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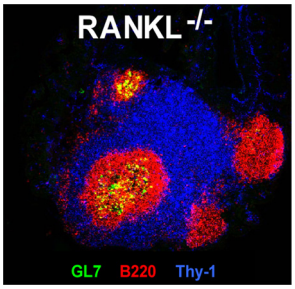
THE JOURNAL OF IMMUNOLOGY

In This Issue

RANKLing Intestinal Antigen Uptake



Microfold (M) cells are specialized epithelial cells in the follicle-associated epithelium (FAE) of the Peyer's patches (PP) and the isolated lymphoid follicles of the intestine. These cells are important for the sampling of particulate Ags, including commensal bacteria, from the intestinal lumen. In this issue, Knoop et al. (p. 5738) found that the TNF superfamily member receptor activator of NF-κB ligand (RANKL) was required for M cell development. Mice deficient in RANKL demonstrated a severe reduction in M cell numbers in the FAE of the PP that was associated with a defect in particulate Ag uptake in PP follicles and impaired intestinal IgA responses. Administration of exogenous RANKL could rescue the development of M cells and associated Ag uptake. This exogenous RANKL also caused an increase in villous M cells that were capable of taking up particulate Ags and transporting them across the epithelium. Neutralizing anti-RANKL Ab also caused a dramatic reduction in M cells, indicating that the M cell defect in RANKL-deficient mice was not due to the general developmental defects that these mice display. RANK, the receptor for RANKL, was expressed in intestinal epithelial cells, whereas RANKL was expressed by subepithelial stromal cells in PP domes. This study suggests that the RANK:RANKL interaction is required for the induction and maintenance of intestinal Ag-sampling M cells, and this information could be of use in mucosal vaccine development.

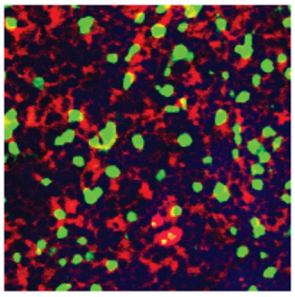
Activation amid Adenosine

Extracellular adenosine accumulates in inflamed tissues and tumors, especially under hypoxic conditions, and can suppress inflammatory responses. Its immunosuppressive activities may protect against excess inflammation but may also shield tumors from immune attack. To understand how extracellular adenosine might alter T cell responses, Ohta et al. (p. 5487) analyzed the effects of adenosine receptor A2AR signaling during T cell activation. Although only minor suppression of T cell proliferation was observed, IFN-γ production was severely inhibited by A2AR agonists. This pattern of IFN-γ suppression despite continued proliferation was observed in both $CD4^+$ and $CD8^+$ T cells. Additionally, IL-2 production and cytotoxic activity were suppressed, but no increases in apoptosis or Th2 skewing were detected. Reduced IFN-γ was still observed several days after A2AR agonist removal, suggesting that adenosine treatment resulted in the persistent impairment of T cell effector functions. These data indicate that an adenosine-rich environment allows T cell expansion but protects tissues against inflammatory responses and may allow tumors to escape immune attention by inhibiting T cell effector functions.

Stopping Anthrax at Death's Door

Bacillus anthracis, the causative agent of inhalational anthrax, suppresses macrophage responses via lethal toxin (LT), one of its virulence toxins. It has therefore been presumed that alveolar macrophages at the site of infection can do little to protect the host against anthrax. However, human autopsies and studies with mouse models of inhalational anthrax have demonstrated that *B. anthracis* is effectively cleared from human and mouse alveolar space. To attempt to explain these observations, Wu et al. (p. 5799) asked whether human alveolar macrophages (HAM) were resistant to the immunosuppressive effects of LT. Indeed, compared with RAW 264.7 macrophages, HAM were resistant to LT-mediated cytokine suppression and MAPK inhibition. In addition, both human and mouse alveolar macrophages were resistant to LT-mediated apoptosis. Although anthrax toxin receptors were present in HAM at the mRNA level, little or no protein expression was observed, supporting an observed failure of protective Ag (PA), an LT component, to bind to HAM. HAM therefore appear to be protected from the immunosuppressive effects of LT and thus, rather than serving as a target for *B. anthracis* infection, may instead act as an obstacle that the pathogen must overcome to cause disease.

How DCs Establish Oral Tolerance



Although the mechanism by which they act is unclear, dendritic cells (DCs) in the mesenteric lymph nodes (MLN-DCs) are known to be important for the induction of tolerance to the harmless bacteria and food Ags that are constantly present in the intestine. Onodera et al. (p. 5608) found that MLN-DCs, but not splenic DCs, constitutively expressed the immunoregulatory enzyme IDO, which has been implicated in many forms of immunological tolerance. Previous in vitro studies demonstrated that IDO could be induced in DCs through an interaction between CTLA-4 on regulatory T cells (Tregs) and B7 molecules on DCs. Suggesting that this interaction might also occur in vivo, the IDO-expressing MLN-DCs, but not splenic DCs, were observed to colocalize with Tregs. Indeed, CTLA-4 expression in Tregs was important for IDO expression in these DCs, but not for the DC/Treg colocalization. The subset of MLN-DCs that expressed IDO also produced CCL22, which was involved in IDO induction through CCR4 signaling in Tregs. Additional experiments suggested

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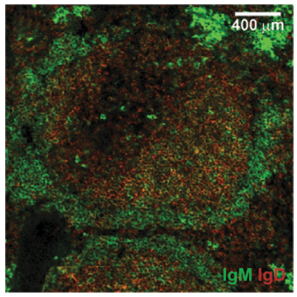
that induction of CCL22 expression in these DCs could be triggered by the phagocytosis of apoptotic cells. Taken together, these data allowed the authors to propose a model of DC-mediated oral tolerance induction requiring CCL22:CCR4 and CLTA-4:B7 interactions that lead to the expression of IDO in MLN-DCs.

