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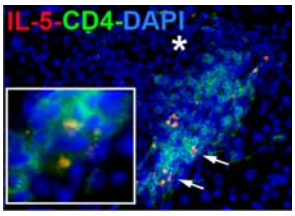
In This Issue

Stopping Diabetes in Its Tracks



Galectin-1 (gal-1) is an endogenous lectin that is able to down-regulate inflammation and induce T cell apoptosis. These qualities suggest that therapeutic use of this lectin might support tolerance induction in autoimmunity and transplantation, leading Perone et al. (p. 2641) to assess the effects of soluble gal-1 administration on autoimmune diabetes in NOD mice. Mice treated with gal-1 were protected from diabetes development without general immunosuppression and with no apparent toxicity. Analysis of insulitis in mice treated with gal-1 compared with that in vehicle-treated mice demonstrated an infiltrate that did not invade or damage the islets and consisted of reduced IFN-γ-secreting T cells and increased $CD4^+$ T cells expressing IL-4, IL-5, and IL-10. The prevention of diabetes in gal-1-treated mice was dependent on the down-regulation of the Th1 response and was inhibited by blockade of IL-10. However, gal-1 did not directly alter T cell polarization but instead caused apoptosis of the pathogenic Th1 cells, including β cell-reactive T cells, while sparing Th2 cells and regulatory T cells. Gal-1 therapy was also effective in curing subclinical cases of diabetes and reversing β cell autoimmunity in ongoing diabetes in NOD mice. These data demonstrate the therapeutic potential of gal-1 in autoimmunity and reveal novel mechanisms by which endogenous lectins may regulate tolerance.

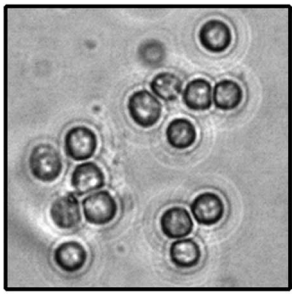
Colonic Cross-Talk

Intraepithelial γδ T cells (γδ IEL) are important for intestinal epithelial repair following injury. To determine the mechanism by which these cells respond to mucosal injury, Ismail et al. (p. 3047) used microarray analysis to examine the genome-wide transcriptional response of γδ IEL to dextran sodium sulfate (DSS)-induced colonic damage. DSS treatment in wild-type mice was shown to induce a complex transcriptional program that included up-regulation of genes involved in cytoprotection, immunoregulation, inflammatory cell recruitment, and innate antimicrobial activity. Comparison of this gene profile with that induced by DSS treatment in γδ IEL from germ-free mice indicated that commensal bacterial were required for the expression of most of the proinflammatory genes and a subset of the cytoprotective and antibacterial genes analyzed. A reciprocal regulatory relationship between these microbes and γδ IEL was suggested by analysis of $TCR\delta^{-/-}$ mice, which demonstrated that γδ IEL inhibited opportunistic invasion of commensal bacterial following DSS treatment. Taken together, these data indicate a complex role for γδ IEL in restoring homeostasis after mucosal epithelial damage and suggest a role for cross-talk between these cells and commensal bacterial in the regulation of mucosal immunity.

Taking Control of NF-κB

The NF-κB transcription factors are key players in the regulation of both innate and adaptive immunity. The inhibitory IκB family of proteins and the NF-κB1 and NF-κB2 precursor proteins, p105 and p100, sequester NF-κB proteins in the cytoplasm to prevent their activity. To clarify the physiological role of p105, which has been implicated in protection from inflammation and autoimmunity, Chang et al. (p. 3131) analyzed mice that lacked p105 but expressed mature NF-κB1 ($p105^{-/-}$ mice). These mice spontaneously developed T cell-dependent chronic intestinal inflammation resembling human inflammatory bowel disease. Examination of the T cell populations in $p105^{-/-}$ mice compared with those of wild-type mice revealed a reduction in naive T cells and a corresponding increase in effector/memory T cells, with a particularly pronounced increase in Th17 cells. This enhanced T cell activation was not due to impairments in regulatory T cell (Treg) development or function but could be linked to an increase in the resistance of effector $CD4^+$ cells to Treg-mediated suppression. The specific increase in Th17 cell differentiation was suggested to be caused by enhanced IL-16 production by macrophages in $p105^{-/-}$ mice. Thus, NF-κB1 p105 regulates T cell differentiation and homeostasis by both T cell-intrinsic and indirect mechanisms and has a critical role in the prevention of chronic inflammation.

En-abl-ing Neutrophils



Recruitment of neutrophils from the blood into the tissues requires β_2 integrin-mediated adhesion, which is induced by inflammatory stimuli and in turn activates signaling pathways that are not fully understood. In fibroblasts, the activity of the nonreceptor tyrosine kinase c-Abl has been shown to be regulated by integrins, but its potential role in neutrophil integrin signaling has not been addressed. Cui et al. (p. 3233) analyzed neutrophil adhesion and found that c-Abl kinase was not required for "inside-out" activation of β_2 integrin via TNF-α. However, c-Abl was activated in response to β_2 integrin engagement and its activity was required for β_2 integrin-mediated sustained adhesion and spreading of neutrophils. This kinase was recruited to β_2 integrin following cellular adhesion and formed a complex with the integrin via interactions between its SH3 domain and the talin head domain, which in turn interacted with the β_2 integrin cytoplasmic domain. Further analysis of c-Abl intracellular interactions suggested that this kinase regulated neutrophil adhesion following β_2

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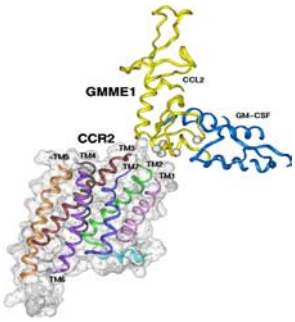
integrin ligation via modulation of Vav activity. Taken together, these data identify an important role for c-Abl in integrin-mediated neutrophil adhesion that is critical to host defense.

