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Top Reads

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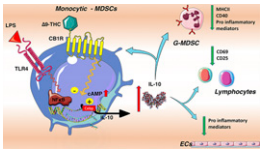
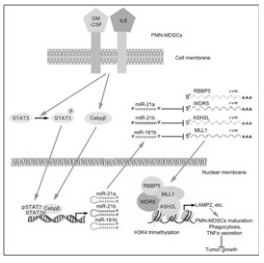
Anti-Inflammatory Effects of Δ9-THC



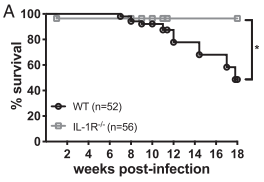
In this Top Read, Joffre et al. (p. 3339) demonstrate that Δ9-tetrahydrocannabinol (Δ9-THC) has strong and sustained anti-inflammatory properties in mice with acute inflammation. Δ9-THC treatment reduced indices of organ injury and improved the clinical status of endotoxemic mice. Compared with healthy controls, endotoxemic mice receiving Δ9-THC showed an early increase in circulating IL-10 and concomitant decreases in circulating IL-6 and CCL2. The anti-inflammatory effects of Δ9-THC were reversed by administration of a cannabinoid receptor type 1 inverse-agonist. Similar to normal mice, Δ9-THC was anti-inflammatory in splenectomized mice. However, clondronate depletion of monocytes did not increase IL-10 in response to Δ9-THC, suggesting that blood monocytic myeloid-derived suppressive cells were responsible for the Δ9-THC–induced IL-10 upregulation. Blockade of IL-10 receptor signaling did not impact Δ9-THC–induced changes in IL-10, IL-6, or CCL2, implying that the reduction of IL-6 and CCL2 are IL-10 independent. Δ9-THC treatment also reduced activation of innate and adaptive leukocytes in the spleen, most notably, neutrophils, B cells, and $CD4^+$ T cells. As cannabinoids are becoming more widely used, these data suggest the endocannabinoid system may represent a novel therapeutic target for inflammatory disorders and raises the potential of using cannabinoids to promote inflammatory resolution and to reduce organ injury in sepsis and injury.

Regulation of MDSCs by MLL1



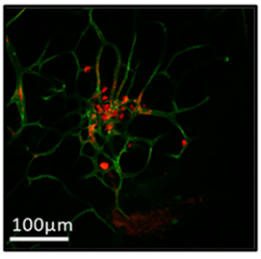
The H3K4 methyltransferase mixed-lineage leukemia 1(MLL1) is required for the regulation of hematopoietic stem cell homeostasis. Whereas disruption of the MLL1-complex is associated with acute leukemia, its exact role in myeloid cells remains unknown. In this Top Read, Zhang et al. (p. 3400) carried out a microarray analysis to identify differentially expressed genes during expansion and activation of myeloid-derived suppressor cells (MDSCs). The core components of the MLL1-complex, *Wdr5*, *Ash21*, and *Mll1*, were concurrently downregulated in activated MDSCs in vitro and in vivo. Overexpression of *Wdr5*, *Ash21*, and *Mll1* reversed the accumulation and suppressive abilities of polymorphonuclear MDSCs (PMN-MDSC) by promoting them to differentiate into mature neutrophil-like cells. Activation of MDSCs with GM-CSF and IL-6 induced Stat3 and Cebpβ, as well as the expression of miR-21a, miR-21b, and miR-181b, which targeted the 3′ untranslated regions of *Wdr5*, *Ash21*, and *Mll1*, respectively. Knockdown of these miRNAs also suppressed expansion and function of PMN-MDSCs induced by GM-CSF and IL-6. Thus, this study identifies a suppressive role for the MLL1-complex in PMN-MDSC expansion, activation, and differentiation that may be targeted therapeutically in patients with cancer or other inflammatory diseases.

IL-1R Tolerance and Cachexia in *Toxoplasma gondii* infection



In this Top Read, Melchor et al. (p. 3329) further elucidate the role of IL-1 during *Toxoplasma gondii* infection. Compared with wild-type (WT) mice, those that were IL-1R–deficient ($IL\text{-}1R^{-/-}$) and infected with *T. gondii* had increased cell death in the liver and adipose tissue during acute infection. However, $IL\text{-}1R^{-/-}$ mice had significantly improved long-term survival with no reduction in parasite burden, implicating a role for IL-1 in disease tolerance rather than resistance. The ability of $IL\text{-}1R^{-/-}$ mice to survive chronic infection was associated with their ability to recover from cachexia, an immune-metabolic disease of muscle wasting associated with chronic *T. gondii* infection. Furthermore, studies using mice deficient in either IL-1α or IL-1β showed that, relative to uninfected controls, both knockout strains where partially protected from weight loss by 12 w postinfection, but failed to fully regain body mass. These data suggest that both IL-1α and IL-1β contribute to chronic cachexia during *T. gondii* infection. Thus, this study demonstrates that IL-1R signaling triggered by IL-1α and IL-1β plays an important role in the innate inflammatory response during *T. gondii* infection and indicates a critical function for IL-1R as a regulator of host homeostasis.

