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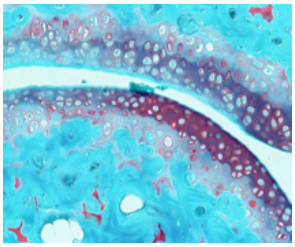
THE JOURNAL OF IMMUNOLOGY

In This Issue

Aching Joints Addled by α_9 Integrin



Rheumatoid arthritis (RA) is a chronic inflammatory disease that attacks the synovial tissue between joints and destroys cartilage and bone. RA-associated pathology is mediated by interactions between extracellular matrix (ECM) proteins and synovial-resident cells. Kanayama et al. (p. 8015) have pinpointed $\alpha_9\beta_1$ (α_9) integrin and its ligands as key contributors to RA pathogenesis. The α_9 integrin was expressed on synovial fibroblasts and macrophages from arthritic joints and mediated interactions with the ECM-associated ligands osteopontin and tenascin-C. Synovial fibroblasts isolated from arthritic foci also expressed the α_9 integrin receptor VCAM-1 and promoted the recruitment of synovial macrophages and other inflammatory cells to joints through this interaction. Engagement of α_9 integrin on synovial fibroblasts and macrophages induced differential production of cytokines and chemokines and further contributed to RA pathogenesis. The investigators developed a specific anti-α_9 integrin mAb that effectively inhibited the production of inflammatory modulators and reduced RA severity in mice treated before or after the onset of arthritic symptoms, providing more evidence for α_9 integrin as a regulator of RA. The latter experiments suggest that α_9 integrin may be a potentially important molecule for new therapies targeting RA.

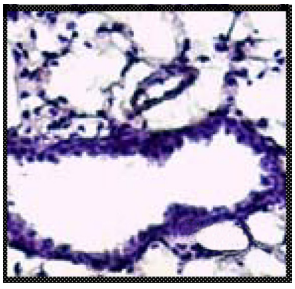
Salmonella Dismisses Activated T Cells

Salmonella enterica is a pathogenic bacterium responsible for typhoid fever and severe gastroenteritis in humans and livestock. Th1-polarized $CD4^+$ T cell responses are associated with protection against *Salmonella* infection in both humans and mice, but some evidence suggests that these responses are blunted during infection. Srinivasan et al. (p. 7838) present new data indicating that *Salmonella* infection causes a significant reduction of *Salmonella*-specific $CD4^+$ T cells after clonal expansion. Mice exposed to live or heat-killed *Salmonella typhimurium* (HKST) showed similar frequencies of activated $CD4^+$ T cells at early times, while significantly fewer Ag-specific $CD4^+$ T cells were observed at later times in infected mice. This T cell "culling" was not due to Ag specificity or naive clonal T cell frequency and could not be overcome by the inclusion of additional *Salmonella* flagellin Ag during infection. Apoptosis was observed in a significant portion of *Salmonella*-specific $CD4^+$ T cells isolated after the peak of clonal expansion in infected mice compared with mice given HKST. T cell "culling" was dependent on the presence of SPI-2 (*Salmonella* pathogenicity island-2) and up-regulation of the inhibitory receptor PD-LI (programmed death ligand-1) on T cells in infected mice. These findings identify a new tactic used by bacteria to elude adaptive immune responses by specifically targeting activated T cells.

LPS Primes Platelet Aggregation

The release of bacterial byproducts, including LPS, into the bloodstream activates a spectrum of inflammatory responses during sepsis. Thrombocytopenia and platelet aggregation are observed often in septic individuals or LPS-treated mice, leading Zhang et al. (p. 7997) to analyze the mechanism of LPS-induced platelet activation. Human platelets were activated to secrete both dense and α granules but did not aggregate in vitro when treated solely with LPS. Significant aggregation was noticeable upon treatment with both LPS and the platelet agonists thrombin or collagen. Platelets expressed molecules involved in LPS detection, including TLR4, MD-2, CD14, and MyD88, and aggregation was dependent on TLR4/MyD88-mediated pathways. A role for this pathway was confirmed in vivo, as platelet-dependent thrombus formation was induced rapidly by LPS in wild-type but not in MyD88-deficient mice. As in other systems, LPS activation of the TLR4 pathway stimulated NO production and guanylyl cyclase activity. This was confirmed by the detection of cGMP in LPS-stimulated platelets and the inhibition of aggregation upon treatment with specific inhibitors that blocked either NO or cGMP production. These data define a new role for LPS-driven platelet activation and aggregation driven by TLR4- and MyD88-mediated signaling events.

