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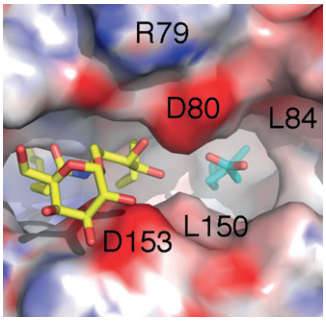
THE JOURNAL OF IMMUNOLOGY

In This Issue

May the Best Glycolipid Win



Natural killer T cells expressing the invariant Vα14-Jα18 TCR α-chain (Vα14*i* NKT cells) are a lineage of T cells that have roles in both innate and adaptive immune responses through recognition of glycolipid Ags. NKT cell detection of glycolipid Ags complexed with CD1d molecules influences downstream Th cell polarization, which led Sullivan et al. (p. 141) to investigate the NKT cell-associated mechanisms contributing to Th cell biasing. Treatment of mice with α-galactosyl ceramide (αGalCer) or the αGalCer analog C-glycoside induced a Th1-biased response, but a Th2-biased response was observed in mice treated with the structurally different αGalCer analog OCH. Compared with αGalCer, OCH and C-glycoside showed reduced TCR avidity and stability when bound to CD1d, with C-glycoside/CD1d complexes having the weakest in vitro interactions with the TCR. Surprisingly, C-glycoside contributed indirectly to Th1 cell polarization in mice by inducing significantly more IFN-γ production from NK cells compared with OCH. C-glycoside and αGalCer, but not OCH, formed stable complexes with CD1d on the surface of APCs in vivo and induced sustained stimulation of NKT cells in mice. These results indicate that C-glycoside can induce Th1 polarization through protracted in vivo TCR stimulation of NKT cells, thus revealing that glycolipid pharmacokinetic properties influence Th cell biasing.

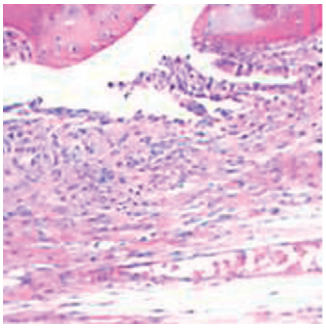
Evasion through Dimerization

Staphylococcus aureus has developed multiple strategies to elude destruction by complement, including secretion of staphylococcal complement inhibitor (SCIN), which inhibits C3 convertase enzymes. Jongerius et al. (p. 420) now show that SCIN facilitates dimerization of convertases and reduces binding to complement receptors, thus hindering phagocytosis of complement-coated bacteria. SCIN was shown to induce dimerization of C3bBb C3 convertases (SCIN-convertases), but dimerization of SCIN-convertases was not required for inhibition of C3 convertase activity in fluid phase, as a mutant lacking the dimerization motif (SCINΔC3b_2) inhibited convertase as effectively as SCIN. In contrast, dimeric SCIN-convertases dramatically inhibited neutrophil phagocytosis of *S. aureus* in vitro, but phagocytosis was only partially blocked by monomeric convertases formed with SCINΔC3b_2. Phagocytosis inhibition by dimeric SCIN-convertases was attributed to weaker binding of C3b in these complexes to complement receptor 1 (CR1) and complement receptor of the Ig superfamily (CRIg). In addition, CR1 bound weakly to the surface of *S. aureus* opsonized with dimerized SCIN-convertases, suggesting that these complexes concealed the bacterial surface from CR1. These results provide more evidence of the unique strategies pathogens develop to elude the complement system.

