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Top Reads

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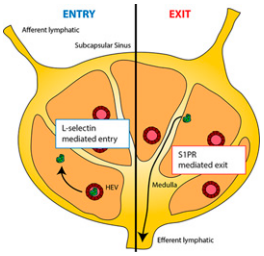
Lymph Node–Resident Neutrophils

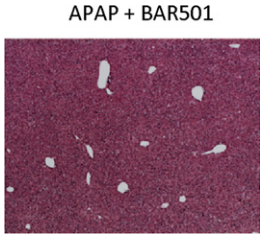


The immune function of lymph nodes (LN) is dependent on the constant recirculation of lymphocytes. In this Top Read, Bogoslowski et al. (p. 2552) demonstrate that at steady state, neutrophils entered the LN via L-selectin, where they remained for up to 24 h. Neutrophils exited the efferent lymphatics via a sphingosine-1-phosphate (S1P)-dependent mechanism. Sterile injury to the footpad did not recruit neutrophils to the popliteal LN, whereas injection with *Staphylococcus aureus* increased neutrophils 100-fold, demonstrating that they are responsive to pathogens for LN entry. When compared with wild mice, popliteal and mesenteric LN neutrophil numbers in specific pathogen-free (SPF) mice showed no difference in absolute numbers of resident neutrophils. Cohousing SPF and wild mice, however, significantly increased the numbers of neutrophils present in both inguinal and popliteal LN, indicating a role for the microbiome in maintaining resident populations. Infection of the footpad with a low dose of *S. aureus* resulted in robust recruitment of neutrophils to the LN via high endothelial venules (HEV). In contrast, chronic L-selectin blockade for 48 h to deplete resident neutrophil populations reduced their recruitment following infection, suggesting that LN-resident neutrophils recruit additional neutrophils during infection. Thus, this study demonstrates the presence of neutrophils in LN at steady state and that these cells have the capacity to recirculate via L-selectin and HEV.

Noninvasive Monitoring of *Gata3* Expression

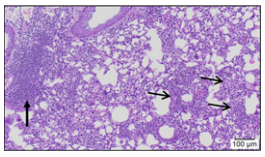
The transcription factor GATA-3 is critical for the development and differentiation of T cells and innate lymphoid populations. To monitor GATA-3 expression noninvasively at the single-cell level, Rao et al. (p. 2600) generated a strain of knock-in reporter mice, termed GATIR, by inserting an expression cassette encoding a bright fluorescent marker into the 3′-untranslated region of the endogenous *Gata3* locus. Unlike previously described strains of *Gata3* reporter mice, GATIR animals could be maintained as a homozygous line. Importantly, GATIR mice showed preserved physiological *Gata3* expression and no alterations in the development of GATA-3–dependent lymphoid cell populations. Cultures of naive T cells from homozygous GATIR mice under polarizing conditions showed that only differentiation into the Th2 subset resulted in strong upregulation of reported-mediated fluorescence and *Gata3* transcript levels. In contrast, reporter expression decreased to background levels in Th1 and Th17 cells. Additionally, analysis of bone marrow cells showed bright fluorescence in innate lymphoid cell subset 2 (ILC2) progenitors. Finally, patterns of reporter expression in cell populations from hetero- and homozygous GATIR mice were incompatible with monoallelic *Gata3* expression. In conclusion, this study demonstrates that GATIR mice are a noninvasive tool for monitoring Th2 polarization and ILC2 progenitor identification at the single-cell level.

Novel Treatment for Acetaminophen-Induced Hepatitis



In this Top Read, Biagioli et al. (p. 2535) show that acetaminophen (APAP)-induced acute liver damage can be reduced by activation of the G protein–coupled, secondary bile acid receptor, GPBAR1. APAP-induced liver damage was more pronounced in mice lacking the Gpbar1 gene ($Gpbar1^{-/-}$). Conversely, treatment of wild-type (WT) mice with the GPBAR1 agonist BAR501 reduced the severity of APAP-induced liver damage. Exposure to APAP increased the percentage of proinflammatory macrophages in the liver of both WT and $Gpbar1^{-/-}$ mice. However, treatment of WT mice with BAR501 increased the percentage of macrophages with an anti-inflammatory phenotype. WT mice lacking macrophages were protected from APAP-induced liver damage. Transfer of macrophages from either WT or $Gpbar1^{-/-}$ mice into macrophage-depleted WT mice resulted in liver damage, with the most pronounced disease observed in mice receiving $Gpbar1^{-/-}$ macrophages. The authors demonstrated that exposure to APAP increased expression of adhesion molecules and CCL2 in liver sinusoidal cells and increased expression of proinflammatory cytokines, as well as chemokine receptors, including CCR2, in macrophages. These APAP-induced effects on liver sinusoidal cells and macrophages were reversed with treatment of BAR501. Thus, these data present GPBAR1 as novel target for the potential treatment of liver damage caused by APAP.

