The Journal of Immunology

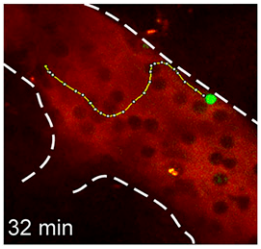
Top Reads

J Immunol 2019; 203:2747-2748; ;
doi: 10.4049/jimmunol.1990021
http://www.jimmunol.org/content/203/11/2747

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

Monitoring the Movement of Tregs

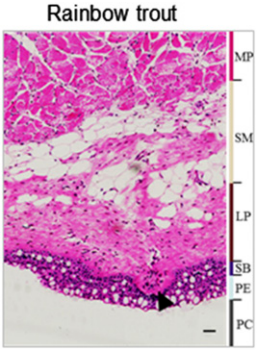


Recruitment of regulatory T cells (Tregs) is essential for limiting inflammation in the periphery. However, the molecular mechanisms governing the recruitment of Tregs remains poorly characterized. In this Top Read, Snelgrove et al. (p. 2850) used intravital microscopy to investigate adhesion and transmigration of Tregs in the skin using a two-challenge model of contact hypersensitivity. Four hours after primary challenge with Ag, 26% of adherent Tregs underwent transmigration, a process dependent on CCR4. One day after Ag challenge, adherent Tregs no longer underwent transmigration; instead, they remained in prolonged contact with the endothelium, migrating over its surface. Four hours after a second Ag challenge, Treg migration was restored but was independent of CCR4 and dependent on the CCR6/CCL20 pathway. Importantly, 24 h after Ag challenge, endothelial cells expressed MHC class II (MHCII), and blockage of these Ag presenting molecules reduced Treg recruitment and attachment to the endothelium. Overall, this study reveals the dynamics of Treg recruitment to the skin and an unexpected role for MHCII in the process.

T Cells Drive Inflammation in Malt1 Protease Deficiency

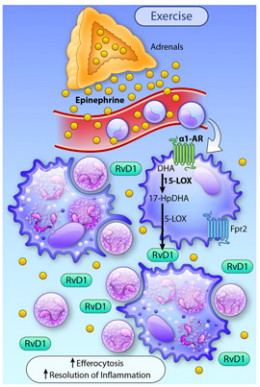
Malt1 protease-deficient (Malt1PD) mice are known to spontaneously develop high serum Ab levels, increased numbers of effector T cells, and decreased numbers of regulatory T cells (Tregs). In this Top Read, Martin et al. (p. 2791) elucidate the pathways driving disease and the contribution of environmental factors to disease progression. Noting that IgG1 and IgE plasma titers correlated with increased cellularity in gut draining lymph nodes of Malt1PD mice, the authors found that commensal and food-derived Ags in these mice led to B cell activation via BCR in conjunction with pattern recognition receptors. However, B cell activation to commensal and food Ags was not the driving factor in the autoimmunity of Malt1PD mice. Tregs harvested from Malt1PD mice inhibited proliferation of both wild-type (WT) and Malt1PD T cells in vitro but were unable to prevent expansion of pathogenic T cells in vivo. Further analysis of the Malt1PD CD4 T cell populations revealed the expansion of an IFN-γ^{hi}Nrp1^{+}Foxp3^{-}CD4^{+} effector subset in Malt1PD mice, which was absent in WT populations. The presence of WT Tregs or the lack of a polyclonal T cell response resulted in a failure of the IFN-γ^{hi}Nrp1^{+}Foxp3^{-}CE4^{+} T cells to expand and correlated with a disease-free phenotype. Together, these data demonstrate that in Malt1PD mice, Tregs are unable to control the expansion of the IFN-γ^{hi}Nrp1^{+}Foxp3^{-}CD4^{+} effector subset that drives Malt1PD autoimmunity.

Evolution of Pharyngeal Mucosal Immunity



Whereas pharyngeal mucosa (PM) is a critical line of first defense in mammals, its evolutionary origins and role in microbiota homeostasis remain unknown. In this Top Read, Kong et al. (p. 3054) demonstrate that rainbow trout, an early vertebrate, have diffuse MALT in the PM but are lacking organized lymphoid structures, such as a tonsil. Following infection with the parasite *Ichthyophthirius multifiliis*, the authors detected high levels of parasite-specific mucosal IgT and a dominant proliferation of IgT^{+} B cells, demonstrating a local mucosal immune response against a pathogen in a pharyngeal organ of a nonmammalian species. Moreover, trout pharyngeal symbiotic bacteria were found to be mainly coated with secretory IgT, and to a much lesser degree by IgM and IgD, indicating a role for mucosal Ig in the immune exclusion of teleost pharyngeal bacteria. Therefore, this study reveals that mucosal adaptive immune responses in the PM involve a process of convergent evolution between tetrapods and nontetrapods.

