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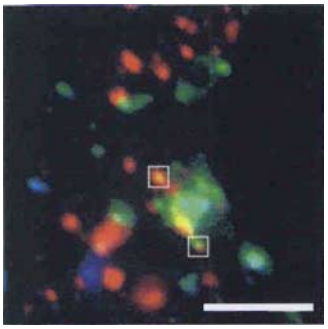
In This Issue

How to Effect a Targeted Delivery



How to deliver an Ag to the most appropriate subcellular compartment for the most effective presentation is of interest to anyone who studies immune responses and develops new vaccine strategies. Mi et al. (p. 7550) investigated exploiting the localization of the neonatal Fc receptor (FcRn) to the endolysosomes of APCs as a tool to target Ag. The authors created fusions of the N-terminal epitope of myelin basic protein (MBP) with mouse IgG1-derived recombinant Fc molecules. To deliver Ags to FcRn-expressing APCs with more efficiency, Fc fragments were generated to have increased affinity for FcRn at pH 6.0–7.4. Unfortunately, T cell proliferative responses demonstrated that this greater affinity could not be seen in vivo due to the decreased half-life of the targeted Ag. Specificity of fusion protein binding and Ag presentation due to the FcRn vs the FcγRs was verified by using an aglycosylated form of Fc-MBP. Thus, the authors demonstrate that in vitro Ag presentation efficiency can be improved by lysosomal targeting of the Ags through the participation of FcRn, but Ag persistence becomes the determining factor in vivo.

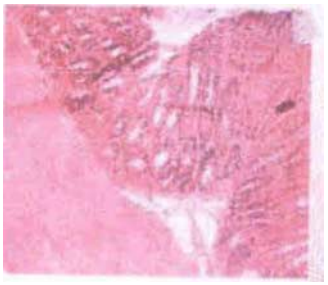
The H Factor

Immunology students may view memorizing the alternative complement pathway with dread, but new work by Huang et al. (p. 8068) will give them a greater incentive to do so. Building on previous work showing that linking the complement inhibitor Crry to a fragment of complement receptor 2 (CR2) accentuated the efficacy of this molecule, the authors created complexes of alternative complement pathway inhibitor factor H (fH) linked to the same fragment of CR2. In mice, the new complex (CR2-fH) was more effective at blocking C3 deposition than the fH available in the serum. Because CR2 is a receptor that targets the products of C3 activation, it was not surprising that the efficacy of this complex was dependent on CR2 and C3 interactions. What was surprising was that CR2-fH or CR2 linked to a dimeric fH (CR2-fHfH) provided complete protection from intestinal ischemic reperfusion injury (IRI), as serum fH provided no protection despite the role that the alternative pathway plays in intestinal IRI. CR2-fH and CR2-fHfH also provided protection from remote lung injury in the intestinal IRI model. CR2-fH reduced injury by locally blocking levels of C3 deposition, a function of being targeted to the site of injury. Thus, these data indicate that the alternative pathway plays an important role in controlling both intestinal and lung injury in a recognized model of intestinal IRI.

Vaccinia and OX40

Used in a live virus preparation, vaccinia virus (VACV) immunization is best known for protecting recipients against smallpox. Therefore, how the virus generates protective immunity is of great interest. To address this question, Salek-Ardakani et al. (p. 7969) examined how the TNFR-related molecule OX40, otherwise known as CD134, contributed to the generation of $CD8^+$ T cells specific for VACV. Aided by the recent discovery of the VACV epitopes responsible for $CD8^+$ T cell responses, the authors determined that OX40-deficient mice infected with VACV had a 50% decrease in virus-specific $CD8^+$ T effector cells. Generation of IFN-γ and TNF-α was also reduced in VACV-infected $OX40^{-/-}$ animals when compared with wild-type infected mice. Adoptive transfer experiments of OX40-deficient $CD8^+$ TCR transgenic T cells in the context of VACV infection confirmed that the strong cytokine and memory responses seen in wild-type mice were a result of OX40 expression on T cells. In addition, OX40-deficient mice were not able to protect themselves against a lethal challenge of VACV. This protection was CD8 dependent, as depletion of the $CD8^+$ T cells in wild-type VACV-challenged mice resulted in 100% mortality. Thus, the OX40 costimulatory pathway plays an important role in boosting anti-VACV $CD8^+$ T cell responses.

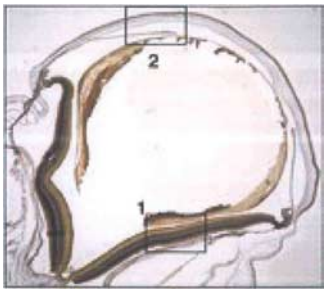
Neutrophils Crossing the Mucosa



A common hallmark of inflammatory mucosal conditions is the transmigration of neutrophils across the epithelial barrier. The severity of both infectious and autoimmune inflammation of intestinal and pulmonary mucosa is correlated with the degree of neutrophil infiltration. Pazos et al. (p. 8044) used in vitro and in vivo models, as well as human tissue from patients with inflammatory bowel disease (IBD), to comprehensively investigate how neutrophils travel to the lumenal surface of the gastric epithelium. The neutrophil chemoattractant hepoxilin A_3, an eicosanoid produced by 12-lipoxygenase and secreted at the apical surface of gastric epithelium, creates the gradient that bridges the last step in neutrophil recruitment across tight epithelial junctions to the lumen. The authors demonstrated that hepoxilin A_3 is a substrate for the multidrug resistance protein 2

(MRP2), an apical efflux ATP-binding cassette transporter. Both in vitro and in vivo models of intestinal inflammation showed that inflammation increased the expression of MRP2. Intestinal inflammation could be reduced by blocking the synthesis of hepoxilin A_3 or inhibiting the ability of MRP2 to function. Examination of biopsies from patients with IBD showed an increase in MRP2 expression. Taken together, the data not only explain how neutrophils cross the final tight epithelial junction that separates them from the lumen but also point to a novel therapeutic target in neutrophil-dependent inflammation.