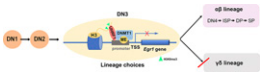
Bmi1 Maintains B-1 Cell Self-Renewal Ability



One of the most striking features of murine fetal-derived innate-like $CD5^+$ B-1 (B-1a) cells, is their unique origin and self-replenishing ability. However, the mechanism by which these IgM-secreting cells self-renew is poorly understood. In this Top Read, Kobayashi et al. (p. 3262)

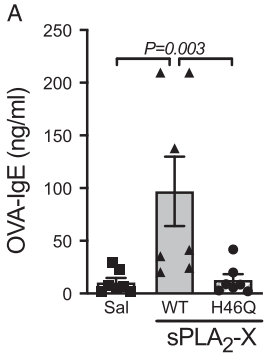
show that compared with other lymphoid cell subsets, *Bmi1* is highly expressed in B-1a cells. Whereas deletion of *Bmi1* did not alter the number of mature conventional B cells, the number of peritoneal B-1a cells was significantly reduced. *Bmi1*-deficient peritoneal B-1a cells lost their self-renewal ability upon transplantation into wild type mice. However, self-renewal ability of *Bmi1*-deficient cells was restored either by overexpression of *Bmi1* or deletion of *Ink4-Arf*, a well-known target of *Bmi1*. Furthermore, transplantation of fetal liver cells with a B cell–specific deletion of *Bmi1* failed to repopulate peritoneal B-1a cells, suggesting that *Bmi1* may be involved in the development of B-1 progenitors to mature B-1a cells. Deletion of *Bmi1*, however, did not alter fat-associated lymphoid clusters, the reported niche for B-1a cells. Microarray analysis suggested that lysine demethylase 5B (*Kdm5b*) as another possible target of *Bmi1*, which was elevated in *Bmi1*-deficient B-1a cells in a stress setting, suggesting that *Kdm5b* may also regulate self-renewal. Thus, this study demonstrates that *Bmi1* plays a vital role in self-renewal and maintenance of fetal-derived B-1a cells, which is an important step in developing pluripotent stem cell–derived B-1 cells for immune cell therapy.

UHRF1 Controls Thymocyte Fate Decisions via EGR1



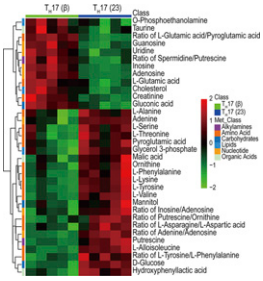
In this Top Read, Zhang et al. (p. 3248) showed that ubiquitin-like containing PHD ring finger 1 (UHRF1) is an epigenetic modifier that controls thymocyte development. A significant reduction in thymocyte cellularity and thymus size was observed in mice with a conditional knock out, in which thymocytes specifically lacked UHRF1(*Uhrf1*$^{-/-}$). Single cell RNA sequence analysis revealed an accumulation of double negative (DN) and immature single positive (ISP) thymocytes in *Uhrf1*$^{-/-}$ mice, suggesting a role in the developmental transition from DN to double positive (DP). The role of UHRF1 was specific to αβ T cell lineages, which was confirmed using mixed bone marrow chimeric mice wherein the *Urf1*$^{-/-}$ cells were enriched for IL-17^{+} RORγt^{+} γδ T cells. The loss of UHRF1 resulted in uncontrolled expression of early growth response 1 (EGR1), which enhanced γδ T development and impaired αβ T cell development. Compared with wild type cells, *Uhrf1*$^{-/-}$ thymocytes had a significantly different pattern of H3K9me3 and H3K4me3 near the *Egr1* promoter. These data indicate that UHRF1 represses EGR1 through epigenetic modifications during thymic development.

Adjuvant Properties of Endogenous Phospholipase A_2



In this Top Read, Ogden et al. (p. 3097) demonstrate that a recombinant version of a secreted endogenous phospholipase A_2 group X (sPLA$_2$-X) protein can act as an adjuvant during peripheral sensitization to inhaled Ags. Following airway challenge with OVA, mice sensitized with i.p. injections of sPLA$_2$-X plus OVA showed an increase in airway hyperresponsiveness and increases in the recruitment of type 2 immune cells to the airway, cytokine production by lung leukocytes, and serum levels of IgE and IgG. Studies using a mutant version of sPLA$_2$-X, which lacked enzymatic activity but maintained secondary protein structure, showed that the adjuvant properties of sPLA$_2$-X in the lung are dependent on its enzymatic activity. However, the enzymatic activity of sPLA$_2$-X was not required for increased recruitment of innate lymphoid cells into the peritoneum, suggesting that different adjuvant pathways are required for innate and adaptive immune responses to sPLA$_2$-X. These results, combined with those from a previous study with bee venom PLA$_2$, indicate that endogenous PLA$_2$ may act as an adjuvant to increase sensitivity to exogenous Ags in the lung.

miR-21 Controls Glycolysis of Pathogenic T_H17 Cells



Activation of lymphocytes results in enhanced cellular metabolism via glycolytic pathways. In this Top Read, Qiu et al. (p. 3160) sought to characterize the networks regulating glycolysis in pathogenic T_H17 cells. Compared with homeostatic T_H17 cells from the ileum, analysis of pathogenic T_H17 cells from the CNS of mice with experimental autoimmune encephalomyelitis (EAE) showed upregulation of glycolytic pathway genes. T_H17 cells derived in vitro showed enhanced chromatin accessibility at glycolytic genes with NF-κB binding sites and also showed that *miR-21* targets the E3 ubiquitin ligase *Peli1*–c-Rel pathway to promote glucose metabolism in T_H17 cells. Consistent with these observations, pharmaceutical inhibition of this pathway reduced expression of key glycolytic pathway gene expression in activated, pathogenic T_H17 cells and prevented the development of EAE. Thus, this study identifies the *miR-21*–*Peli1*–c-Rel axis as a key metabolic regulator of pathogenic T_H17 cells and identifies a possible therapeutic target for the treatment of T_H17-mediated autoimmune disorders.