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THE JOURNAL OF IMMUNOLOGY

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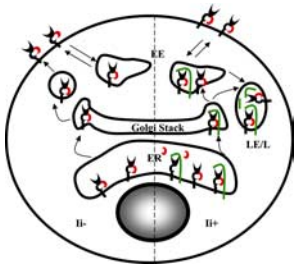
A New Partner for Invariant Chain



The MHC class I-related molecule FcRn, which is expressed in a variety of cell types, protects IgG from degradation and transfers maternal IgG across the placenta. The intracellular trafficking pathway of FcRn is similar to that of MHC class II, leading Ye et al. (p. 2572) to assess whether the invariant chain (Ii) was involved in this process. Immunoprecipitation experiments supported by confocal microscopy indicated that both human and mouse FcRn specifically associated with Ii in HeLa cells and dendritic cells (DCs). Ii binding to FcRn did not appear to interfere with FcRn function and, interestingly, did not require the CLIP peptide. Removal of the FcRn cytoplasmic tail, which contains several targeting motifs, allowed the authors to demonstrate that Ii could drive FcRn into the early endosomes, suggesting that Ii might affect FcRn intracellular trafficking. In HeLa cells, human immature DCs, and mouse bone marrow-derived DCs, Ii targeted FcRn to the late endosomal/lysosomal compartment, further supporting a role for Ii in the modulation of FcRn localization. Compartment localization was controlled by the cytoplasmic tail of Ii, as determined by analysis of a chimeric molecule consisting of the extracellular domain of FcRn fused to the intracellular tail of Ii. These data identify a novel mechanism regulating FcRn intracellular trafficking and have important implications for the broad spectrum of immune functions that involve FcRn modulation of IgG.

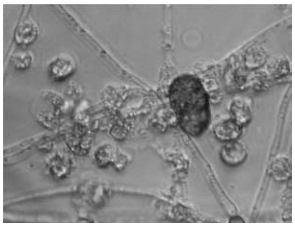
Orchestrating the NKT Response

Although NKT cells are known to participate in immune responses to infection, the natural course of the NKT cell response to microbial infection has not been described. To examine this course, Chiba et al. (p. 2292) followed the fate of NKT cells during infection of mice with *Mycobacterium bovis* bacillus Calmette-Guérin. Prior to the MHC-restricted T cell response, NKT cells were activated and expanded. As the adaptive response began to take over, NKT cell proliferation waned and total NKT cell numbers declined to near baseline levels. Contraction of the NKT cell population was attributable to both increased apoptosis and reduced proliferation. Intriguingly, most of the surviving NKT cells were unresponsive to stimulation despite the continued presence of bacteria. A similar pattern of NKT cell activation followed by anergy was observed after a single injection with the TLR4 agonist LPS, suggesting that this phenomenon may occur during the course of many bacterial infections. Thus, NKT cells participate in the early phase of the antimicrobial response and then "pass the baton" to the MHC-restricted T cell response. Further, the data identify NKT cell unresponsiveness as a mechanism by which NKT cell antimicrobial responses may be terminated.

A New Type of Regulatory T Cell

Activation of the aryl hydrocarbon receptor (AhR) by the environmental contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has been shown to lead to immune suppression via effects on $CD4^+$ T cells. To determine the mechanism of this suppression, Marshall et al. (p. 2382) compared the characteristics of suppressive T cells generated in the presence of TCDD, referred to as TCDD-$CD4^+$, with those of conventional regulatory T cells (Treg). Like natural Treg, TCDD-$CD4^+$ produced very little IL-2 and suppressed proliferation and IL-2 production by responder T cells through a cell contact-dependent mechanism. Suppression could be abrogated by costimulation through glucocorticoid-induced TNFR (GITR). However, unlike natural Treg, TCDD-$CD4^+$ did not express FoxP3 and were able to proliferate while exerting their suppressive function. TCDD-$CD4^+$ cells produced high levels of IL-10 after stimulation with anti-CD3 or alloantigen, and microarray analysis demonstrated the up-regulation of several genes characteristic of natural Treg. Interestingly, components of the IL-12R signaling pathway were also up-regulated in TCDD-$CD4^+$ cells, and these cells consequently showed enhanced responsiveness to IL-12. TCDD-mediated activation of the AhR therefore induces the generation of a novel subset of regulatory T cells that may be involved in the suppression of alloimmune and other immune responses in vivo.

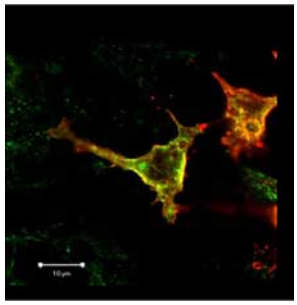
Eosinophils Attack



Eosinophils are involved in chronic airway inflammation and are known to release proinflammatory mediators, but how these cells are activated has not been thoroughly addressed. Because fungal infections have been associated with eosinophilic inflammation, Yoon et al. (p. 2907) investigated the response of human eosinophils to the ubiquitous, nonpathogenic fungus *Alternaria alternata*. *A. alternata* activated human eosinophils in vitro, leading to the release of granule proteins such as eosinophil-derived neurotoxin and major basic protein. Fungal damage resulted from the interaction between eosinophils and *A. alternata*, suggesting that these cells possess fungicidal activity. Surprisingly, the fungal cell wall component β-glucan stimulated eosinophils to degranulate and release chemokines, but chitin, which has been implicated in allergic airway inflammation, did not. Abs and complement were not involved in the response of eosinophils to β-glucan particles, but the eosinophil-expressed β_2 integrin CD11b, particularly its inserted (I)-domain, was vital for

this reaction. The analysis of this interaction between human eosinophils and an environmental fungus has implications for the understanding of eosinophil function as well as asthma and other forms of chronic inflammation.

