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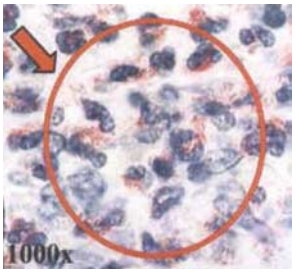
THE JOURNAL OF IMMUNOLOGY

In This Issue

Th17 Wins



Depending on the type of autoimmune disease, different Th cell phenotypes can cause pathogenesis. Stummvoll et al. (p. 1908) have compared the results of adoptively transferring Th1, Th2, and Th17 effector cells in a model of autoimmune gastritis (AIG), which uses the H/K-ATPase proton pump of the gastric parietal cell as the target Ag. The authors found that while i.p. injections of in vitro differentiated Th1 (IFN-γ-secreting), Th2 (IL-4- and IL-5-secreting), and Th17 (IL-17-secreting) effectors with a TCR specific for the H/K-ATPase each induced gastritis, transfer of Th17 effector cells caused the most dramatic pathology with 80% of Th17 recipients showing evidence of destructive gastritis at 4 wk after injection, compared with 60% of Th2 recipients and 20% of Th1 recipients. Th17 recipient animals had elevated levels of IgE in the serum and gastritis with robust polymorphonuclear infiltrate containing eosinophils. Cotransfer of polyclonal T regulatory cells (Treg) reduced the incidence and severity of disease in Th1-injected and Th2-injected mice but was not effective at suppressing AIG in the Th17 group. While the major effect of polyclonal Treg in animals was to inhibit proliferation of Th effector cells, the same effector cells were quite capable of proliferating and producing cytokines ex vivo when removed from the influence of Treg. Taken together, the strong inhibitory effect of Treg on some effector cells makes Treg attractive therapeutic targets for autoimmunity unless disease is caused by a Th17 mechanism.

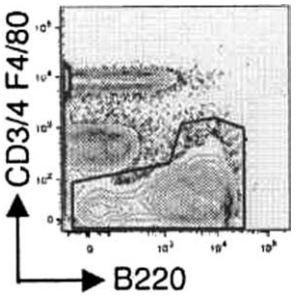
Alphabet Soup-IRF3, TRIM21, IFNβ

Type I IFN responses to viral and bacterial infections are of paramount importance to maintaining immunity. The transcription factor IRF3 is integral to mediating the expression of type I IFNs during infection. However, at the end of a pathogen challenge, IFN responses mediated by the expression of IFNβ, for example, must be turned off. Higgs et al. (p. 1780) have determined that IRF3 is targeted for proteasomal degradation by the E3 ligase Ro52 (TRIM21) after TLR activation, thus inhibiting IFNβ promoter activity. The authors demonstrated that TRIM21 effects its control by interacting with the IRF3 C-terminal SPRY domain, which causes polyubiquitination and proteasomal degradation of IRF3. TRIM21-mediated IRF3 degradation inhibited IFNβ transcription, an effect that could be reversed with the proteasomal inhibitor MG132. Small hairpin RNA (shRNA) targeting of TRIM21 increased IFNβ production following TLR stimulation with poly(I:C). In murine fibroblasts, TRIM21-targeted shRNA enhanced the production of RANTES, a chemokine dependent on IRF3 for transcription, after infection by Sendai virus. Taken together, these results demonstrate that TRIM21 has a novel role in controlling IRF3 by targeting the transcription factor for proteasomal degradation and thus providing a control mechanism for type I IFN responses.