Protection on PAR_2 against Flu



Respiratory tract-resident proteases are key players during influenza virus type A (IAV) infection for the initiation of innate immune responses. Protease-activated receptors (PARs) are activated by some of these lung-associated proteases and can promote inflammatory responses. In this issue, Khoufache et al. (p. 7795) identified a protective role for one of these receptors, PAR_2, during IAV pathogenesis. PAR_2 activation curbed viral replication significantly and induced IFN-γ production in infected human alveolar epithelial cells treated with the PAR_2 peptide agonist SLIGRL-NH_2. The importance of PAR_2-mediated antiviral responses was confirmed in mice infected with lethal doses of IAV, as PAR_2 agonist treatment protected them from severe lung pathology and death. Bronchoalveolar fluids from these mice showed reduced neutrophil recruitment and RANTES secretion and a significant increase in IFN-γ levels as compared with infected mice treated with a control peptide. IFN-γ-deficient mice showed similar susceptibility to IAV infection as their wild-type counterparts,

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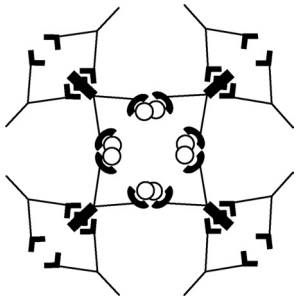
although treatment with PAR_2 agonist did not protect against lethal infection. In contrast, PAR_2-deficient mice were more susceptible to IAV infection than wild-type mice. Taken together, these observations support a link between PAR_2 activation and IFN-γ responses and suggest that PAR_2 may be a potential target for anti-influenza therapy.

Gene Therapy Targets IgE



Allergens can direct allergic responses through crosslinking of FcεRI on the surface of mast cells by allergen-specific IgE molecules. This fateful interaction leads to the release of inflammatory molecules such as histamine and can have lethal outcomes, including anaphylaxis. Ota et al. (p. 8110) describe a novel gene therapy-based method to modulate allergic responses by suppression of IgE production. Mice treated with a plasmid encoding a mouse-specific single-chain anti-IgE showed expression of this molecule for several weeks. This treatment resulted in significant serum IgE neutralization, as well as a dramatic reduction of IgE heavy chain mRNA expression and IgE^+ B cell frequency. Model allergic responses, including OVA immunization or anti-IgD treatment, were restrained in mice treated with the anti-IgE plasmid primarily by the reduction of serum IgE. In vitro, recombinant single-chain anti-IgE inhibited IgE secretion and IgE plasma cell differentiation, indicating that this approach may induce a lasting response to control IgE production. Unexpectedly, this anti-IgE plasmid therapy did not prevent anaphylaxis and appeared to trigger an FcγRIII-driven anaphylaxis reaction via complexes formed by recombinant anti-IgE and IgE. Overall, these results highlight a new strategy in the search for safe and durable therapies to control IgE responses.

