Abs and airway remodeling

Growth of new blood vessels, enlargement of pre-existing ones, and expansion of lymphatics and epithelial cell hyperplasia occur in chronically inflamed airways. However, factors inducing this “airway remodeling” are not known. Aurora et al. (p. 6319) found extensive reorganization of vascular beds and epithelial cell hyperplasia in tracheae of wild-type C57BL/6 mice but not of syngeneic mice lacking B cells, T cells, or both (Rag1−/−) by 4 wk postinfection (p.i.) with Mycoplasma pulmonis. Bacteria had disseminated to livers and kidneys only in mice deficient in T or B cells. Invading lymphatics in infected wild-type mice were positive for vascular endothelial growth factor receptor-3. Dramatic remodeling of blood and lymphatic vasculature was seen by 14 days p.i. in B cell-deficient mice given serum from infected wild-type mice starting at day 3 p.i. Tracheae of the recipients exhibited proliferation of endothelial cells and immune complex deposition. Whereas infected wild-type and Rag1−/− mice had neutrophils in their tracheae 14 days p.i., only wild-type mice had high numbers at 31 days p.i. Infected wild-type mice had neutrophils with low levels of CD62L and macrophages with high levels of MHC class II compared with control animals. Multiplexed real-time PCR for expression of 15 genes in bronchoalveolar lavage samples indicated up-regulation of macrophage/neutrophil activation genes in infected Rag1−/− but not wild-type mice and up-regulation of immune complex signaling pathway genes in wild-type compared with Rag1−/− mice. The data demonstrate that airway remodeling in chronic disease requires both a T cell-dependent antibacterial Ab response and immune complex deposition.

Lymphopenia-driven proliferation of CD8+ T cells

Lymphopenia-driven proliferation (LDP) of naive CD8+ T cells requires IL-7 and TCR-mediated recognition of low-affinity self-peptide/MHC complexes; LDP of memory cells requires IL-15 and self-peptide/MHC complexes. CD11chigh DCs promote LDP of naive and memory CD8+ T cells.

Controlling lethal virus infection

Long-term control of persistent infections of noncytopathic viruses requires both CTL and Abs. It is not known if a CD8+ T cell response in the absence of Ab is sufficient to protect against acute disease and death induced by cytopathic viruses. Fang and Sigal (p. 6829) inoculated CD40−/− mice with ectromelia virus (ECTV), a mouse pathogen that induces mousepox. Although the animals remained healthy for 3 wk, all developed disease and died by 50 days postinfection (p.i.). Control ECTV-infected naturally resistant C57BL/6 (B6) mice remained healthy through 72 days p.i., and CD8−/− mice succumbed to virus infection by day 12 p.i. Spleen virus titers were comparable in B6 and CD40−/− mice but considerably lower than in CD8−/− animals early in infection. Virus titers increased dramatically in CD40−/− mice late in infection, and the animals produced a poor anti-ECTV Ab response compared with B6 mice. Whereas the early CD8+ T cell response in vivo and virus-specific CTL activity in vitro were similar in B6 and CD40−/− mice, the CD40−/− mice had a sustained CD8+ T cell response in late infection in contrast to B6 mice, which developed memory cells. CD8−/− mice adoptively transferred with CD8+ T cells from CD40−/− animals survived ECTV infection as well as B6 mice. Mice lacking B cells had CD8+ T cell, Ab, and viral responses to ECTV infection similar to those of CD40−/− mice and all died by 62 days p.i. Transfer of B6 B cells or anti-ECTV antiserum into CD40−/− mice rendered them resistant to ECTV. The authors conclude that CD8+ T cells are essential during the early phase of infection with highly pathogenic virus ECTV and that virus-specific Abs are required for virus elimination during the late phase.

Dynamics of HIV-specific CD4+ T cell proliferation

Much detail is known about CD4+ T cell destruction and the CD8+ T cell response to HIV infection. Less is known about the CD4+ T cell response. Seth et al. (p. 6948) used three HIV p24 peptides to generate 10 different MHC class II tetramers. HIV p24 tetramer+ cells were identified in four groups of HIV patients: long-term nonprogressors, a patient with a low virus load, patients...
undergoing antiretroviral therapy (ART), and patients off therapy. Highest frequencies of tetramer+ cells were detected in the first two groups. Kinetics of the CD4+ T cell response to HIV throughout the course of the disease was measured using frozen PBMCs taken over a number of years. Analyses on magnetic bead-enriched, tetramer-labeled cells indicated a close relationship between level of viral replication and kinetics of the CD4+ T cell response to the virus. ART decreased the high viral load and high frequency of tetramer+ cells seen before therapy; virus and cell numbers expanded when ART was discontinued and decreased upon resumption of therapy. Cessation of treatment resulted in high viremia and rapid disappearance of HIV p24 tetramer+ cells. The phenotype of HIV p24 tetramer+ T cells identified during acute infection was CCR7+CD45RA+ and was maintained even during periods of low viremia. The memory phenotype was CD28+ and CD27+ or CD27- and IL-7R+ or IL-7R+. The majority of tetramer+ cells produced IFN-γ. The authors conclude that HIV p24-specific effector memory cells initially respond to high levels of HIV Ags but are lost in the face of constant viremia.

