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THE JOURNAL OF IMMUNOLOGY

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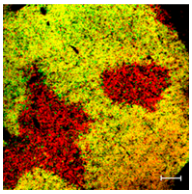
Thymic Atrophy and Virulence



Infection with virulent bacterial, viral, or parasitic pathogens can lead to thymic atrophy, although whether this occurs to prevent pathogen tolerance or is a pathogenic adaptation to escape immune attack is unclear. Until now, neither the mechanism of action for this atrophy nor its effect on thymic emigration of naive T cells during infection had been clarified. Ross et al. (p. 4266) addressed these questions and showed that during systemic *Salmonella* infection, thymic atrophy occurred through an IFN-γ– and glucocorticoid-independent mechanism, and only slightly slowed $CD4^+$ T cell emigration to the periphery. *Salmonella enterica* serovar Typhimurium (STm) infection also caused thymic atrophy in IFN-γ, T-bet–, and ZAP-70–deficient mice, demonstrating that the mechanism of action was also independent of Th1 differentiation or peripheral T cell function. Elevated glucocorticoid levels also showed no effect on this process. Twenty-one days after i.p. administration of STm (at the peak of atrophy), double positive thymocytes decreased by 95% and immature $CD4^+$ single positive (SP) thymocytes decreased by 30-fold compared with uninfected controls. However, the authors found only a 6-fold reduction in mature CD4SP cells, a 4-fold reduction in $CD4^+$ recent thymic emigrants in the spleen, and no effect on the mesenteric or axillary lymph nodes. Taken together, these data help elucidate how thymic involution occurs during *Salmonella* infection while the immune system maintains $CD4^+$ T cell migration.

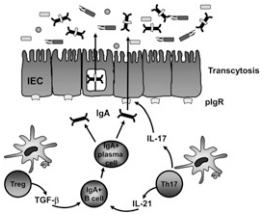
Indifferent Deubiquitinases

Negative regulation of NF-κB signaling is important to the proper control of innate and adaptive immunity and involves the activity of multiple ubiquitin-modifying enzymes, including the central regulator A20. In B cells, A20 and the deubiquitinase CYLD share several molecular targets. Although A20 deficiency results in profound defects in B cells, the role of CYLD in B cell activity has been controversial. To address discrepancies in the literature regarding the B cell phenotype of CYLD deficiency, Chu et al. (p. 4437) developed mice with B cells lacking both CYLD and A20. Surprisingly, CYLD deficiency did not exacerbate the effects of A20 deficiency on B cell development and activation, although it did cause a slight reduction in splenocyte numbers. In response to BCR stimulation, A20/CYLD-deficient B cells showed slightly enhanced proliferation and increased IL-6 levels that correlated with increased NF-κB activity compared with B cells lacking only A20. IL-6 production and NF-κB activity did not, however, differ between A20/CYLD-deficient and A20-deficient B cells following LPS stimulation. The authors conclude that CYLD and A20 do not cooperate to a significant degree in the regulation of B cell development and activation.

Serpin Tangles NETs

Neutrophil extracellular traps (NETs) are released from neutrophils during the programmed cell death process known as NETosis. NETosis can protect against the spread of infection, but excess NETs can cause inflammatory damage and exacerbate autoimmunity. Because mice lacking the cytoplasmic protein SerpinB1, which inhibits neutrophil serine proteases, had a high degree of neutrophilic death, Farley et al. (p. 4574) investigated the potential role of SerpinB1 in the regulation of NETosis. Compared with wild-type cells, PMA-treated *serpinb1*$^{-/-}$ neutrophils demonstrated increased NET production that was associated with increased nuclear expansion. PMA-induced NET production in both wild-type and *serpinb1*$^{-/-}$ neutrophils was dependent on NAPDH oxidase. NET induction by several other mediators was also increased in *serpinb1*$^{-/-}$ neutrophils but did not require NAPDH oxidase. SerpinB1 translocated into the nucleus early during NETosis in wild-type cells, suggesting its early involvement in this process. Whereas wild-type mice successfully cleared *Pseudomonas aeruginosa* lung infection, *serpinb1*$^{-/-}$ mice were unable to clear the bacteria and had greatly increased NET production. Recombinant SerpinB1 could block NET generation in both wild-type and SerpinB1-deficient cells but did not affect the production of reactive oxygen species. These data suggest that the protease inhibitor SerpinB1 acts downstream of a variety of inflammatory stimuli to protect the host from excess NET production.

