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T Cell Help in Tumors

Not only is CD4+ T cell help necessary for the clonal expansion of activated CD8+ T cells, it is also necessary for increased tumor infiltration by these cells. Wong et al. (p. 3122) have constructed an elegant study that examines whether this help is delivered during CD8+ T cell priming in the secondary lymphoid organs or if the presence of CD4+ T cells in the tumor microenvironment is important. Using the RIP-Tag2-HA model of spontaneous pancreatic insuloma development, the authors demonstrated that recipient RIP-Tag2-HA mice that received hemagglutinin (HA)-specific CD4+ T cells (SFE), low avidity HA-specific CD8+ T cells (Clone 1), and a recombinant vaccinia virus expressing HA (vacHA) had much greater tumor destruction than RIP-Tag2-HA mice that received Clone 1 and vacHA vaccine alone. One of the benefits of this model is that tumor size could be determined by blood glucose levels; as such, hypoglycemia was a sign of tumor growth and tumor destruction was indicated by hyperglycemia. The provision of tumor-specific CD4+ T cell help from the SFE cells not only enhanced tumor destruction but clonally expanded the vacHA-primed CD8+ T cells and increased intratumoral CD4+ and CD8+ T cells. To dissect out the importance of CD4+ T cell help during priming from intratumoral interaction, Clone 1 cells were primed in vivo in the presence of D011.10 CD4+ T cells with a vaccine expressing both OVA and HA. This produced even greater clonal expansion of Clone 1 cells but 10-fold less CD8+ T cell infiltrate in pancreatic insulomas than mice that received the SFE cells and vacHA. Thus, the authors demonstrate that tumor-specific CD4+ T cell help is necessary for CD8+ T cell tumor infiltration and destruction and that this function is separate from the CD4+ T cell influence on CD8+ priming in the secondary lymphoid organ.

CD27 Enhances CD8+ T Cell Memory

A TNF receptor family member, CD27 is a costimulatory molecule present on naive CD8+ T cells, NK cells, and some B cells. In response to influenza A infection, mice deficient in CD27 produce normal effector CD8+ T cells that are cytotoxic and produce IFN-γ; however, the total number of responding pulmonary T cells is reduced. To determine what role CD27 plays in regulating antiviral CD8+ T cells, Dolfi et al. (p. 2912) treated influenza-infected mice with a blocking anti-CD27L Ab. Consistent with the data from CD27+/− mice, blocking CD27L had no effect on the function of Ag-specific effector CD8+ T cells generated during infection but did decrease the number of CD8+ T cells. This was due to a defect in CD4+ T cell help, as anti-CD27L had no effect on the production of antiviral CD8+ T cells in class II-deficient mice. Interruption of the CD27-CD27L interaction during viral infection increased the number of CD8+ T cells undergoing CD95/Fas-mediated apoptosis. However, this was only during the primary response to viral infection, as no qualitative or quantitative differences were seen in the generation of influenza Ag-specific CD8+ T cells after secondary infection and anti-CD27L treatment. Taken together, these data demonstrate that CD27 costimulation enhances antiviral T cell memory by promoting survival of effector cells during the primary response.

Chlamydia vs IFN-γ

Chlamydia infections are a costly drain on the U.S. healthcare system; an effective animal model with which to study these infections is therefore important. The current model of Chlamydia muridarum infection in mice has shown conflicting evidence about the role of IFN-γ, which is known to be essential for the cure of human infection. Li et al. (p. 3375) used intranasal immunization of mice with chlamydial protease-like activity factor (CPAF) and CpG to examine the role of IFN-γ when Ag-specific T cells were adoptively transferred into infected mice. The authors found that Ag-specific CD4+ T cells that produced IFN-γ infiltrated the genital tract and that local IFN-γ secretion was correlated with C. muridarum clearance. The importance of IFN-γ was confirmed, as IFN-γR-deficient mice were not able to clear the bacteria after adoptive transfer of the CPAF-specific CD4+ T cells from IFN-γR−/− vaccinated mice, but the same cells transferred into C. muridarum-challenged IFN-γ−/− mice mediated clearance. Finally, bacterial immunity was dependent on the MHC II pathway, because MHCI-deficient β7−/− mice vaccinated with CPAF + CpG completely resolved C. muridarum infection as did vaccinated wild-type mice. Thus, as in human disease, IFN-γ is necessary for murine antichlamydial immunity, and targeting the MHC II pathway with soluble Ag could be a possible vaccination strategy in mice, but more importantly, in humans.