Vaccinating against EAE

oral delivery of purified fimbrine colonization factor Ags (CFA), which increase the virulence of enterotoxigenic Escherichia coli, does not elicit Ig protection against “traveler’s diarrea.” However, high Ab titers and a response dominated by Th2 cells were elicited by a live attenuated Salmonella vector expressing enterotoxigenic E. coli CFA/I developed by Pascual and colleagues. Jun et al. (p. 6733) in the Pascual laboratory looked at the effect of Th2-type response to Salmonella-CFA/I vaccine on a Th1 cell-dominant autoimmune disease, experimental autoimmune encephalomyelitis (EAE). SJL/J mice developed serum Abs after oral administration of the vaccine. Vaccinated mice had milder clinical manifestations of EAE induced by an enterotoxigenic proteolipid peptide and recovered by 21 days after EAE induction compared with control mice injected with PBS or empty vector. Spinal cord sections of Salmonella-CFA/I-vaccinated mice lacked the demyelination and inflammatory cell infiltrates seen in controls. Lymphocytes from various organs of vaccinated mice produced high levels of IL-13, IL-4, and IL-10 and low levels of IFN-γ after ex vivo stimulation with the enterotoxin peptide compared with lymphocytes from control mice. The data showed that reduced clinical and histopathological parameters in EAE in SJL/J mice orally vaccinated with Salmonella-CFA/I occurs by immune deviation to a Th2 response.

Lung transplant ischemia-reperfusion injury

patient injury from ischemia-reperfusion injury is the most common cause of mortality early after lung transplantation. Neutrophils have been implicated in the injury; however, their precise role has not been determined. Belperio et al. (p. 6931) found elevated levels of CXCL3, CXCL7, and CXCL8 in bronchoalveolar lavage fluid of patients with ischemia-reperfusion injury compared with healthy controls. To study the implications of this finding, the investigators developed a rat model of cold ischemia-reperfusion injury. Microvascular permeability, as determined by leakage of Evans blue dye, peaked at 16 h after transplantation in lung allografts and isografts vs sham-operated controls; injury in both groups resolved at 24 h. By 48 h, another increase in lung microvascular permeability was seen only in the allografts. Increased myeloperoxidase, CXCL1 and CXCL2/3 protein and CXCLR2 mRNA levels were seen in lung tissues from both types of grafts at 8 and 16 h. Chemokine and CXCLR2 levels decreased to control levels at 24 h, but CXCL2/3 protein and CXCLR2 mRNA levels in the allograft lungs increased again at 48 h. Allograft recipients that had been passively immunized with neutralizing anti-CXCR2 Ab 24 and 3 h before allograft lung transplantation had lower levels of myeloperoxidase and attenuated ischemia-reperfusion injury at 16 h after transplantation compared with controls. The experiments demonstrate an association between several CXC chemokines, neutrophil sequestration, and acute lung injury following post-lung transplantation ischemia-reperfusion injury in a rat model.

Cyclin T1 expression in T cells

Activation of primary T cells by mitogens or costimulation with anti-CD3/anti-CD28 Abs up-regulates cyclin T1. Activation also stimulates HIV replication via a Tat-associated kinase, a complex of cyclin T1 plus cyclin-dependent kinase 9 (CDK9). However, the signaling pathway and mechanism responsible for cyclin T1 up-regulation by PHA or PMA are unknown. Marshall et al. (p. 6402) found increased protein levels of cyclin T1 and CDK9 in PBLs from healthy donors stimulated with PHA and/or PMA. PHA, but not PMA, stimulated cyclin T1 mRNA expression with slow kinetics; cycloheximide increased the rate of cyclin T1 mRNA accumulation, and actinomycin D increased its half-life. PHA did not stimulate a luciferase reporter lentivirus construct under control of the cyclin T1 promoter transfected into PBLs, but control LTR-luciferase viruses were stimulated by PHA. Pretreatment of PBLs with a specific JNK inhibitor prevented PHA-induced phosphorylation of c-Jun and up-regulation of cyclin T1 mRNA and cyclin T1 and CDK9 protein; the inhibitor had no effect on PMA-induced c-Jun phosphorylation. A calcineurin inhibitor blocked cyclin T1 mRNA and protein up-regulation and prevented accumulation of CDK9 protein but had no effect on JNK activity in PHA-treated cells. Pretreatment of cells with an inhibitor of a calcium-independent protein kinase C blocked PMA-stimulated cyclin T1 protein up-regulation; cyclin T1 protein half-life increased in PBLs treated with cycloheximide before PMA stimulation. Anti-CD3 Ab treatment of PBLs also up-regulated cyclin T1 and CDK9 protein levels. Both mitogens increased expression of RNA polymerase II and induced phosphorylation of its C-terminal domain. The data indicate that PHA and PMA act by different mechanisms to increase cyclin T1 protein levels by up-regulating mRNA levels and by stabilizing cyclin T1 protein, respectively, in stimulated quiescent T cells.

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