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In This Issue

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Alarming News for Psoriasis

Alarmins, such as endogenous damage-associated molecular patterns secreted by immune cells, are released from damaged or necrotic cells and initiate an inflammatory response. These alarmins can play important roles in the induction of inflammatory diseases, such as cutaneous psoriasis. ATP, through purinergic signaling, can induce dendritic cells (DCs) to mature and stimulate Th17 responses, although the stimuli that induce Th17 responses in the skin are not well understood. Using human skin epidermal–dermal explants, Killeen et al. (p. 4324) hypothesized that ATP signaling through purinergic receptor P2X7R stimulates a Th17 inflammatory response and is implicated in the pathogenesis of psoriasis. Cutaneous P2X7R stimulation initiated an inflammatory response by upregulating IL-1β and IL-6 mRNA and the expression of CXCL10, TNFR1, and a variety of other innate inflammatory factors. Ex vivo stimulation of cutaneous explants with ATP led to DC maturation, characterized by an increase in the expression of HLA-DR and CD86, and differentiation into inflammatory DCs, which secreted higher levels of alarmins. These P2X7R-stimulated DCs triggered Th17 differentiation in $CD4^+$ T cell cultures at the transcriptional and posttranscriptional levels, and treatment of nonlesional psoriatic explants with ATP showed an increase in factors associated with psoriasis pathogenesis, such as vascular endothelial growth factor, IL-6, and IL-23. In this study, the authors establish a role for purinergic signaling that induces inflammation and Th17 responses in the pathogenesis of psoriasis.

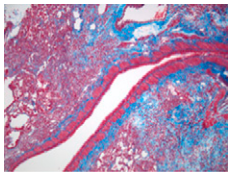
Caspase Control of Mtb

Host control of *Mycobacterium tuberculosis* requires a complex struggle between host immune responses and pathogen evasion mechanisms. Whereas Th1 cell effector responses are necessary to control the bacteria, these responses need to be modulated so that inflammation doesn't overwhelm the host. T cell–Ig and mucin-domain-containing molecule-3 (Tim3) often acts to downregulate these Th1 effector responses. Building on evidence that Tim3 stimulates secretion of the inflammatory molecule IL-1β from *M. tuberculosis*–infected macrophages, Jayaraman et al. (p. 4196) examined the mechanism of IL-1β–mediated killing. IL-1β was found to increase TNF secretion and TNFR1 surface expression in macrophages, leading to increased TNF signaling. This in turn led to caspase-3 activation, which was necessary for bacterial killing, a conclusion confirmed through the use of inhibitors. Additionally, efferocytosis was also required for IL-1β–mediated *M. tuberculosis* killing. Thus, the authors have described a complex cascade involving Tim3, IL-1β, TNF secretion/signaling, caspase-3 activation, and efferocytosis that results in *M. tuberculosis* restriction within the host.

InterFeriNg with SLE

The degree of disease severity in systemic lupus erythematosus (SLE) is characterized by an increase in serum autoantibodies and pathological inflammation driven by the deposition of serum autoantibodies as immune complexes in organs, such as the kidneys. The role of type I IFNs (IFN-I) in the pathogenesis of SLE is controversial. Previous studies showing an exacerbation of SLE in the absence of TLR9 along with an increase in IFN suggested that these two pathways may be linked in SLE. To evaluate the function of IFN-I in TLR9-regulated SLE disease parameters, Nickerson et al. (p. 3889) backcrossed the SLE mouse model MRL/MpJ-$Fas^{lpr/lpr}$/2J to IFN-I receptor subunit–deficient mice, *Ifnar1*$^{-/-}$, and/or *Tlr9*-deficient mice (*Tlr9*$^{-/-}$). Proteinuria, a measure of kidney disease, was elevated in *Tlr9*$^{-/-}$ mice but decreased in *Tlr9*$^{-/-}$/*Ifnar1*$^{-/-}$ mice, suggesting that exacerbation of disease in *Tlr9*$^{-/-}$ mice requires IFN-I signaling. SLE-associated splenomegaly and lymphadenopathy were reduced with the loss of IFN-I signaling, and the elevated concentrations of serum IgG typically observed in *Tlr9*$^{-/-}$ mice were limited in *Tlr9*$^{-/-}$/*Ifnar1*$^{-/-}$ mice. Although *Ifnar1* deficiency did not alter the levels of anti-nucleosome autoantibody titers, IFN-I signaling contributed to the production of anti-RNA autoantibodies. Thus, the authors clarify the role of IFN-I in TLR9-regulated disease parameters and conclude that IFN-I signaling is an important mediator of SLE pathogenesis.