Memory T Cells and IL-7Rα

The expression of IL-7Rα has been hypothesized to be important for Ag-specific CD4+ and CD8+ memory T cell survival. To test if this was true, Haring et al. (p. 2855) infected mice that constitutively expressed IL-7Rα in both CD4+ and CD8+ T cells (IL-7RαTg) with Listeria monocytogenes and followed the survival of memory CD4+ and CD8+ T cells. Surprisingly, they found that constitutive expression of IL-7Rα had no effect on the expansion and survival of CD8+ T cells responding to infection or on their ability to produce IFN-γ. Although there was a slightly increased expansion of Ag-specific CD4+ T cells in these mice, the surviving memory T cells were comparable in number and phenotype to those in wild-type mice. IL-7RαTg mice were equally able to protect themselves against a secondary Listeria infection and had similar expansions of CD4+ and CD8+ Ag-specific T cells as did wild-type mice. Naïve mice that received the same lethal challenge of Listeria did not survive.

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The authors concluded that IL-7Rα constitutive expression does not play a role in improving the survival or increasing the number of Ag-specific memory T cells following either primary or secondary bacterial infection.

**Epithelial Stat1 in Innate Defense**

An active role in host defense to paramyxovirus has been hypothesized for respiratory epithelia, but because many of the relevant molecules are also found in immune cells, this has been difficult to prove. Shornick et al. (p. 3319) have used the common mouse paramyxovirus (Sendai virus (SeV)) to recapitulate early events in viral respiratory infection to address this problem. The authors demonstrated that SeV infection activated IFN-β and Stat1 in airway epithelial cells. Based on this evidence, they infected Stat1-deficient (Stat1<sup>-/-</sup>) mice with SeV and found that these mice were extremely susceptible to infection compared with wild-type mice. Moreover, the virus was predominantly localized in the airway epithelia in Stat1<sup>-/-</sup> mice but was undetectable in wild-type epithelia. The respiratory pathology seen in Stat1<sup>-/-</sup> mice was comparable with severe paramyxoviral human infection and was characterized by increased viral replication and neutrophil recruitment. Infection increased TNF-α and CXCL2 production over wild-type levels in Stat1<sup>-/-</sup> epithelia both in vitro and in vivo, and TNF-α blockade reversed the production of CXCL2. While irradiated wild-type mice reconstituted with Stat1<sup>-/-</sup> bone marrow were still resistant to infection, Stat1<sup>-/-</sup> mice reconstituted with wild-type bone marrow maintained their susceptibility, thus confirming that Stat1 in the airway epithelia was responsible for maintaining viral resistance. Taken together, these data demonstrate that Stat1 signaling in the airway epithelia is critical for defense against SeV respiratory infection.

