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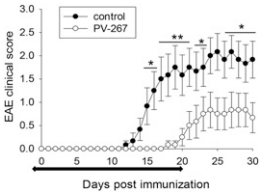
A Small Molecule Step toward Treating MS

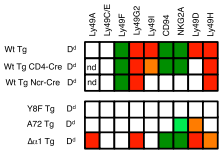


Multiple sclerosis (MS) is characterized by the presentation of autoantigens by MHC II molecules that trigger activation of and cytokine production by autoreactive T cells and subsequent destructive inflammatory processes. Sixty percent of MS patients express the disease-associated MHC II allele HLA-DR2b (DRB1*15:01) that presents various myelin Ags, leading to an immune response against the myelin nerve sheath and disease symptoms. Different therapeutic attempts, such as modifying downstream inflammation, specific immunotherapy, and T cell–targeted approaches, have been only modestly successful due to undesirable immune responses and safety concerns. In this study, Ji et al. (p. 5074) describe the development of PV-267, a small molecule inhibitor of peptide binding and presentation by HLA-DR2b. Using the crystal structure to visualize key interactions of HLA-DR2 with bound MBP85–99 peptide, the authors identified a five-residue sequence, PV-267, exhibiting high HLA-DR2 binding affinity and selectivity. PV-267 inhibited both Ag-induced cytokine production and proliferation of HLA-DR2b–restricted T cells from an MS patient. This inhibitory effect did not affect anti-CD3–stimulated T cells, showing that inhibition was specific for MHC:peptide-mediated signaling. PV-267 specifically inhibited responses from HLA-DR2b–restricted T cells but not from nonspecific T cells or PBMCs from healthy donors expressing other MHC molecules. The authors evaluated the efficacy of PV-267 on experimental autoimmune encephalomyelitis (EAE) prevention and treatment using HLA-DR2b transgenic mice inoculated with MOG35–55 peptide. Treatment with PV-267 prior to induction of EAE significantly delayed disease onset and severity, whereas treatment with PV-267 after EAE onset ameliorated disease and led to a faster recovery. These results support the use of a small molecule inhibitor of HLA-DR2b as a promising therapeutic strategy for the treatment of MS with minimal risk of off-target effects.

Modulating To Escape Abs

Antibodies mediate tissue damage through either Ab-mediated complement activation or FcγR opsonization of cellular targets. Although several pathways that protect against complement-mediated destruction have been described, no parallel pathways protecting against FcγR ligation by Abs have been elucidated. Here, Stowell et al. (p. 5013) describe a novel phenomenon, termed "Ag modulation," whereby Ab-induced alterations to recognized Ags lead to a reduction in surface-bound Abs. To evaluate cellular clearance and protection against Ab-mediated clearance, the authors used an Ag–Ab model in which RBCs expressing the HOD model Ag (Ag^+), which provides several distinct immunological epitopes, function as cellular targets in Ag-negative (Ag^-) recipients. I.v. transfer of Ag^+ and Ag^- RBCs into mice passively immunized with an anti-HOD Ab (anti-Fy3) resulted in a significant decrease in the survival of Ag^+ RBCs compared with Ag^- RBCs. Interestingly, these experiments also identified a population of Ag^+ RBCs that were resistant to clearance as a result of a process termed "Ag modulation," whereby the amount of detectable Ag on Ag^+ RBCs decreased after transfer into anti-Fy3 immunized mice. RBC clearance was directly correlated with the level of surface Ab, with higher Ab levels leading to faster clearance. Clearance and Ag modulation were also observed in mice lacking either the C3 or C5 components of the complement pathway, but not in mice lacking functional FcγR, suggesting that both of these processes are independent of the complement pathway and require the FcγR. In this study, the authors provide evidence of a novel pathway protecting against FcγR-mediated Ab damage.

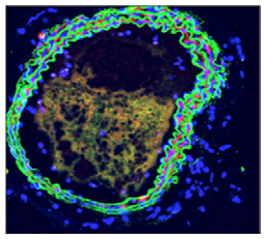
Approaches to NK Cell Education



Natural killer cells mount rapid cytotoxic responses following recognition of missing or aberrant self and have been shown to adapt to the presence of specific MHC I molecules through a process known as NK cell education. This education results in modifications in the cell's repertoire of MHC I–specific receptors and in functional tolerance of self-MHC I through changes in receptor responsiveness termed licensing. The Ly49 receptors on murine NK cells, as well as the LILRB receptors on human NK cells, can recognize MHC I both on other cells (trans) and on the NK cell itself (cis). To reconcile discrepant data regarding the roles of cis versus trans MHC I recognition in NK cell education, Bessoles et al. (p. 5044) analyzed how NK cells maturing under steady state conditions were affected by cell type–specific deletion of MHC I or expression of Ly49A variants. Deletion of H-$2D^d$ expression in either NK cells or T cells, which eliminated Ly49A:MHC interactions in cis or in trans, respectively, significantly impaired NK cell function. Similarly, NK cells were unable to undergo functional adaptation if they expressed an Ly49A variant specifically unable to interact with its H-$2D^d$ ligand in cis, one unable to interact in trans, or one lacking an intact ITIM domain. Taken together, these data demonstrated that both cis and trans interactions between Ly49A and H-$2D^d$ were necessary for NK cell licensing. Interestingly, modification of the MHC I receptor repertoire in NK cells was found to require cis, but not trans, interactions. NK cell education therefore requires "tutoring" via both cis and trans interactions between MHC I

molecules and NK cell receptors, suggesting that these two different types of interactions may perform distinct functions.

Provoking Platelets



Platelets express TLR4 and participate in sepsis following this receptor's stimulation by LPS. Because TLR4 and the receptor for the proinflammatory cytokine IL-1 act through common intracellular signaling components, Brown et al. (p. 5196) investigated mechanisms by which platelets might produce and/or be activated by IL-1. Human platelets were found to express IL1R1, but not IL1R2, and IL-1β acted on IL1R1 to promote its own production via an autocrine loop. The active IL-1β produced by platelets was associated with microparticles shed by these cells. Similar to the action of LPS, IL-1β stimulation led to activation of MyD88 and resulted in atypical platelet activation that included a failure to stimulate degranulation. Effective LPS-mediated stimulation in both human and mouse platelets was found to require signaling through IL-1R1 and splicing of pro–IL-1β heteronuclear RNA to its active form. Using a model of arterial thrombosis to visualize activated platelets in vivo, the authors found that IL-1β accumulated over time in platelets immobilized in occlusive thrombi. This accumulation did not require de novo RNA synthesis, suggesting IL-1β production occurred by the mechanism of posttranscriptional RNA splicing observed in vitro. These data connect thrombosis to the development of chronic inflammation and reveal a mechanism by which IL-1β and LPS work together to activate platelets.