The Pulmonary Exploits of MMP-8



Pulmonary fibrotic diseases, including idiopathic pulmonary fibrosis (IPF), can be devastating to the affected individual. Matrix metalloprotease 8 (MMP-8), a type I collagen–degrading proteinase, has been shown to reduce lung inflammation while increasing fibrosis in a bleomycin-induced model of pulmonary fibrosis. As a result, Craig et al. (p. 4283) examined the specific role of MMP-8 in pulmonary disease pathogenesis. They found that both *Mmp-8* mRNA and protein levels were elevated in samples from whole lungs and broncheoalveolar lavage of bleomycin-treated wild-type mice. In addition, both pulmonary lymphocytes from IPF patients expressed increased levels of MMP-8 compared with controls. Bleomycin-treated *Mmp-8*$^{-/-}$ mice had reduced levels of fibrosis and greater levels of inflammation compared with wild-type bleomycin-treated controls. TGF-β, IL-13, MCP-1, and IFN-γ levels were all comparable in the two groups but the lungs of *Mmp-8*$^{-/-}$ mice had higher levels of MIP-1α and IP-10. IP-10 and MIP-1α were responsible for both the *Mmp-8* $^{-/-}$ lung inflammation and fibrotic responses,

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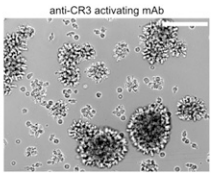
as genetic deletion of either chemokine reversed the *Mmp-8*$^{-/-}$ response to bleomycin, increasing fibrosis and reducing inflammation. Thus, through its action to limit MIP-1α and IP-10, MMP-8 can decrease inflammation and increase fibrosis, making it an attractive target for therapy in fibrotic diseases of the lung.

The NET Effect of ECM



The release of neutrophil extracellular traps (NETs), a combination of DNA fibers and antimicrobial molecules, through NETosis, a cell-death pathway leading to cytoplasmic membrane destruction, is a primary mechanism of antimicrobial defense against extracellular pathogens, including *Candida albicans*. The neutrophil β2 integrin complement receptor 3 (CR3) recognizes β-glucan, a structural component of fungi, and previous studies demonstrated a role for the extracellular matrix (ECM) in modulating this response. In this issue, Byrd et al. (p. 4136) sought to identify the receptor/ligand recognition event required for the NET response to fungal pathogens. Upon priming with different chemoattractants and stimulation with Mn^{2+}, neutrophil cell aggregation was observed in the presence of β-glucan and fibronectin (Fn), a matrix component, but not β-glucan alone. Blocking of either CR3 binding or ERK phosphorylation inhibited this aggregation. Immobilization of Fn with β-glucan induced NET formation and significantly decreased the viability of yeast, which could be rescued with the addition of DNase I. NET formation in the presence of *C. albicans* hyphae grown on Fn was reduced by blocking either CR3 or β-glucan, and was found to be independent of the respiratory burst triggered by CR3 recognition of β-glucan. In conclusion, the authors demonstrate a novel regulatory mechanism of NETosis in which NET formation in response to fungi is mediated by CR3 recognition of β-glucan in the context of the ECM.