p110δ Controls "Innate" B Cells



The p110δ isoform of the PI3K p110 catalytic subunit is known to be important for conventional B cell development and function. However, its role in B-1 and marginal zone (MZ) B cell activity is unknown, because p110δ-deficient mice lack these subsets of "innate" B cells. To fill this gap in our knowledge, Durand et al. (p. 5673) analyzed the effects of a specific p110δ inhibitor, IC87114, on B-1 and MZ B cell function. Use of this inhibitor demonstrated that p110δ was important for Akt phosphorylation in response to signaling through the BCR, TLR9, and chemoattractant receptors in B-1, B-2, and MZ B cells. IC87114 also inhibited both the TLR-driven proliferation of B-1 and MZ B cells and chemotaxis of these cells toward CXCL13 and sphingosine 1-phosphate. Furthermore, p110δ activity was found to be involved in MZ B cell localization in the spleen and in TLR-stimulated Ab production in B-1 and MZ B cells. In vivo, p110δ was required for the production of natural Abs, including pathogenic self-reactive Abs, and p110δ inhibitors could inhibit autoantibody production. These data indicate that the p110δ isoform of PI3K is required for many of the functions of "innate-like" B cells, and inhibitors of this subunit could be useful in the treatment of B cell-driven autoimmunity.

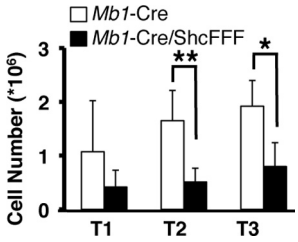
Tracking Down Human Th17 Cells

The recently identified proinflammatory Th17 subset of T cells has been the subject of intense study, but the lack of a specific cell surface marker has hindered analysis of human Th17 cells. In this issue, Brucklacher-Waldert et al. (p. 5494) found that IL-17A was specifically expressed on the surface of human Th17 cells. This cytokine was not presented by the IL-17R and was not observed to have a transmembrane domain, but may instead have been expressed in heterodimers with IL-17F. The IL-17A$^+$CD4$^+$ T cells stably secreted IL-17A and expressed RORγt, supporting their identification as Th17 cells. Following in vitro stimulation with PMA and ionomycin, these IL-17A$^+$ T cells demonstrated increased levels of basal activation and up-regulation of costimulatory molecules, adhesion molecules, and CCR6 compared with cells lacking IL-17A. T cells expressing surface IL-17A also coexpressed CD161, providing further support for a Th17 phenotype. Interestingly, analysis of Th1, Th17, and Th1/17 clones (which expressed an intermediate level of cell surface IL-17A) revealed that Th1/17 and Th17 cells demonstrated phenotypic plasticity in response to IL-12 and IL-23. Human Th17 cells can therefore be clearly identified by the expression of IL-17A on the cell surface, and the use of this marker should allow more rapid progress in the understanding of the roles these cells play in human host defense and autoimmunity.

SCF + IL-25 + Complexity = Allergy

Both stem cell factor (SCF) and IL-25 promote Th2-driven allergic responses in the lung by acting on a variety of cell types. Dolgachev et al. (p. 5705) analyzed the effects of blocking SCF to better understand how these factors might influence one another and airway inflammation in mice. Anti-SCF treatment reduced leukocyte accumulation in the lungs and Th2 cytokine production in the lungs, but not the lymph nodes, of allergic mice. SCF depletion also caused a reduction in IL-25 expression, and further analysis identified eosinophils as a major source of IL-25. To further address the role of IL-25 during allergic inflammation, the authors examined IL-25-induced cytokine production and determined that Th2 cytokine-producing, IL-25-responsive cells were increased in both lung and bone marrow during chronic allergic responses. IL-25 administration could exacerbate airway hyperreactivity (AHR) and reconstitute AHR in anti-SCF-treated mice, suggesting that both SCF and IL-25 were important for asthmatic disease. IL-4-producing, IL-25-responsive cells in both the lung and bone marrow were found to express CD11b and GR1, and these cells were depleted in both tissues following SCF neutralization in the airways. Together, these data demonstrate that local blockade of SCF can have systemic effects and suggest that SCF could serve as an attractive therapeutic target for the suppression of allergic asthmatic responses through the down-regulation of IL-25 and Th2 cytokines.

Survival via Shc



The adaptor protein Shc links multiple receptors to Ras signaling and is important for T cell development at the β selection checkpoint. Signaling through Ras is required for B cell development, but the potential role of Shc in B cell development has not been determined. Giles et al. (p. 5468) took two genetic approaches to tease apart the specific steps of B cell development in which Shc might be involved. They created transgenic mice conditionally expressing a dominant-negative Shc protein (ShcFFF) and also conditionally deleted *Shc1* at different stages of B cell development. Analysis of B cell development in these mice revealed a nonredundant role for Shc in the pre-pro-B to early pro-B cell transition, a step at which Ras signaling is also required. Pro-B cells from mice with impaired Shc signaling were defective in their ability to respond to IL-7 despite normal expression of the IL-7R. In fact, pro-B cells expressing ShcFFF underwent apoptosis in response to IL-7, although their IL-7-driven proliferation was not impaired. Signaling via Shc therefore plays a role in the IL-7-mediated survival pathway in pro-B cells and is critical for early B cell development in the bone marrow.

Summaries written by Jennifer Hartt Meyers, Ph.D.