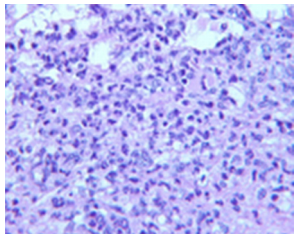
Th17 Development Needled by Notch

Notch signaling pathways are critical for T cell activation and $CD4^+$ T cell differentiation through their role in transcriptional regulation. Mukherjee et al. (p. 7381) provide a new insight into the role of the Notch ligand Delta-like 4 (Dll4) in Th17 differentiation. The authors confirmed that dendritic cells treated with TLR ligands, especially LPS, up-regulated the expression of Delta-like ligands, especially Dll4. Dll4 expression was required for IL-17 production in splenocytes stimulated ex vivo with both LPS and Ag, and IL-17 production was blocked in these cells by treatment with an anti-Dll4 Ab. IL-17 and IFN-γ were produced in culture in naive $CD4^+$ T cells upon treatment with Dll4 and Th17-skewing cytokines (IL-6, TGF-β, and IFN-γ), and IL-17 production was further potentiated under these conditions by a secondary stimulation with anti-CD3 and anti-CD28. The involvement of Notch signaling in Th17 differentiation was supported by data showing the inhibition of IL-17 production in Dll4-treated cells in the presence of γ-secretase inhibitor, a Notch activation inhibitor. Dll4 treatment enhanced the expression of the Th17-associated transcription factor *Rorc*, and binding sites for the Notch transcriptional complex were identified in both the *Rorc* and *Il17* promoters. Together, these data indicate an important role for Dll4 and Notch signaling in Th17 differentiation.

WASp Prods *i*NKT Cell Activation

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency caused by mutations in the *WASP* gene and is linked with defects in T cells, marginal zone B cells, and NK cells. Astrakhan et al. (p. 7370) now show that invariant NKT (*i*NKT) cells are dependent on the WAS protein (WASp) for activation and homeostasis. *i*NKT cells are a heterogeneous T cell subgroup expressing both NK cell surface markers and a lipid Ag-specific invariant αβ TCR. In $WASp^{-/+}$ heterozygous mice, $WASp^+$ *i*NKT cells showed a selective advantage for migration from the thymus to peripheral tissues, especially the liver and spleen. This effect was more pronounced in adult WASp-deficient mice that had a similar number of *i*NKT cells in the bone marrow and thymus but significantly fewer in the liver and spleen when compared with wild-type mice. In young mice, *i*NKT cell migration to peripheral tissues and cell proliferation during maturation were also profoundly reduced by WASp deficiency. Mature *i*NKT cell dysfunction in the absence of WASp was due in part to a defect in TCR signaling, whereas defects in homeostasis and tissue retention were associated with reduced CD11a integrin expression. Together, these results define a role for WASp in *i*NKT cell activation and homeostasis and offer a deeper understanding of the immune defects associated with WAS.

Tyk2's Ties to Autoimmunity



Mounting evidence suggests that different autoimmune diseases share common susceptibility genes. Tyrosine kinase-2 (Tyk2) is a signaling molecule involved in cytokine responses mediated through the JAK/STAT pathway and has been linked to susceptibility to arthritis and lupus. In this issue, Spach et al. (p. 7776) define Tyk2's role in experimental allergic encephalitis (EAE) using a serendipitous inbred mouse strain. The *Tyk2* gene in B10.D1-$H2^q$/SgJ (B10.D1) mice has an isogenic missense mutation (2538 G→A) compared with the wild-type substrain B10.Q/Ai. EAE susceptibility was determined following immunization of these mice with myelin oligodendrocyte glycoprotein peptide$_{79-96}$ (MOG_{79-96}). B10.D1 ($Tyk2^A$) mice were EAE resistant, while wild-type B10.Q/Ai ($Tyk2^G$) mice showed typical EAE symptoms. The $Tyk2^A$ resistance phenotype was recessive, as F_1 hybrids were also susceptible to EAE. Protection offered by genetic resistance factors cannot always contend with infections and other environmental stimuli. This held true for B10.D1 ($Tyk2^A$) mice that lost resistance to EAE upon immunization with MOG_{79-96} in parallel with exposure to pertussis toxin (PTX). Genetic susceptibility and PTX treatment were also associated with a significant increase in RANTES, IL-6, and IFN-γ production following ex vivo stimulation. These data reinforce a role for Tyk2 in the intricate interplay between genes and the environment during autoimmunity.

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