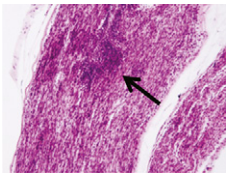
Keeping TABs on Polyubiquitin Chains

K63-linked polyubiquitin chains are essential for the activation of immune cells and interact through the TGF-β–activated kinase 1 (TAK1)-binding protein (TAB) 2 and TAB3 to activate NF-κB and MAPK signaling. To clarify the roles of TAB2 and TAB3 in the activation of B cells and macrophages, Ori et al. (p. 4037) generated conditional *Tab2*-deficient and *Tab3*-deficient mice. Stimulation with mitogens showed that TAB2 or TAB3 alone was not required for cell proliferation, cell cycle progression, or IL-6 production in B cells; however, double knockout *Tab2*/*Tab3*-deficient mice (DKO) had impaired B cell activation. Despite the importance of TAB proteins in NF-κB activation, no change was observed in NF-κB activation in B cells in single- or double-deficient mice. Although CpG DNA, anti-IgM, and anti-CD40 stimulation showed profound defects in the activation of MAPKs in B cells in both *Tab2*-deficient and DKO mice, no effect was seen on the phosphorylation and activation of TAK1. In vivo experiments demonstrated that TAB2 and TAB3 are required for the development of marginal zone and B-1a but not bone marrow or splenic B cells. Macrophage-specific deletion of *Tab2* and/or *Tab3* did not affect NF-κB or MAPK signaling or cytokine production in response to TLR stimuli. Thus, the authors demonstrate that TAB2- and TAB3-mediated recognition of K63-linked polyubiquitin is specific to the cell type and the stimulus for the activation of MAPK but not NF-κB.

ADAM17 Accelerates Diapedesis

The process of a lymphocyte rolling, adhering, and ultimately diapedesing its way across and through the endothelium can be an arresting sight and is an important immunological event. Tsubota et al. (p. 4236) have elucidated the mechanism by which diapedesis occurs, testing their hypothesis that metalloproteinases control this process. In the presence of a metalloproteinase inhibitor, human monocytes took twice as long to complete diapedesis through endothelial tissue, independent of whether the endothelia were inflamed. The inhibitor had no effect on the adhesion or locomotion of the monocytes but did cause an increase in their surface expression of the integrin Mac-1 during migration through the endothelium. ADAM17, a metalloproteinase that cleaves Mac-1, was identified as being responsible for the effect seen with the metalloproteinase inhibitor. Genetic deletion of monocytic ADAM17 mimicked the slower diapedesis observed with the metalloproteinase inhibitor. The authors conclude that monocytic ADAM17 enhances migration through the endothelium by accelerating diapedesis, possibly through the cleavage of Mac-1 that occurs upon interaction with the endothelium.

AIREing toward Neuropathy



Autoimmune destruction of the peripheral nervous system (PNS) results in chronic inflammatory demyelinating polyneuropathy (CIDP). Dysfunction in the Autoimmune Regulator (Aire) has been linked to CIDP and autoimmune peripheral neuropathy, which resembles CIDP and develops in NOD mice with a partial loss of Aire function (NOD.Aire$^{GW/+}$). Loss of Aire reduces thymic self-antigen expression to ∼10% of wild-type levels. This reduction includes PNS-specific proteins recognized by T cells, suggesting that T cell dysregulation underlies PNS autoimmunity. Because IFN-γ is a predominant cytokine produced by CD4$^+$ T cells infiltrating the sciatic nerve in NOD.Aire$^{GW/+}$ mice, Zeng et al. (p. 3895) examined its role in CIDP development. Genetic ablation of IFN-γ in NOD.Aire$^{GW/+}$ mice led to complete protection from clinical signs of neuropathy and to the absence of immune infiltration into the sciatic nerve, demonstrating that IFN-γ is required for the development of autoimmune peripheral neuropathy. Although IFN-γ–sufficient NOD.Aire$^{GW/+}$ CD4$^+$ T cells transferred neuropathy to immunodeficient NOD.scid mice, adoptive transfer of IFN-γ–ablated NOD.Aire$^{GW/+}$ CD4$^+$ T cells into NOD.scid mice prevented neuropathy. IFN-γ production is partly controlled by B7-1/B7-2 costimulation, and blockade of B7-1/B7-2 accelerated neuropathy and enhanced immune infiltration. Taken together, the authors demonstrate that in the context of Aire dysfunction, the development of autoimmune peripheral neuropathy is modulated by the distinct and opposing effects of T cell costimulatory pathways and IFN-γ production.