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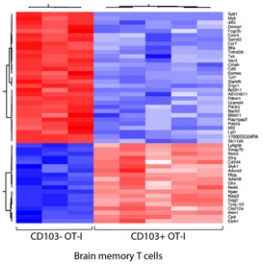
THE JOURNAL OF IMMUNOLOGY

In This Issue

Getting to Know Brain Residents



Resident memory T (Trm) cells have been recently identified as distinct from central and effector memory T cells and reside within nonlymphoid tissue. To better define the characteristics of these cells, Wakim et al. (p. 3462) compared the gene expression profiles of brain $CD8^+$ Trm and circulating memory T cells following acute infection with vesicular stomatitis virus (VSV). In a model of intranasal infection with OVA-expressing recombinant VSV following adoptive transfer of OT-I TCR transgenic T cells, $CD103^+$ Trm persisting in the brain after infection failed to undergo recall expansion upon removal from the brain. Unlike splenic memory T cells, brain Trm could not be rescued from apoptosis by IL-7 or IL-15, and MHC class II was not necessary for their survival. However, $CD103^+$ brain Trm effectively protected against a secondary brain infection with *Listeria* expressing OVA. Microarray analysis of memory T cells following VSV-OVA infection revealed that, compared with splenic memory T cells and $CD103^-$ brain memory T cells, $CD103^+$ Trm from the brain had a distinct molecular signature. Genes differentially expressed in $CD103^+$ Trm included those encoding inhibitory receptors, IFN-stimulated genes, transcription factors, and migration molecules. These data provide a basis for the understanding of the function of $CD8^+$ $CD103^+$ Trm, which in this study are demonstrated to be a distinct memory cell population.

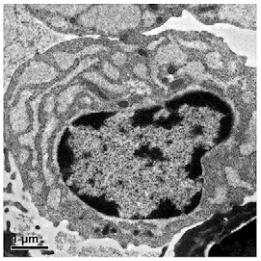
Malicious Marginal Zone B Cells

Protection from *Listeria monocytogenes* infection in Rag-1–deficient mice suggests that some facet of adaptive immunity impairs anti-*L. monocytogenes* defense. IL-10 has been shown to increase susceptibility to *L. monocytogenes* infection, but its cellular source in this context is not known. Lee and Kung (p. 3319) analyzed mice deficient in different cell types to better understand the immune response to this pathogen. Following *L. monocytogenes* infection, mice lacking B cells, but not other cell types, had significantly improved survival, reduced bacterial loads, and decreased splenic IL-10 production, relative to wild-type mice. Marginal zone B (MZB) cells from wild-type mice were found to produce IL-10 when stimulated with heat-killed *L. monocytogenes* via TLR2 and TLR4. Adoptive transfer of MZB cells into Rag-1– or IL-10–deficient hosts prior to *L. monocytogenes* infection resulted in increased bacterial loads, increased IL-10 production, and decreased IFN-γ production in the spleen compared with control knockout mice. No effect, however, was seen on bacterial load or cytokine production in the liver. Compared with wild-type mice, mice specifically lacking MZB cells had increased survival and reduced splenic bacterial load and IL-10 production following *L. monocytogenes* infection. Thus, IL-10–producing MZB cells, whose localization within the spleen poises them as first-line responders to blood-borne bacteria, appear to be the cell type most detrimental to the host during *L. monocytogenes* infection.

Dermal DC Draining

Dendritic cells (DCs) in the skin migrate to cutaneous lymph nodes (cLNs) during homeostasis and in response to skin inflammation. Several subsets of migratory skin DCs exist, of which relatively little is known about the requirements for $CD11b^+$ dermal DC (dDC) development. Bajaña et al. (p. 3368) hypothesized that the transcription factor IFN regulatory factor (IRF)4, which is important for splenic DC development, would be necessary for $CD11b^+$ dDC development. Comparison of $IRF4^{-/-}$ mice with wild-type mice demonstrated a reduction in all migratory DC subsets except for $CD103^+$ dDCs in the $IRF4^{-/-}$ cLNs during homeostasis. However, normal numbers of epidermal Langerhans cells (eLCs) and increased numbers of $CD11b^+$ and $CD103^+$ dDCs were observed in the skin of $IRF4^{-/-}$ mice, indicating that IRF4 was not necessary for development of these DC subsets. In a model of contact hypersensitivity, $CD11b^+$ dDCs in $IRF4^{-/-}$ mice were unable to migrate to the cLNs and instead accumulated in the dermis. These $IRF4^{-/-}$ $CD11b^+$ dDCs, but not $CD103^+$ dDCs, expressed lower levels of CCR7, a chemokine receptor responsible for trafficking to the cLNs. Analysis of $IRF4^{-/-}$ bone marrow-derived DCs confirmed a cell-intrinsic defect in migration to LNs and toward the CCR7 ligand CCL21. This study reveals an important role for IRF4 in controlling the migration of tissue DCs to draining lymph nodes through regulation of CCR7 expression.

