pneumococcal cell wall polysaccharide. Macrophage rich areas of atherosclerotic lesions were immunostained with the group I and group II Abs that reacted with the PC determinant and oxidized LDL. Differences were seen in the reactivity of the two groups of PC-Abs with apoptotic cells; those of group I reacted with dexamethasone-treated thymocytes at an early stage, whereas those of group II reacted with thymocytes in the late stage of programmed cell death. The data indicate that Abs to PC haptens recognize related Ags in a variety of biological contexts including bacterial infections, autoimmunity, and apoptosis.

Fas-ter killing



Ag-specific CTL immunotherapy can be effective in treatment of tumors. However, loss of one specific target, Fas, often accompanies the malignant phenotype. Chakraborty et al. (p. 6338) studied the use of sublethal irradiation to increase the susceptibility of tumor cells to killing by CTL. A carcinoembryonic Ag (CEA)-expressing MC38 murine colon adenocarcinoma cell line (MC38-CEA$^+$) was subjected to a range of doses of ^{137}Cs irradiation. Irradiated MC38-CEA$^+$ cells had a significant increase in lysis by CEA-specific CTL compared with irradiated control MC38 cells. Anti-FasL, but not anti-ICAM-1, mAb inhibited CTL lysis of irradiated or unirradiated MC38-CEA$^+$ cells. Enhanced expression of Fas and ICAM-1 in both MC38 and MC38-CEA$^+$ cells was detected on the cell surface by flow cytometry and at the mRNA level by PCR. Fas up-regulation in both cell populations was found to last 96 days through four generations. Cells in tumors arising from MC38-CEA$^+$ cells injected into C57BL6 mice and irradiated in vivo had higher levels of Fas expression by immunohistochemistry compared with nonirradiated tumors. A combination of tumor irradiation and adoptive transfer of CEA-specific CTL resulted in a significant decrease in tumor growth rate with 50% of the mice resolving their tumors. The data suggest that a combination of

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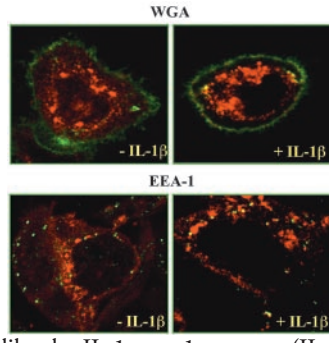
low-dose radiation and specific immunotherapy can lead to effective anti-tumor treatments.

A decoy scavenger



One avenue for treatment of chronic and acute inflammatory disorders is to control the availability of the proinflammatory cytokine IL-1. Bourke et al. (p. 5999) used freshly isolated human polymorphonuclear neutrophils (PMN) to examine the interaction of the membrane-bound IL-1 type II receptor (IL-1RII) with IL-1. Unlike the IL-1 type 1 receptor (IL-1RI), IL-1RII does not mediate cellular responses to IL-1 and has been called a decoy for IL-1 binding. Radiolabeled IL-1β incubated with the PMN disappeared rapidly from the medium at 37°C; radiolabeled IL-1β bound at 4°C rapidly internalized after subsequent incubation at 37°C and was released to the medium in a degraded form. Binding and internalization of IL-1β was blocked by prior incubation of PMN with a mAb to IL-1RII but not with a mAb to IL-1RI. Specific inhibitors of receptor-mediated and clathrin-mediated endocytosis inhibited IL-1RI internalization, as did sodium azide. IL-1RII reappeared on the cell surface ~15 min after internalization even in the presence of cycloheximide. Immunohistochemistry on a cell line stably transfected with IL-1RII demonstrated that the receptor colocalized with wheat germ agglutinin-labeled surface glycoproteins and the early endosome marker EEA-1 after exposure of the cells to IL-1. The data suggest that the IL-1RII is a decoy receptor that scavenges IL-1 before it can interact with the IL-1RI signaling receptor.

