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THE JOURNAL OF IMMUNOLOGY

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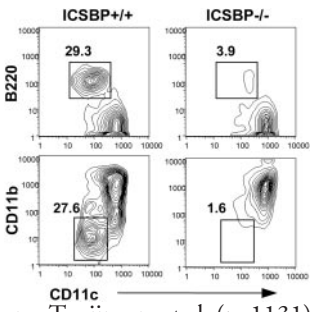
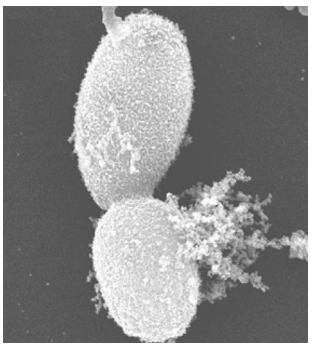
Plasmacytoid dendritic cell development



Dendritic cells are the most effective of the APCs, activating lymphocytes to mediate an immune response and tolerizing T cells to self-Ags. Two distinct subsets of dendritic cells, myeloid dendritic cells and the type I IFN-producing plasmacytoid dendritic cells, have been identified in mice and humans. Tsujimura et al. (p. 1131) examined the developmental regulation of both myeloid and plasmacytoid dendritic cells in mice lacking the transcription factor IFN consensus sequence binding protein (ICSBP)/IRF-8. ICSBP/IRF-8 knockout mice lacked plasmacytoid dendritic cells, and although myeloid dendritic cells were present, they failed to mature upon Toll-like receptor stimulation. Transfection of ICSBP/IRF-8 into cultured bone marrow cells from ICSBP/IRF-8 knockout mice rescued the development of plasmacytoid dendritic cells and restored the ability of both plasmacytoid and myeloid dendritic cells to mature in response to Toll-like receptor signaling. The data show that the transcription factor ICSBP/IRF-8 controls the development of plasmacytoid dendritic cells and the Toll-like receptor-mediated maturation of myeloid dendritic cells, demonstrating molecular differences between these two dendritic cell lineages.

Doing double duty



Antimicrobial peptides are abundant in the storage granules of phagocytic cells and on the surface of mucosal tissues. Some antimicrobial peptides have been shown to possess chemotactic properties. The chemokine CCL28 is selectively expressed in mucosal tissues such as the salivary and mammary glands, the trachea, and the colon, and it signals through the receptors CCR10 and CCR3. Hieshima et al. (p. 1452) investigated the antimicrobial activity of CCL28. The tissues where CCL28 is expressed secrete low-salt fluids that would satisfy the requirement of most antimicrobial peptides for low-salt conditions for their activity. The authors found that CCL28 exerted antimicrobial activity by rapidly inducing membrane permeability under low-salt conditions against a broad range of organisms, including both Gram-positive and Gram-negative bacteria and *Candida albicans*. The C terminus of human CCL28 showed sequence homology with the candidacidal peptide histatin-5. CCL28 was highly expressed in epithelial cells of both mouse and human salivary glands and was secreted in human saliva and milk at high concentrations. The authors also found that in mouse salivary glands, CCL28 chemoattracts CCR10 expressing CD3-B220^{low} cells that, morphologically, are typical plasma cells. The findings thus indicate that CCL28 possesses dual functional properties in mucosal immunity.

Call up the reserves

TCRs interact with an array of ligands of varying potency to mediate responses such as thymocyte selection, proliferation, and cytokine secretion. Because only a small percentage of the TCRs on a cell appear to be needed for a response to agonist ligands, what is the role of the "extra," or reserve, receptors? Receptor reserve theory postulates that a maximal response can be achieved by an agonist occupying only a small percentage of available receptors, whereas weak or partial agonists must bind more receptors to achieve a maximal response. McNeil and Evavold (p. 1224) examined the effect of reducing TCR levels on CD4$^+$ T cell responses to altered peptide ligands of varying efficacy. They limited the available TCRs either by using dual receptor T cells or by blocking with anti-TCR Fab. In keeping with the proposals of receptor reserve theory, they found that T cells need more available receptors to respond to low-affinity ligands than they do to respond to high-affinity ligands. The results point to possible mechanisms whereby excess TCRs enable T cell responses to weak ligands.

Contraceptives and autoimmunity

Because of an increased incidence among women and increased remission rates during pregnancy, there is considerable interest in the role of sex hormones in the autoimmune disease multiple sclerosis. Subramanian et al. (p. 1548) investigated the effect of orally administered ethinyl estradiol, an estrogen compound found in oral contraceptives, on the onset and progression of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. They found that ethinyl estradiol protects against the development of actively induced EAE when given at initiation of the disease and ameliorates disease progression when administered after its onset. The authors showed that ethinyl estradiol inhibited infiltration of CD4$^+$ T cells into the CNS, as well as decreasing chemokine and proinflammatory cytokine production, serum IgG2a levels, and matrix metallo-proteinase-9 expression. The level of TGF-β3 expression increased in the CNS of EAE mice following ethinyl estradiol treatment. Ethinyl estradiol thus appears to act by inhibiting T cell and macrophage migration into the

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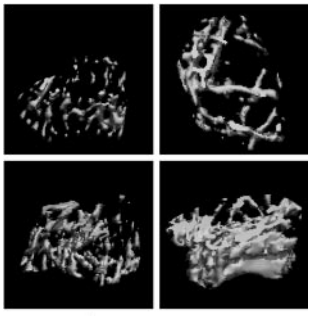
CNS. The work suggests oral contraceptives as a candidate for investigation in treating ongoing autoimmune inflammatory disease.