Stress Triggers Leukocyte Flight

Stress-induced mobilization of leukocytes is part of early rapid responses to injury or infection, but the fundamental mechanisms driving leukocyte movement are poorly understood. Dimitrov et al. (p. 503) have investigated this phenomenon by characterizing the leukocyte subsets responsive to epinephrine in human peripheral blood based on changes in chemokine receptor and adhesion molecule expression. Low levels of epinephrine were infused into healthy male adults to mimic mild stress and to specifically activate PBMCs expressing β_2-adrenergic receptors. Five cytotoxic effector cell subsets that all shared a $CD62L^{-}CD11a^{bright}CXCR1^{bright}$ phenotype increased significantly and rapidly in peripheral blood following epinephrine infusion compared with placebo treatment. They included $CCR7^{-}CD45RA^{+}CD8^{+}$ T cells, γδ T cells, NKT-like cells, cytotoxic NK cells, and proinflammatory monocytes. Except for monocytes, adhesion of each of these subsets to activated epithelium was reversed in vitro by epinephrine treatment, confirming in vivo observations. Identification of these epinephrine-induced subsets in the circulation highlights the importance of cytotoxic effector cells as first responders to assaults on the immune system.

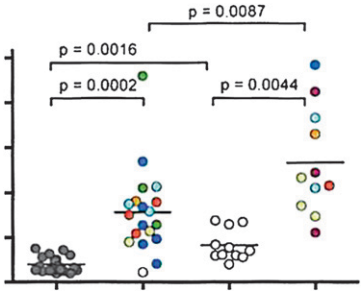
Fibrinogen Feeds into Arthritis



Surprisingly little is known about the causes of rheumatoid arthritis (RA) at a molecular level beyond the observations that the clotting protein fibrin accumulates in the joints of RA sufferers and that RA development is also correlated with increasing levels of autoantibodies against citrullinated proteins, including the fibrin precursor fibrinogen. Ho et al. (p. 379) have developed a new mouse model of fibrinogen-induced arthritis (FIA) that resembles RA pathogenesis in humans. In this study, DBA/1 and SJL mice immunized with human fibrinogen developed arthritis symptoms. Higher levels of proinflammatory cytokines, including TNF-α, IFN-γ, IL-6, and IL-17, were produced by splenocytes from mice with FIA compared with control mice, suggesting a link between fibrinogen-specific T cells and arthritis. Similar to human RA sufferers, FIA-afflicted mice displayed immune complex formation and Ab responses against anti-cyclic citrullinated peptides and rheumatoid factor. Transfer of fibrinogen-specific T cells or plasma

from fibrinogen-immunized mice also induced arthritis, providing further evidence that fibrinogen is an arthritogenic Ag. This new mouse model implicates fibrinogen as a key player in initiating Ab and T cell responses responsible for arthritis development. Further studies are needed to confirm these findings in humans.

Exhausting Long-Term Relationships



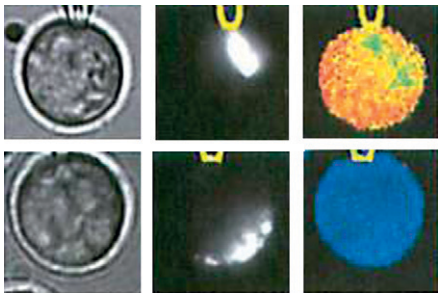
In this issue, two articles explore new roles of the inhibitory TCR coreceptor programmed death 1 (PD-1) in T cell responses to chronic viral infections. PD-1 is upregulated during persistent Ag exposure and has been linked to T cell exhaustion. Salisch et al. (p. 476) have determined that PD-1 expression on HIV- or SIV-specific T cells can also serve as a gauge of low-level viral replication. Increased PD-1 expression correlated positively with viral load and negatively with total $CD4^+$ T cell counts in rhesus macaques infected with a pathogenic SIV, confirming similar observations in HIV-infected humans. Nonpathogenic live attenuated SIV (LASIV) infection did not correlate with a global increase in PD-1 expression on memory T cells, but PD-1 expression was detected on SIV-specific $CD8^+$ T cells during infection with LASIV, even in the absence of detectable virus replication. PD-1 expression declined on $CD8^+$ T cells specific for SIV epitopes that were subject to escape mutations, and together these results showed that maintenance of PD-1 expression required very little viral replication. These findings were confirmed in HIV-infected humans, in which the frequency and expression of PD-1 on HIV-specific $CD8^+$ T cells were lower in HIV-infected elite controllers than in chronically infected individuals. Thus, PD-1 not only is a marker and mediator of exhaustion but also may be a sensitive indicator of viral replication.