**Fc Receptors and Tuberculosis**

The significance of humoral immunity in Mycobacterium tuberculosis infection has been debated for some time; however, B cells have recently been shown to be necessary for protection against this bacterium in mice. Maglione et al. (p. 3329) hypothesized that B cells mediated their protective effects through the Abs produced in infection and the engagement of Fc receptors. When C57BL/6 mice deficient in the inhibitory FcγRIIB (RIIB<sup>-/-</sup>) were infected with <i>M. tuberculosis</i>, there was less pulmonary infiltrate, greater IFN-γ production, and reduced bacterial burden when compared with infected wild-type mice 30 days after infection. Infected RIIB<sup>-/-</sup> mice also had reduced lung neutrophilia, an indicator that correlates with better disease outcome in humans. Infected RIIB<sup>-/-</sup> mice had increased expression of MHC II, B7.1, and B7.2 and enhanced macrophage production of Th1-associated IL-12p40, all correlating with the reduced bacterial burden at the 30-day postinfection time point. To test the role of activating Fc receptors, which share a common γ-chain, in <i>M. tuberculosis</i> infection, the authors infected Fc γ-chain-deficient mice and found significantly greater mycobacterial burden in the lungs and spleens. Compared with wild-type controls, these mice had significantly reduced IFN-γ-producing T cells, increased pulmonary neutrophilia, and increased Th2-associated IL-10 production. Thus, Fc receptors play an integral role in controlling mycobacterial responses and immunity by controlling the Th1/Th2 balance.

**TREM-Activated Innate Immunity**

Triggering receptor expressed on myeloid cells-1 (TREM-1) is an orphan receptor that elicits a proinflammatory response through an ITAM when cross-linked. Found on monocytes, macrophages, and neutrophils, TREM-1 has been shown to amplify cellular responses to LPS, which signals through TLRs. Dower et al. (p. 3520) used microarrays to characterize global gene expression changes that occurred when human monocytes were treated with a cross-linking anti-TREM-1 Ab, with LPS, or with both. Choosing a short time point (2 h) to reflect events directly induced by treatments, the authors demonstrated that both TREM-1 activation and LPS treatment induced proinflammatory molecules such as TNF family members, chemokines (i.e., CXCL3, CXCL2, CXCL5, and CCL3), matrix metalloproteinases, and COX-2. TREM-1 activation also induced SPP1 (osteopontin) and M-CSF, whereas LPS alone induced genes including IL-23 and G-CSF. There was synergy between the two stimuli administered in combination that led to an increase in IL-1β and GM-CSF proteins, and this increase was Wortmannin sensitive, indicating that it was regulated by the PI3K pathway. TREM-1 activation also suppressed the IL-12p40 and IL-23 that were induced by LPS, but this effect was not PI3K sensitive, indicating that TREM-1 signaled through different pathways. Taken together, these data elucidate the function of TREM-1 in monocyte signaling and provide evidence for cross-talk between TREM-1 and TLR during early inflammatory events.

**Building Better siRNA**

Synthetic small interfering RNA (siRNA) duplexes are recognized by TLR7 on plasmacytoid dendritic cells and cause secretion of IFN-α. So while the nucleotide duplexes can cause sequence-specific degradation of messenger RNA, the immunological consequences have made drug development and siRNA-based therapies difficult. To get around this problem, Eberle et al. (p. 3229) used biochemical modifications and reside replacement strategies to determine whether they could create a siRNA that was effective at silencing an mRNA target without eliciting an IFN-α response. This strategy was based on the hypothesis that the receptor responsible for the immunostimulatory effects of siRNA could differentiate a greater specificity of structure than the RNA-induced silencing complex (RISC) that is responsible for RNA interference (RNAi). RNA was modified at the 2'-position to remove the 2'-oxygen (deoxy derivative) or add a methyl group (2'-O-methyl derivative). EGFP or β-galactosidase in transfected cells were the target mRNAs, and IFN-α responses were measured from oligonucleotide-treated human PBMCs. Oligonucleotides with 2'-O-methyl groups on adenosine or uridine residues inhibited both IFN-α secretion and the gene silencing activity. When uridine residues were substituted with 2'-deoxyuridine or thymidine, IFN-α secretion was reduced. However, only thymidine substitutions could achieve comparable RNA silencing as unmodified oligos with a reduced stimulation of the type I IFN response. These data indicate the possibility of using siRNA in therapeutic applications without adverse immune side effects.

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