Commensal Control



Th17 cells can participate in the pathogenesis of colitis but may also protect against intestinal inflammation. Gut colonization with commensal bacteria can augment intestinal levels of both Th17 cells and IgA, leading Cao et al. (p. 4666) to examine the potential involvement of Th17 cells in IgA expression and intestinal homeostasis. Compared with wild-type intestines, intestines of mice lacking the IL-17R demonstrated reduced levels of both IgA and the polymeric Ig receptor (pIgR) that is important for IgA secretion. Transfer of Th17 cells specific for a microbiota Ag into TCRβxδ$^{-/-}$ mice increased intestinal IgA and pIgR expression, which could be abolished by IL-17A neutralization. Microbiota-specific Th17 cells could also directly induce IgA production from B cells, and IL-17 acted synergistically with TNF-α to induce pIgR expression in human epithelial cells. These data were related

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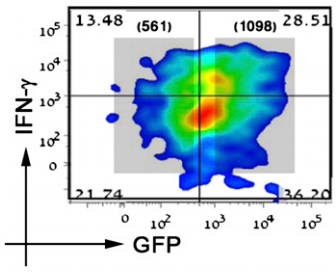
to the in vivo regulation of murine intestinal inflammation by the observation that IL-17R deficiency or IL-17 blockade increased the severity of colitis. In addition, IL-17R$^{-/-}$ mice had increased translocation of commensal bacteria and an associated increase in serum IgG specific for commensal Ags compared with wild-type mice. Taken together, these data suggest that microbiota-specific Th17 cells regulate IgA secretion and pIgR expression and thereby support intestinal homeostasis.

Handing Off Oncoproteins

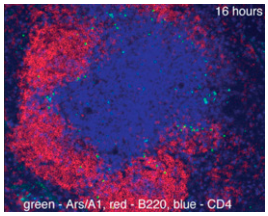


T cells can acquire molecules, including Ras GTPases, from other cells through a variety of cell contact-dependent processes. Mutations in Ras GTPase family members are common in cancers such as melanoma. Vernitsky et al. (p. 4361) assessed whether mutated Ras oncoproteins could transfer from melanoma cells to T cells, including tumor-infiltrating lymphocytes (TILs), and affect their activity. The HLA-A2^{+} melanoma cell line MEL526 was stably transfected with GFP-linked H-RasG12V or GFP alone and cocultured with TILs. GFP-H-RasG12V but not GFP alone was observed to efficiently transfer to CD3^{+} TILs. H-Ras transfer was higher to cells expressing HLA-A2 than those that were HLA-A2^{-}, but transfer did not require strict TCR specificity. Within the adopting T cells, GFP-H-RasG12V localized to the inner aspect of the plasma membrane and induced the phosphorylation of ERK1/2 and production of IFN-γ. CD8^{+} T cell acquisition of GFP-H-RasG12V but not of the mutant GFP-H-RasC184S enhanced these cells' cytolytic activity, as measured indirectly by CD107a expression. H-Ras transfer from MEL526 to TILs required cell–cell contact and was partially dependent on the proper functioning of the actin cytoskeleton, but did not require MEL526 lysis. This study introduces the possibility that oncoproteins could be transferred from melanoma cells to TILs and thereby act as danger signals to stimulate TIL effector functions.

Beyond Malaria Medicine

Dihyrdroartemisinin (DHA) is currently used to treat malaria infection. However, DHA, a derivative of *Artemisia annua* L., which has been part of the Chinese herbal compendium for centuries, also affects tumor cell growth and angiogenesis. Because little is known about the effect of DHA on T cell function, Zhao et al. (p. 4417) asked how exposure to DHA would affect Th cell differentiation and regulatory T cell (Treg) development. They found that DHA partially suppressed both Th1 and Th2 cell differentiation and almost completely suppressed Th17 development. In contrast, DHA promoted the generation of Foxp3^{+} Tregs through the TGF-βR:Smad signaling pathway. These findings led the authors to test the effects of DHA treatment in mice with EAE induced through peptide immunization. They found that a nontoxic 25mg/kg dose of DHA prevented the onset of EAE when administered daily during the induction of disease. DHA treatment after disease induction also led to a reduction in the clinical score of mice compared with untreated controls. Finally, the authors found that DHA functioned through an mTOR-dependent pathway, reducing the phosphorylation of p70S6K and S6, indicating reduction in mTOR signaling. Expression of a constitutively active form of Akt reversed the DHA-mediated suppression of the mTOR pathway and restored Th17 differentiation. This study presents ample data that DHA plays an important role in T cell regulation and that this drug may be useful for more than just treating malaria.

Tolerant Enforcers



Anergic autoreactive B cells make up 2–5% of the murine B lymphocyte repertoire and ~2.5% of human peripheral B cells and persist for several days after being anergized. Aviszus et al. (p. 4275) showed why such a potentially dangerous cell population should survive using a dual-reactive BCR transgene model, Ars/A1. Ars/A1 mice have BCRs that bind to a ubiquitous self-Ag, as well as the hapten *p*-azophenylarsonate (Ars), which renders their B cells anergic. Transfer of Ars/A1 B cells into mice immunized with various foreign Ags conjugated to Ars resulted in selective suppression of anti-Ars IgG immune responses and impairment of Th cell development. ELISPOT analysis confirmed that this was due to actual suppression of IgG-producing effectors. Even more surprising, they found inhibition of the anti-Ars response could be achieved by adoptively transferring as few as ~4000 Ars/A1 B cells into immunized recipients. In addition, this suppression was found to be independent of IgM or IL-10 secretion, but was dependent on MHCII expression. Taken together, these data suggest that the body maintains these autoreactive, anergic B cells as a regulatory mechanism to enhance self-tolerance and protect against autoimmunity.