In the second article, Frank et al. (p. 277–286) show that $CD4^+$ Th cells are required during early HSV-1 infection to prevent $CD8^+$ T cell exhaustion and to preserve HSV-1 latency in the trigeminal ganglia (TG). Mice depleted of $CD4^+$ T cells could not maintain HSV-1 latency in the TG during effector T cell responses 8–35 d post infection (dpi), but they recovered control of latent infection by 56 dpi. Effector $CD8^+$ T cells specific to an immunodominant HSV-1 glycoprotein B peptide ($gB_{498–505}$) displayed reduced HSV-1 Ag gB peptide avidity and polyfunctionality in the TG of mice depleted of $CD4^+$ T cells (nonhelped) compared with $CD4^+$ T cell-intact (helped) mice. The avidity of gB-specific $CD8^+$ T cells was significantly higher in the TG than in noninfected lungs during memory formation, implicating a role for these cells in HSV-1 latency. Reduced functionality of gB-specific effector $CD8^+$ T cells in nonhelped mice correlated with increased PD-1 expression, indicating partial exhaustion, but functionality was preserved in nonhelped mice by blockade of PD-1 with programmed death ligand-1. These data show that $CD4^+$ T cell help during primary HSV-1 infection contributes to the development of high-avidity $CD8^+$ T cell responses, which may be crucial to formation of a memory T cell pool that can preserve latency.

Out of Frame but in the Mix

Experimental HIV vaccines using DNA or adenovirus vectors have produced mixed results in clinical trials but are still considered as frontrunners because they can induce T cell responses that limit or control HIV replication, thereby limiting disease progression. Previous studies of CTL responses to HIV or SIV infection and vaccination have revealed that little is understood regarding HIV/SIV Ag processing. In their paper, Maness et al. (p. 67) describe the observation that vaccination of *Mamu-A*02*$^+$ rhesus macaques with recombinant DNA or adenovirus vectors including all SIV genes except envelope (*env*) unexpectedly induced strong CTL responses against an Env peptide. This potent response mapped to a *Mamu-A*02*–restricted Env peptide, $Env_{788–795}$RY8 (RY8), which was shown previously to induce a subdominant response during SIV infection, compared with other peptides. The source of the RY8 peptide was identified as a portion of *rev* exon 2 that overlapped *env* in the DNA plasmid encoding the reverse transcriptase (*rev*) gene. RY8 peptide presentation was attributed to translation from an alternate reading frame in the *rev* plasmid and was also observed in a Rev-expressing recombinant adenovirus. These findings reveal that unanticipated open reading frames may provide sources of T cell epitopes that have the potential to dramatically alter the intended outcomes of vaccine trials.

Mitochondrial Road Block



Immunological synapse (IS) formation between Th cells and APCs is required to initiate Th cell activation. The essential role of Ca^{2+} influx through Ca^{2+} release-activated Ca^{2+} (CRAC)/Orai1 channels for Th cell activation is widely accepted, but the comparative influence of local Ca^{2+} influx at sites like the IS or global influx throughout the plasma membrane has not been resolved. Schwindling et al. (p. 184) now show that Ca^{2+} influx through any area of the plasma membrane induces mitochondrial accumulation at the IS, and mitochondrial colocalization with the IS promotes local Ca^{2+} influx at this site. They confirmed previous observations that mitochondrial movement to the plasma membrane during IS formation entailed Ca^{2+} influx through CRAC channels and also observed that mitochondrial translocation required actin rearrangement. Mitochondria moved to the site of IS formation upon Ca^{2+} influx, but this movement was independent of the Ca^{2+} entry site. Local Ca^{2+} entry at the IS was facilitated by the ability of nearby mitochondria to take up Ca^{2+}, which prevented inactivation of CRAC channels and supported higher levels of Ca^{2+} influx. These observations therefore link the spatial position of mitochondria to the mechanism of Ca^{2+} entry during IS formation.

Summaries written by Christiana N. Fogg, Ph.D.