Eyeing Suppression



Exposure of T cells to ocular pigment epithelium renders them unable to respond to TCR stimuli. However, after interaction with these specialized cells, T cells are capable of suppressing the activation of their bystanding brethren. With the knowledge that retinal pigment epithelial cells (RPEs) secrete soluble T cell-suppressive factors, Sugita et al. (p. 7525) asked whether RPEs secrete factors that generate T regulatory cells (Treg). They found that RPEs secreted CTLA-2α, a cathepsin L (CathL) inhibitor that converted $CD4^+$ T cells into Treg in vitro. These Treg were of the $CD4^+CD25^+FoxP3^+$ phenotype and secreted TGF-β. RPE cells treated with small interfering RNA to CTLA-2α were unable to induce the generation of Treg. The activity of CathL in T cells was responsible for the conversion to Treg, as CTLA-2α suppressed CathL activity in T cells and T cells increased their expression of FoxP3 in the presence of a CathL inhibitor. TGF-β signaling was implicated in the action of CTLA-2α, because TGF-βRII was necessary for Treg induction. Thus, the secretion of CTLA-2α from RPEs induces the production of Treg and explains the T cell-mediated immune tolerance in the posterior portion of the eye.

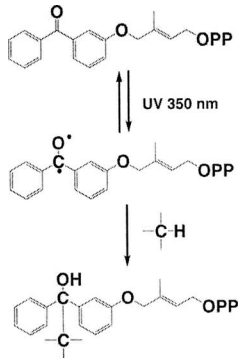
Filling a Gap in HIV Research

Until now, there has been no good cellular model to study the latent stage of HIV and try out new therapeutics for viral control. Latency allows viral evasion of immune responses as well as avoidance of the effects of antiretroviral therapy. Because HIV specifically exploits the events inherent in $CD4^+$ T cell clonal expansion and subsequent contraction, the use of clinical samples and chronically infected cell lines are of limited use. To address this deficiency in the experimental toolkit, Marini et al. (p. 7713) have developed an elegant model for HIV latency using human primary $CD4^+$ T cells. The authors took human $CD4^+$ T cells activated with Ag-loaded dendritic cells, infected the T cells in vitro, and then brought them back to quiescence with IL-7. At rest, cellular activation markers, cell proliferation, and viral replication were eliminated but could be rescued by stimulation with Ag-loaded dendritic cells or anti-CD3/CD28. This secondary stimulation caused higher levels of cell death in HIV-1-infected cultures compared with uninfected cultures, a difference that was not seen during primary stimulation. Thus, the authors have developed a novel system to study the mechanism of HIV latency and $CD4^+$ T cell interaction with the virus.

Viruses That Make You Share

Both CMV and EBV generate $CD8^+$ T cell responses that are characterized by a few dominant TCR clonotypes. These TCRs can be "public," meaning that they are shared between MHC-matched individuals. Previous work from this group has analyzed the nature of public TCRs and found that the generation of epitope-specific TCRβ-chains can be linked to more efficient production of TCRβ through a process they term "convergent recombination." In this work, Venturi et al. (p. 7853) analyzed almost 3000 TCRβ sequences from both CMV- and EBV-infected patients to determine what causes the sharing of TCRs in $CD8^+$ T cell responses to two HLA-A*0201-restricted viral epitopes. The amino acid sequence analysis indicated that the shared TCR β-chains were produced as efficiently as possible, characterized by the necessity of fewer nucleotide (N region) additions and by the nucleotide sequences that encoded them having greater variety. In silico analysis of random VDJ recombination confirmed that the most common shared sequence was produced more frequently than others. Thus, TCRβ production frequency helps determine how individual $CD8^+$ T cell responses to CMV and EBV generate shared TCRβ sequences.

Not the Usual Suspects



A subset of $\gamma\delta$ T cells, Vγ2Vδ2 T cells, recognize small, nonpeptide prenyl pyrophosphates that are synthesized by bacteria and apicomplexan parasites. These molecules, including (*E*)-4-hydroxy-3-methylbut-2-enyl-pyrophosphate (HMBPP) and isopentenyl pyrophosphate (IPP), are recognized by the Vγ2Vδ2 TCR. However, an APC is necessary for recognition, as these prenyl pyrophosphates do not directly bind the Vγ2Vδ2 TCR. Mutation of CDRs of these TCRs abrogates recognition, again pointing to the need of an APC scaffold for Ag recognition. However, identifying a specific Ag presentation molecule for these unique Ags has been unsuccessful. To identify this elusive molecule, Sarikonda et al. (p. 7738) used photoaffinity analogues of HMBPP that are capable of being presented to $\gamma\delta$ T cells by cross-linking to the surface of tumor cells. They found that tumor cell lines lacking MHCI, MHCII, β_2-microglobulin, and CD1, as well as lines from a variety of tissues and individuals, were all able to present the HMBPP analog. This suggests a nonpolymorphic common binding partner that does not encompass any of the usual suspects. The search for the novel Ag presentation molecule of these unique but important Ags will have to continue.

Summaries written by Kira R. Gantt, Ph.D.