A New Way to Target CCR2



The chemokine receptor CCR2 has been implicated in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) and other inflammatory diseases and can be inhibited by N-terminal truncated forms of its ligand, CCL2. Rafei et al. (p. 2620) fused a truncated form of CCL2 to GM-CSF and examined the utility of the resultant fusokine, named GMME1, in targeting CCR2. GMME1, through a mechanism requiring CCR2, inhibited T cell activation and cytokine production, inhibited Ab production by plasma cells, and induced macrophage apoptosis. In splenocytes from mice with EAE, GMME1 treatment induced the down-regulation of inflammatory genes and promoted T cell apoptosis. Signal transduction in $CD4^+$ T cells from these mice was subverted by GMME1 administration, resulting in an asymmetrical activation of the MAPK pathway and blockade of AKT and STAT3 activation. Reconstitution of mice with $CCL2^{-/-}$ mesenchymal stem cells engineered to secrete GMME1 suppressed EAE induction with associated reductions in proinflammatory cytokines, myelin oligodendrocyte glycoprotein-specific Abs, and T cell infiltration into the spinal cord. These data suggest that GMME1 induces immune suppression, possibly through apoptosis of CCR2-expressing cells, and could thus serve as an effective therapeutic molecule for the suppression of undesired immune responses in autoimmunity and transplantation.

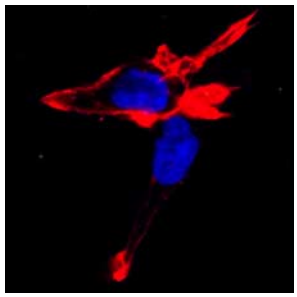
Extra Sneezes from the Flu

Infections with some respiratory viruses during infancy have been linked to an increased risk of asthma in childhood. To address the possibility that viral infection might augment atopic responses, Al-Garawi et al. (p. 3095) analyzed the effects of infection with influenza A, which promotes Th1 responses, on subsequent challenge with the house dust mite (HDM) allergen. Compared with HDM exposure in the absence of viral infection, exposure to a low dose of HDM during the peak of acute influenza A infection increase eosinophilic inflammation, Th2 cell expansion, mucous production, and airway hyperreactivity and resulted in pronounced lung dysfunction. IL-5 and IFN-γ production was also increased, while IL-4 was decreased and HDM-specific IgG1 and IgG2a responses were augmented. Interestingly, this enhanced atopic response occurred despite the presence of influenza A-induced Th1-type proinflammatory cytokines and elevated numbers of plasmacytoid dendritic cells in the lung. However, mice exposed to HDM during the resolution phase of influenza A infection demonstrated reduced lung inflammation compared with uninfected mice. As allergen exposure rarely occurs in isolation, this study provides insights into how allergy and asthma may develop in vivo in the context of a common viral infection.

Immunosuppression via IL-21

Interleukin 21 is a type I cytokine that is secreted after Ag stimulation of $CD4^+$ T cells and is necessary for Ig production. A murine model of systemic lupus erythematosus (SLE), the BXSB-*Yaa* model, has shown increased expression of IL-21 and the immunosuppressive cytokine IL-10 as the mice age and autoimmunity progresses. Spolski et al. (p. 2859) took this knowledge and investigated what role IL-21 played in regulating IL-10 and its immunosuppressive effects. They found that IL-10 production was decreased in mice lacking the IL-21 receptor but was increased in mice transgenic for IL-21, confirming that IL-21 controlled the expression of IL-10. In addition, IL-21 was not able to induce IL-10 production in T cells from *Stat3*-deficient mice when compared with wild-type T cells, indicating that IL-21 caused the production of IL-10 through a STAT3-dependent mechanism. IL-21 transgenic mice had a defect in Ig production compared with wild-type mice after immunization with OVA, consistent with the suppressive phenotype of these mice. IL-10 was increased in vitro by IL-21 treatment in normal T cell as well as those with Th1 and Tc1 phenotypes. In addition, the presence of IL-21 during TCR priming resulted in T cells with IL-10-dependent immunosuppressive activity. Thus, the authors demonstrate how IL-21 mediates immune suppression through IL-10 in a STAT3-dependent pathway.

Checking the Inflammasome



Inflammasomes are multiprotein complexes that, during inflammatory responses to infection or cellular stress, activate caspase-1, which is required for the generation of mature IL-1β and IL-18. The "apoptosis-associated speck-like protein containing a caspase recruitment domain" (ASC) is vital for the recruitment of caspase-1 to the inflammasome. Regulation of the inflammasome is necessary to prevent excessive inflammatory responses, but mechanisms by which this might occur are largely unknown. Bryan et al. (p. 3173) examined the subcellular distribution of endogenous ASC and determined that localization of this adaptor protein controls inflammasome activity. ASC was consistently sequestered in the nucleus in resting monocytes and macrophages but quickly redistributed to the cytosol following infection or stimulation with pathogen-associated molecular patterns. In the cytosol, ASC formed perinuclear aggregates that contained the inflammasome components NLRP3 and caspase-1. Retention of ASC in the nucleus completely ablated inflammasome-mediated IL-1β processing and release, indicating that translocation of ASC to the cytoplasm was required for inflammasome activity. This observation of inflammasome regulation suggests a mechanism by which spontaneous activation of caspase-1 and the consequent undesired inflammatory activity may be held in check.

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