Sweating to Resolve Inflammation



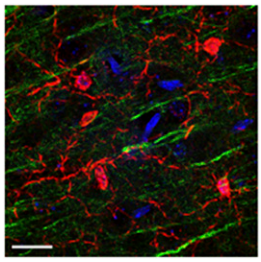
Numerous studies have demonstrated a positive impact of exercise on noncommunicable diseases. Exercise stimulates the release of catecholamines, which may contribute to the anti-inflammatory effect of exercise. Nevertheless, the precise mechanisms underlying how exercise influences the inflammatory process remain unknown. In this Top Read, Zheng at al. (p. 3013) demonstrated that, compared with sedentary controls, mice performing a 4-wk treadmill exercise regimen displayed higher macrophage phagocytic activity, enhanced levels of resolvin D1 (RvD1) and RvD1 synthesis genes, and earlier neutrophil clearance following an acute inflammatory challenge. Macrophages from mice treated with epinephrine displayed higher levels of both RvD1

and 15-lipoxygenase-1 protein, which were reduced to normal levels by the addition of α1 adrenergic receptor (α1-AR) antagonist. Similarly, stimulation of macrophages with an α1-AR enhanced macrophage phagocytosis and RvD1 production. Finally, administration of an α1-AR antagonist during acute inflammation abolished exercise-enhanced neutrophil clearance, macrophage phagocytosis, and RvD1 biosynthesis. Collectively, these results indicate that exercise-stimulated epinephrine enhances resolution of acute inflammation in an α1-AR–dependent manner and provides mechanistic insight into the beneficial effects of exercise.

IL-15 Signaling during SIV Infection

Despite the potential benefit of IL-15 in driving expansion of antiviral effector and memory cells during HIV/SIV infection, several lines of evidence suggest that IL-15 activity may also potentiate HIV/SIV disease progression. In this Top Read, Okoye et al. (p. 2928) treated two cohorts of SIVmac239-infected rhesus macaques (RM), one with chronic infection, the other with a primary infection, with a rhesusized, IL-15–neutralizing mAb. In both cohorts, anti–IL-15 treatment resulted in depletion of NK cells from blood and tissues through the treatment period, transient depletion of $CD8^+$ effector memory T cells, and $CD4^+$ and $CD8^+$ effector memory T cell hyperproliferation. Despite the loss of NK cells and perturbations in effector memory T cell homeostasis, the magnitude and kinetics of SIV replication, $CD4^+$ T cell depletion, and SIV disease progression were not significantly different between anti–IL-15–treated animals and controls. However, prolonged anti–IL-15 treatment during primary SIV infection accelerated reactivation of rhesus macaque rhadinovirus, a simian γ-herpesvirus closely related to human herpesvirus type 8/Kaposi's sarcoma–associated herpesvirus. Collectively, these data indicate that, although IL-15 signaling is not a regulator of SIV pathogenesis, it may play a role in maintaining control over oncogenic herpesviruses in SIV-infected, immunodeficient RM.

Monocytes Induce Long-Term Microgliosis in Sepsis



This Top Read demonstrates that early monocyte infiltration of the brain during sepsis results in prolonged microglial activation. Although sepsis is the leading cause of death for patients in intensive care units, the potential impact of sepsis on the CNS remains unknown. Trzeciak et al. (p. 2979) analyzed brain immune cells during early sepsis and in postseptic mice to determine the pathological link between sepsis and the development of chronic brain injury. Monocytes infiltrated the brain early during the onset of sepsis, but their numbers returned to basal levels by 48 h postsepsis induction. Brain-resident microglia exhibited an activated morphology within 24 h of sepsis induction. Analysis of the brains of mice surviving sepsis revealed a second wave of neutrophil and monocyte infiltrates at day 14 postsepsis and correlated with an increase in the number of microglia. Microglia numbers remained elevated, although neutrophil and monocyte numbers returned to normal levels 50 d postsepsis. This increase in microglia numbers also correlated to neuron dendrite loss at 50 d postsepsis. CCR2 knockout (KO) mice, wherein monocytes do not leave the bone marrow and therefore cannot infiltrate the brain, showed no expansion of microglia in sepsis-recovered brains. Additional studies showed that the increase in the number of microglia was due to self-renewal and expansion of resident microglia. M-CSF levels, which were increased in wild-type mice early in sepsis, were absent in CCR2 KO mice, suggesting that $CCR2^+$ monocytes expressing M-CSF drive the sustained proliferation and activation of microglia. Together, these data present new pathways that could be used to help prevent chronic brain injury caused by sepsis.