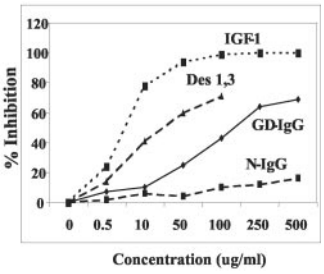
Tumor responsiveness to IFN-γ

IFN-γ sensitization of tumor cells to Fas-mediated apoptosis is used therapeutically and has been shown to be more effective against primary as opposed to metastatic tumors. Liu and Abrams (p. 6329) studied IFN-γ-induced gene expression and IFN-γ-mediated signaling to determine the mechanism of reduced responsiveness of some neoplastic cells to IFN-γ treatment. The authors used two sets of paired cell lines: human primary and metastatic colon adenocarcinoma, and mouse primary and metastatic mammary carcinoma. Both primary tumor cell lines had higher Fas mRNA and higher levels of cell surface Fas than their counterpart metastatic tumor cells before or after IFN-γ treatment. Genome level screening indicated that the intensity of genes up- or down-regulated by IFN-γ was much greater in the primary than in the metastatic tumor cells. Specific gene expression profiling identified two genes differentially involved in responsiveness to IFN-γ. IFN consensus sequence binding protein (ICSBP) and caspase-1 were induced by IFN-γ to higher levels in the primary tumor cells. Fas-mediated death was observed only under conditions where both ICSBP and caspase-1 were coexpressed. The inability of metastatic tumor cells to express more than modest levels of ICSBP and caspase-1 after IFN-γ treatment or to undergo Fas-mediated apoptosis suggests a mechanism by which tumors can escape IFN-γ-based anti-tumor therapies.

OX40 and cryptococcal infection

OX40 is up-regulated on activated T cells 1–2 days after Ag encounter. However, the role of this costimulatory signal during pathogen infection is not clear. Humphreys et al. (p. 6125) studied the impact of OX40 expression on the pulmonary eosinophilia induced in C57BL/6 mice by *Cryptococcus neoformans* (Cn) infection. Eosinophilia, Cn CFU, and $CD4^+$ T cell levels peaked at 11–14 days postinfection. Administration of OX40L:Ig fusion protein to Cn-infected mice at various times after infection increased OX40-expressing $CD4^+$T cell infiltration into the lungs but had no effect on uninfected mice. After day 12, OX40L:Ig-treated infected mice exhibited significantly lower levels of Cn and eosinophils and increased intracellular IFN-γ production compared with untreated Cn-infected animals. These results were dependent on IFN-γ and IL-12 as OX40L:Ig-treated Cn-infected IFN-γ and IL-12 knockout mice were unable to reduce the pathogen burden or eosinophilia below that of Cn-infected wild-type mice. The numbers of $CD4^+$ T cells in OX40L:Ig-treated Cn-infected IFN-γ and IL-12 knockout mice increased to levels comparable to those seen in Cn-infected wild-type mice. The results suggest a novel strategy to enhance immunity to eosinophil-inducing infectious diseases through the manipulation of the OX40 costimulatory signal.

Graves' disease



Autoreactive IgGs are known to be involved in some of the manifestations of Graves' disease (GD) including T cell infiltration into orbital tissues. However, the mechanism by which GD-specific IgG (GD-IgG) from patients' sera stimulate expression of T cell chemoattractants IL-16 and RANTES is not well understood. Pritchard et al. (p. 6348) examined orbital and skin fibroblasts from control and GD patients for chemokine production and T cell chemotaxis. GD cells, but not cells from non-GD patients, produced IL-16 and RANTES and influenced T cell migration after treatment with GD-IgG. Insulin-like growth factor-1 (IGF-1) and the IGF-1R-specific ligand, Des (1–3) IGF-1, mimicked the GD-IgG effect, implicating the IGF-1R in the interaction with GD-IgG. An IGF-1R-specific Ab completely attenuated the GD-IgG effects on cell migration and chemoattractant expression, as did transient transfection of a dominant negative IGF-1R mutant receptor into the GD fibroblasts. Flow cytometry indicated that GD fibroblasts expressed higher levels of IGF-1R than controls. A total of 80% of ^{125}IGF-1 was displaced by GD-IgG in competitive binding assays, confirming a direct interaction between GD-IgG and IGF-IR. The data suggest therapy aimed at blocking IGF-IR activation might be beneficial in treating GD.

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