X-ing Out XBP-1



Several transcription factors work together to orchestrate the differentiation of Ab-secreting plasma cells (ASCs). One of these transcription factors is X-box binding protein 1 (XBP-1), which acts in the unfolded protein response that is important for production of large amounts of Ig. To resolve conflicting data regarding the role of XBP-1 in ASC development, Taubenheim et al. (p. 3328) used a cell division-based approach to quantitatively assess ASC function in XBP-1–deficient B cells. XBP-1 deficiency did not affect the proliferation or survival of B cells following stimulation with LPS or

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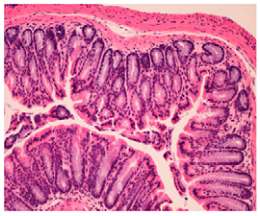
CD40L + IL-4. In response to a variety of stimuli, B cells lacking XBP-1 also upregulated Blimp-1 and IRF4 and downregulated B220 comparably to wild-type B cells. Although these XBP-1–deficient cells successfully acquired a plasma cell phenotype, they produced significantly lower levels of soluble Ig. These results were upheld in vivo by the observation that B cells lacking XBP-1 differentiated into plasma cells that secreted significantly less Ig than controls. XBP-1–deficient cells also had abnormal morphology, particularly with respect to the endoplasmic reticulum. In immunized mice, T cell-dependent development of XBP-1–deficient plasma cells proceeded normally but resulted in dramatically reduced Ag-specific IgG1 secretion. This study clarifies XBP-1 activity by revealing its importance in Ig production by, but not differentiation of, ASCs.

Mucosal Protection by p40^{phox}

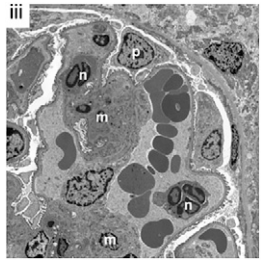


The NADPH oxidase complex generates reactive oxygen species that mediate pro-inflammatory signaling and pathogen destruction in phagocytic cells. Susceptibility to Crohn's disease has been associated with polymorphisms in the gene encoding the p40^{phox} subunit of NADPH oxidase, leading Conway et al. (p. 3631) to investigate the involvement of p40^{phox} in intestinal inflammation. In a model of dextran sulfate sodium (DSS)-induced colitis, p40$^{phox-/-}$ mice had a higher mortality rate and significantly more severe colonic inflammation than wild-type mice. A failure to properly recover from both DSS colitis and an anti-CD40–induced model of innate immune colitis was also observed in p40$^{phox-/-}$ x Rag1$^{-/-}$ doubly deficient mice. Relative to wild-type controls, p40$^{phox-/-}$ mice had greatly enhanced neutrophil recruitment to the colon during DSS colitis, and although neutrophils were found to be protective in this model, their actions required p40^{phox} expression. To address the mechanism of p40^{phox} action in colitis, the authors used an integrative bioinformatic approach and identified 10 genes involved in both NAPDH oxidase activity in human neutrophils and colonic inflammation in murine DSS colitis. These genes included those encoding CCR1, which was upregulated during colitis in the absence of p40^{phox}, and several glycan-modifying enzymes, which could regulate leukocyte trafficking and wound healing and were downregulated in p40$^{phox-/-}$ mice during colitis. Together, these data suggest that p40^{phox} is necessary for the resolution of intestinal inflammation via the regulation of neutrophil recruitment and glycan modifications.

The Road to Thymic Atrophy

Infection can cause thymic atrophy through mechanisms that vary according to the pathogen. Having previously determined that *Mycobacterium avium* could infect the murine thymus and cause thymic atrophy, Borges et al. (p. 3600) sought to elucidate the mechanism responsible for atrophy. Infection with a highly virulent, but not a low-virulence, strain of *M. avium* resulted in severe thymic atrophy associated with peripheral lymphopenia and high thymic bacterial loads. Thymic atrophy was not observed in *M. avium*-infected mice deficient in either IFN-γ or inducible NO synthase, despite mycobacterial burdens similar to those of wild-type mice. Although required for thymic atrophy, IFN-γ did not act directly on T cells, but instead affected macrophages. Infection with the highly virulent strain of *M. avium* led to a slight upregulation of corticosterone independently of IFN-γ, and treatment with a steroid receptor antagonist reverted thymic atrophy. However, IFN-γ was necessary for the exacerbation of dexamethasone-induced thymocyte death observed following infection. Analysis of thymocyte populations during infection with virulent *M. avium* revealed reductions in cell numbers at all developmental stages, including the early thymic precursors. Taken together, these data suggest that progressive thymic atrophy following virulent *M. avium* infection is mediated by IFN-γ–activated macrophages producing NO, glucocorticoid-mediated thymocyte apoptosis, and a potential reduction in seeding of the thymus from the bone marrow.

Mac-1 Modulates Lupus



The course of the autoimmune disease systemic lupus erythematosus (SLE) is influenced by a wide variety of factors acting together to cause organ damage, including nephritis. Rosetti et al. (p. 3714) developed a humanized mouse model of SLE to investigate the mechanisms responsible for organ damage. Transfer of sera from patients with active SLE into mice expressing human FcγRIIA but lacking the integrin Mac-1 led to marked nephritis, and transfer of these "pathogenic sera" was associated with glomerular deposition of human IgG. Arthritis was also induced by transfer of some of these pathogenic sera in Mac-1$^{-/-}$ mice and was associated with neutrophil accumulation in the joints. Although Mac-1 expressed on macrophages is thought to clear circulating immune complexes (ICs), Mac-1 deficiency did not alter the levels of circulating or deposited ICs from those observed in Mac-1–sufficient mice. Nephritis in FcγRIIA^{+} Mac-1$^{-/-}$ mice occurred in the absence of macrophages but was associated with a high level of glomerular neutrophil accumulation. Intravital microscopy in hFcγRIIA-expressing mice revealed that Mac-1 deficiency significantly slowed FcγRIIA-dependent neutrophil slow rolling and enhanced neutrophil responsiveness to a local chemoattractant stimulus. These data help explain the linkage between polymorphisms in the genes encoding Mac-1 and FcγRIIA and human SLE development and reveal Mac-1 as an important regulator of neutrophil recruitment leading to IC-mediated organ damage.

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