Role of Tregs during Exacerbation of Lung Fibrosis



In this Top Read, Moyé et al. (p. 2429) demonstrate that regulatory T cells (Tregs) suppress infection-induced exacerbation of lung fibrosis in mice. Following infection with *Streptococcus pneumoniae*, the number of Tregs increased in both bronchoalveolar lavages (BAL) and lung tissue of mice with established lung fibrosis. Depletion of Tregs increased levels of TNF-α, IL-6, and

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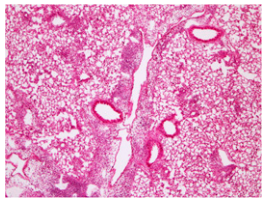
TGF-β1, which significantly exacerbated lung fibrosis following *S. pneumoniae* infection. The number of Tregs in BAL and lung tissue of mice with *S. pneumoniae*–induced exacerbated fibrosis was significantly expanded by treatment with an IL-2/anti–IL-2 mAb complex (IL-2C). Treg expansion attenuated infection-induced exacerbation of lung fibrosis with similar efficacy as antibiotic treatment and significantly reduced levels of TNF-α, IL-6, and TGF-β1. Of interest, IL-2C treatment also expanded lung γδ T cells. However, depletion of γδ T cells during *S. pneumoniae* infection did not affect fibrosis exacerbation. Thus, the ability of Tregs to suppress infection-induced exacerbation of lung fibrosis highlights a new potential therapeutic strategy for this disease.

COPA Syndrome Perturbs Thymic Tolerance



To date, the cell types and mechanisms facilitating the autoimmune arthritis and lung disease associated with COPA syndrome remain unknown. In this Top Read, Deng at al. (p. 2360) generated a germline knock-in mouse bearing one of the same missense mutations in the *coatomer protein complex subunit α (Copa)* gene found in patients (*CopaE*$^{241K/+}$). All mutant mice spontaneously developed interstitial lung disease (ILD), the organ manifestation that most strongly impacts the prognosis and clinical course of COPA patients, and had a significant increase in the percentages of activated cytokine-secreting T cells. Although introduction of the E241K *Copa* point mutation had no impact on B cell numbers and the generation of autoantibodies, these mice had more single-positive (SP) thymocytes. Additional studies revealed that mutant *Copa* in the thymic epithelium was necessary and sufficient to increase SP thymocytes in *CopaE*$^{241K/+}$ mice. The increase in SP thymocytes resulted from a defect in negative selection, an increase in pathogenic, autoreactive T cells, and a decrease in Ag-specific regulatory T cells in peripheral tissues. Thus, this study introduces a new mouse model of COPA syndrome and identifies Copa as a player in the regulation of tolerance by thymic epithelial cells.

IRF8 Promotes NLRP3 Inflammasome Activation

In this Top Read, Karki et al. (p. 2514) provide insights into the role of IFN regulatory factor 8 (IRF8) in mediating noncanonical inflammasome activation in response to Gram-negative bacteria. Compared with those from wild-type (WT) animals, bone marrow–derived macrophages (BMDM) from IRF8 knockout mice (*Irf8*$^{-/-}$) infected with Gram-negative bacteria showed decreased production of IL-18 and IL-1β, but not inflammasome-independent cytokines. In addition, BMDM lacking either IRF8 or caspase-11, but not NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), were protected from pyroptotic cell death, suggesting that IRF8 contributes to caspase-11–mediated NLRP3 inflammasome activation. Reduced activation of caspase-11 and caspase-8 in *Irf8*$^{-/-}$ BMDM resulted in decreased gasdermin D cleavage following infection with Gram-negative bacteria. Compared with WT BMDM, IFN-β production by *Irf8*$^{-/-}$ BMDM was reduced following infection with Gram-negative bacteria or treatment with either LPS or poly(I:C). *Irf8*$^{-/-}$ BMDM supplemented with recombinant IFN-β during Gram-negative bacterial infection showed increased levels of IL-18 and IL-1β, as well as restored cleavage of caspase-1 and gasdermin D. Loss of IRF8 did not alter the induction kinetics of IFN-inducible proteins, guanylate-binding proteins (GBPs), and immunity-related GTPase family member b10 (IRGB10); however, STAT1 activation was defective in *Irf8*$^{-/-}$ BMDM, suggesting that IRF8 and STAT1 regulate NLRP3 inflammasome activation independently of GBPs and IRGB10. Together, these data reveal a pathway wherein IRF8 promotes NLRP3 inflammasome activation during Gram-negative bacteria infection.