The Parasite and the Antibody

In an elegant and extensive article by Ghumra et al. (p. 1988), the authors have attempted to determine how malaria parasites cause erythrocyte rosetting. Known as a virulence factor in the pathogenesis of severe malaria, erythrocyte rosetting consists of an infected erythrocyte binding uninfected erythrocytes, often in the presence of nonspecific IgM. The authors determined that the parasite protein *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) from a virulent strain of malaria was the IgM-binding ligand and identified the IgM-binding domain within this protein to be the Duffy binding-like 4β domain (DBL4β). PfEMP1, a variant erythrocyte surface Ag, is encoded by a parasite *var* gene and expressed at the surface of the infected erythrocyte. Through Ab domain analysis and substitution, the authors found that PfEMP1 binds to the IgM Cμ 4 domain. The amino acid sequence of this IgM domain showed homology with that bound by bacterial Fc-binding proteins on IgG and IgA, suggesting conservation due to important host-microbe interactions. Thus, the authors have shown that PfEMP1 is a polymeric IgM-Fc-binding protein that is similar to bacterial Fc-binding proteins. These findings may lead to elucidating the functional significance of parasite-mediated erythrocyte rosetting.

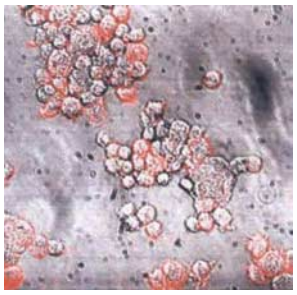
B-eing Sensitive



Contact sensitivity (CS) and the related delayed-type hypersensitivity (DTH) are well characterized types of T cell-mediated inflammation that are often used as models to examine Ag-specific T cell sensitization and recall. However, the early initiation of these responses has been shown to be dependent on B-1-like B cell production of Ag-specific IgM. Kerfoot et al. (p. 1717) have taken this work one step further and determined that activation-induced deaminase (AID), the enzyme responsible for somatic hypermutation, is necessary for the CS initiation pathway to haptens such as 2,4-dinitro-1-fluorobenzene (DNFB). Adoptive transfer of B-1-like B cells into mice defective in AID, which have a defect in CS initiation, rescued their ability to respond to DNFB. The adoptively transferred B-1-like cells were defined as originating in the

peritoneal cavity and expressing CD19 and CD11b; $CD19^{+}CD11b^{-}$ (B-2) cells were not able to rescue CS initiation in AID-deficient mice. The authors also defined a novel splenic population of Ag-binding B cells ($CD19^{+}CD5^{+}$Thy-$1^{int}IgM^{high}IgD^{high}$) in sensitized mice they termed "initiator B cells" that underwent AID-mediated somatic hypermutation. These results led the authors to suggest that "initiator B cells" can respond to small amounts of hapten by having increased IgM receptor gene mutations to facilitate the mediation of the CS initiation response.

PAP2 Effects in Macrophages



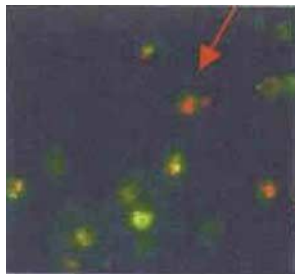
Pancreatitis-associated proteins (PAP) are small secretory proteins that are induced during acute pancreatitis, Crohn's disease, inflammatory bowel disease, and other types of tissue damage. PAP have a protective effect, as reducing levels of PAP by gene knockdown exacerbates pancreatitis. Viterbo et al. (p. 1948) examined the role of PAP2 in modulating macrophage inflammatory responses. They found that clonal rat macrophages (NR8383) cultured with the PAP2 isoform increased the expression of the proinflammatory cytokines IL-1, IL-6, and TNF-α, as well as the immunomodulatory cytokine IL-10, in a dose-dependent manner. Expression of IL-12, IL-15, and IL-18 was unchanged compared with untreated controls. The NF-κB signaling pathway was determined to be involved in PAP2-mediated macrophage changes, because PAP2 treatment caused nuclear translocation of NF-κB and phosphorylation of the IκBα inhibitory protein. In addition, chemical inhibition of NF-κB abrogated PAP2-mediated changes in cytokine production. Primary macrophages from the lung, peritoneum, and peripheral blood, but not the spleen, had similar cytokine responses to PAP2 treatment.