Polypeptide vaccines

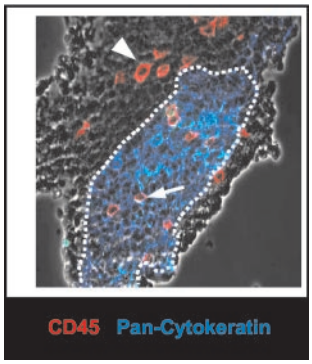
A major challenge in developing effective immunotherapy against tumors has been overcoming limitations imposed by the HLA class I pathway. Exogenous full-length proteins require dendritic cells or other professional APCs for processing for presentation, yet may not induce an immunogenic response. Use of short synthetic peptides is limited by the HLA class I haplotype of the patient. Gnjatic et al. (p. 1191) present an innovative vaccination strategy to overcome the drawbacks of using either full-length proteins or short peptides. The authors used two 30 amino acid polypeptides (30-mers) derived from NY-ESO-1, a protein that is expressed in germ cells and some tumors, to show that $CD8^+$ T cells could be stimulated in the absence of professional APCs. In vitro, these polypeptides were taken up by B cells, T2 cells, and PBLs and proteolytically digested intracellularly to 9 amino acid fragments (nonamers) that were presented by HLA class I molecules. Overlapping nonamers from within the 30-mer were recognized by a $CD8^+$ T cell clone specific to one of the nonamers. These findings offer the possibility of eliciting $CD8^+$ T cell responses against a protein by vaccinating a patient with a series of overlapping peptides regardless of the class I determinant(s) contained within the peptide.

Increased bone density in B6-*gld* mice

Although it is not intuitively obvious, there are many similarities between the immune system and bone. Their origins, development, and maintenance share many support cells and processes, including Fas-mediated apoptosis. Katavic et al. (p. 1540) used these similarities to explore bone homeostasis in the C57BL/6 mouse model of generalized lymphoproliferative disorder (B6-*gld*) that lacks a functional Fas ligand. B6-*gld* mice were found to have greater total bone mineral density and increased trabecular bone volume compared to $B6^{+/+}$ mice. Ovariectimized B6-*gld* mice lost one-fifth as much bone mass as similarly treated $B6^{+/+}$ mice and had enhanced osteogenic regeneration after bone marrow ablation of the tibiae as determined by bone density scans. Osteoclast-like cells in bone marrow cultures were fewer in ovariectimized and bone marrow-ablated B6-*gld* animals, and osteoprotegerin (OPG) gene and protein expression were at higher levels in those cells. These differences underscore the importance of the Fas/FasL pathway in the regulation of osteoblast differentiation, activation, and life span and suggest that the higher expression of OPG mRNA and protein in the B6-*gld* animals is critical for the maintenance of terminally differentiated osteoclasts. This study offers the intriguing possibility that OPG is a regulatory link between bone and the immune system.



Where does T cell lineage commitment begin?



Signaling through the Notch family of transmembrane receptors is often involved in the developmental fate of multipotent cells. Conflicting data exist over whether the commitment of lymphocyte progenitors to the T cell lineage occurs in the thymus or in prethymic environments. Harman et al. (p. 1299) examined the role of Notch signaling in intrathymic vs extrathymic T cell lineage-commitment. They showed that although Notch is expressed in fetal liver lymphoid precursors, entry into the thymic epithelial microenvironment is required for Notch activation. Correlating with this finding, the expression of Notch ligand genes on fetal liver stroma was greatly reduced compared with their expression on thymic epithelial cells. The data support a role for Notch in T cell lineage commitment involving sustained interactions with thymic epithelium expressing Notch ligands.

Dendritic cell activation of NK cells

Both dendritic cells and NK cells are important in the initiation of the immune response. While dendritic cells are known to activate resting NK cells, the mechanism of activation is unclear. Using an in vitro coculture system of human monocyte-derived dendritic cells with NK cells, Jinushi et al. (p. 1249) found that different dendritic cell stimuli lead to different, non-overlapping mechanisms of dendritic cell-mediated NK cell activation. LPS-stimulated dendritic cells activated NK cells via release of IL-12, whereas IFN-α specifically induced MICA and MICB expression on dendritic cells, enabling them to activate NK cells. (MICA and MICB are ligands for the activating NK cell receptor NKG2D.) The IFN-α-mediated MICA/B induction was absent on dendritic cells from patients with chronic hepatitis C virus infection, suggesting that this mechanism of NK cell activation may play a role in hepatitis C infection. The data identify a ligand/receptor pair involved in dendritic cell activation of resting NK cells, illuminating the molecular dialogue between NK cells and dendritic cells that serves as an early polarizing event in the immune response.

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