NOD2 versus TLR2



Pattern recognition receptors, including TLRs and the intracellular NOD proteins, sense infection and modulate innate immune responses. The Rho family GTPase Rac1 has been implicated in NF-κB signaling and cytoskeletal reorganization and was previously shown to positively regulate TLR2 signaling. Eitel et al. (p. 2664) assessed whether Rac1 might also play a role in NOD2 signaling and observed that Rac1 was activated following NOD2 stimulation. Inhibition of Rac1 increased NOD2-mediated IL-8 production and NF-κB activity but decreased IL-8 production and NF-κB activity that were dependent on TLR2. These data indicated that Rac1, seemingly paradoxically, inhibited NOD2 activity but promoted TLR2 activity. Experiments to determine the mechanism of Rac1-mediated NOD2 inhibition showed that Rac1 directly associated with NOD2 and induced the recruitment of this complex to the plasma membrane. β-PIX, which interacts with Rac1, was also involved in membrane recruitment of NOD2 and the inhibition of NOD2-mediated IL-8 production but did not affect TLR2-mediated IL-8 production. Finally, Rac1 activity appeared to lead to an association between NOD2 and its negative regulator Erbin. These data delineate a mechanism by which NOD2 signaling may be fine tuned and indicate that Rac1 may, through specific pathways, both promote and down-regulate inflammatory processes.

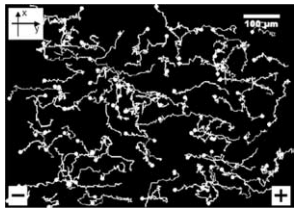
HLA and HIV Transmission

Specific HLA alleles are known to affect HIV-1 pathogenesis. Over a 12-year study period, Tang et al. (p. 2626) analyzed 429 HIV-1 discordant Zambian couples (consisting of an HIV-infected index partner and a cohabiting seronegative partner) to determine the possible association of specific HLA haplotypes with HIV-1 transmission. These couples were divided into 205 pairs between whom viral transmission occurred and 224 who did not transmit the virus during the study period. Extensive statistical analysis of HIV-infected index partners showed that HLA class I allele A*36 was significantly associated with viral transmission, whereas the B*57 and Cw*18 alleles were negatively associated with transmission. The Cw*18 allele was also strongly associated with a low viral load, which is known to decrease the likelihood of HIV transmission, whereas A*36 tended to be associated with higher viral loads. However, the presence of the A*36, B*57, or Cw*18 alleles in the seronegative partners showed no association with viral acquisition. This complex study of a very large cohort of discordant couples identifies a strong contribution of the HLA class I genotype of the infected index partner to HIV transmission. HLA alleles therefore not only affect HIV pathogenesis, but also influence viral transmission.

A Broken Heart without PD-L1

The PD-1/PD-L1 costimulatory pathway suppresses autoimmune kidney disease, leading Lucas et al. (p. 2513) to hypothesize that this pathway might also inhibit the spontaneous macrophage and T cell-dependent, lupus-like disease that develops in MRL-Fas^{lpr} mice. They therefore generated mice deficient in PD-L1 on the MRL-Fas^{lpr} background. Unexpectedly, these PD-L1$^{-/-}$; MRL-Fas^{lpr} mice did not develop kidney disease but instead demonstrated severe myocarditis and pneumonitis and died much earlier than their wild-type (WT); MRL-Fas^{lpr} littermates. This disease was characterized by a massive infiltration of PD-1-expressing macrophages and T cells into the heart and lung. Following disease onset, high levels of autoantibodies specific for cardiac myosin and troponin I were detected in PD-L1$^{-/-}$; MRL-Fas^{lpr} mice but not WT; MRL-Fas^{lpr} mice. This autoimmune pathology was dependent upon the MRL background but not the Fas^{lpr} mutation. Interestingly, transfer of PD-L1$^{-/-}$; MRL$^{+/+}$ bone marrow into WT; MRL$^{+/+}$ mice was sufficient to induce myocarditis and pneumonitis in the recipient mice, albeit to a less severe degree than that seen in PD-L1$^{-/-}$;MRL$^{+/+}$ mice. This decrease in disease severity was associated with a dramatic up-regulation of PD-L1 in the heart and lung endothelial cells. The analysis of disease in this model provides novel insights into the autoimmune susceptibility of MRL mice and potential roles of the PD-1/PD-L1 pathway in protection against autoimmune inflammation.

Electric Attraction



Directed cell migration in response to a chemical gradient is well described. Cell types including neutrophils, epithelial cells, and endothelial cells have also been shown to migrate in response to electric fields, which can be generated in vivo during processes including wound healing. Lin et al. (p. 2465) investigated whether lymphocytes could also exhibit this process of electrotaxis and found that lymphocytes could indeed migrate in response to applied electric currents both in vitro and in vivo. An electric current elicited in a modified transwell system induced the migration of human blood lymphocytes and monocytes toward the cathode. Unlike chemotaxis, this electrotaxis was quite uniform among the different cell subsets studied. Use of a microfluidic device clearly showed that human memory T cells could migrate efficiently toward the cathode of a physiologically relevant electric field. Interestingly, an applied electric field induced the phosphorylation of Erk1/2 and Akt, which are also activated in response to chemoattractants. Finally, intravital microscopy following the application of an electric field to a mouse ear showed that electrotaxis of lymphocytes could also occur in vivo. Electrotaxis may therefore represent an additional mechanism by which lymphocyte positioning is controlled.

Summaries written by Jennifer Hartt Meyers, Ph.D.