In the companion paper by Viterbo et al. (p. 1959) the authors determine the molecular characteristics necessary for their observations of PAP2 effects on macrophage cytokine production. As a member of the Reg3 gene family, PAP2 is classified as part of the group 7 C-type lectin-like proteins, and the authors mutated domains important in the C-type lectin-like proteins to determine their efficacy. They found that truncation of the PAP domain in the N terminus of PAP2 did not affect macrophage cytokine production, but truncation of the last 30 residues of the C terminus of PAP2 completely abrogated its function. Two invariant disulfide bonds in the C-type lectin domain fold were found to be important for PAP2-induced macrophage cytokine production. However, the disulfide bond that is observed in long form C-type lectin proteins was not found to be essential for PAP2 influence on macrophage function. The inability of PAP2 mutants to cause translocation of NF-κB to the nucleus correlated with their inability to cause changes in macrophage cytokine expression, confirming that PAP2 acts on macrophages through an NF-κB-dependent mechanism to modulate the inflammatory environment in pancreatitis. With these two articles, the authors have presented clear evidence of how PAP2 modulates the pancreatic microenvironment and given insight into the biochemical mechanism of how this occurs.

IL-10 Controlling *Borrelia*

Relapsing fever caused by *Borrelia turicatae* is characterized by peaks of bacteremia in the blood that are cleared by specific IgM Abs. Previous work has shown that B cell-deficient mice infected with *B. turicatae* produce high levels of IL-10 that are necessary for controlling bacteremia. In Londoño et al. (p. 2076), this same group now provides a mechanism by which IL-10 controls bacterial levels through a B cell-independent pathway. Using $RAG2^{-/-}$/$IL\text{-}10^{-/-}$ mice they looked at the effect of *B. turicatae* infection and found that these mice had higher bacteremia, higher levels of TNF, and early mortality when compared with infected $RAG2^{-/-}$ mice. Increased apoptosis of lymphocytes and splenocytes was also found in infected $RAG2^{-/-}$/$IL\text{-}10^{-/-}$ mice but could be blocked by the neutralization of TNF, which led to increased NK production of IFN-γ, decreased bacteremia, and decreased mortality. The authors conclude that IL-10 protects animals from high levels of bacteremia during *B. turicatae* infection by protecting innate immune cells from TNF-induced apoptosis and ultimately controlling spirochetemia.

Drak2, Gatekeeper for Neuroinvasion



West Nile virus (WNV) causes viral encephalitis, entering the brain by crossing the blood brain barrier (BBB). However, the mechanism by which this occurs is poorly understood. Combining the hypothesis that WNV elicits a proinflammatory response modulating the BBB and allowing for viral entry with the observation that lymphocyte-expressed DAP kinase-related apoptosis-inducing kinase-2 (Drak2)-deficient mice are more resistant to experimental autoimmune encephalomyelitis, Wang et al. (p. 2084) investigated the role of Drak2 in WNV infection. Drak2 is known to negatively regulate T cell activation and $Drak2^{-/-}$ mice are more sensitive to TCR-mediated stimulation. The authors found that Drak2-deficient mice were more resistant to a lethal challenge of WNV than wild-type mice. Levels of viremia in the peripheral tissues were comparable between $Drak2^{-/-}$ mice and controls, but splenic IFN-γ-expressing T cells were elevated in the absence of Drak2. However, the brains of infected $Drak2^{-/-}$ mice had reduced viral loads, and this correlated with lower numbers of $CD4^{+}$ and $CD8^{+}$ T cells in the brain compared with wild-type mice. Viral Ags were detected in the T cells isolated from both spleens and brains of the infected mice, suggesting that WNV may be entering the CNS by infecting T cells homing to the brain. However, as T cells in the CNS of WNV-infected $Drak2^{-/-}$ mice were more sensitive to apoptosis, these results suggest that Drak2 promotes T cell survival in the brain during WNV encephalitis and exacerbates disease.

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