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Top Reads

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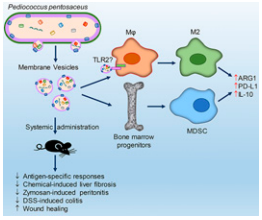
Anti-Inflammatory Extracellular Membrane Vesicles

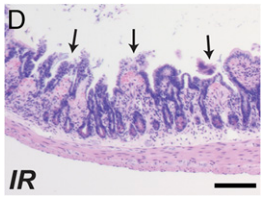


In this Top Read, Alpdundar Bulut et al. (p. 2707) show that extracellular membrane vesicles (MVs) from human commensal bacteria *Pediococcus pentosaceus* promote anti-inflammatory immune responses. Compared with bone marrow–derived macrophages (BMDMs) stimulated with LPS, MV stimulation decreased TNF-α and IL-6, but increased IL-10 secretion in a dose-dependent manner. MV stimulation of BMDM also increased expression of Arg-1 and PD-L1, suggesting that MVs promote an alternatively activated macrophage phenotype. Compared with $CD4^+$ T cells cocultured with untreated macrophages, those cultured with MV-stimulated macrophages showed decreased proliferation. MV treatment of bone marrow progenitor cells increased differentiation of myeloid-derived suppressor cells. Finally, prophylactic treatment with MVs decreased inflammation in mouse models of induced peritonitis and colitis, suggesting that they may be used therapeutically. Wound healing was also accelerated following i.p. administration of MVs. Thus, these data suggest that *P. pentosaceus* MVs may be a potential therapeutic for inflammatory diseases.

Notch Regulation of Human NK Cell Development

Although NK cell developmental intermediates (NKDIs) are known to diverge toward other developmental pathways, the stage at which they fully commit to become an NK cell remains to be elucidated. Previous work has implicated the Notch signaling pathway in regulating NK cell development and, in this Top Read, Nalin et al. (p. 2679) sought to investigate how Notch signaling regulates NK cell plasticity and commitment at distinct intermediate developmental stages in secondary lymphoid tissues (SLTs). Previous work demonstrated that stage 3 NKDIs can develop into innate lymphoid cells (ILCs) and $CD94^+IFN\text{-}\gamma^+$ NK cells. Notch activation in human tonsil–derived stage 3 and 4A NKDIs promoted differentiation of non-NK ILCs at the expense of NK cell differentiation, whereas stage 4B NKDIs were committed to the NK cell lineage despite Notch activation. Functional maturation of NK cells from stage 3 and 4A NKDIs was independent of Notch activation, whereas functional maturation of stage 4B cells required notch signaling. Furthermore, the Notch-dependent effects required simultaneous engagement with stromal cells and were stage specific, with NOTCH1 and NOTCH2 receptors regulating stage 3 NKDIs, and NOTCH1 primarily regulating stage 4A NKDIs. Thus, this study demonstrates stage-specific and stromal-dependent roles for Notch in guiding human NK cell developmental plasticity and maturation.

C5aR2 Is Protective in Gut Ischemia Reperfusion Injury



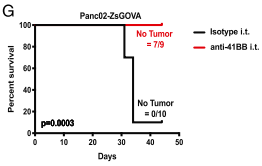
In this Top Read, Wu et al. (p. 2834) show that C5a receptor 2 (C5aR2) is protective in intestinal ischemia-reperfusion (IR) by inhibiting C5a receptor 1 (C5aR1)-mediated neutrophil recruitment to ischemic tissue. Compared with wild-type mice, those lacking C5aR2 ($C5aR2^{-/-}$) had increased neutrophil recruitment and worsened intestinal IR injury. Previous work demonstrated that neutrophils are recruited to the ischemic intestine in a C5aR1-dependent manner. Consistent with these observations, inhibition of C5aR1 in $C5aR2^{-/-}$ mice significantly reduced mucosal injury and neutrophil recruitment following IR, providing evidence that C5aR2 may negatively regulate C5aR1-mediated neutrophil recruitment. Treatment of mice with G-CSF, a potent mobilizer of bone marrow neutrophils, did not increase blood neutrophils in healthy $C5aR2^{-/-}$ mice, suggesting that C5aR2 plays a role in neutrophil mobilization. Despite enhanced tissue injury in $C5aR2^{-/-}$ IR mice, the local proinflammatory cytokine levels were significantly decreased, and IL-10 was restored. These data indicate that C5aR2 has both pro- and anti-inflammatory roles in IR injury, and imbalances in these may affect disease outcome.

SIRPα Deficiency Promotes Hemophagocytic Lymphohistiocytosis

Secondary hemophagocytic lymphohistiocytosis (sHLH), a severe form of cytokine storm syndrome (CSS), is defined by the presence of overactivated macrophages that contribute to dysregulated, inflammation-driven pathological conditions. To further elucidate the mechanisms driving sHLH, Kidder et al. (p. 2821) investigated the role of SIRPα, an inhibitory receptor expressed on macrophages that regulates phagocytosis. In contrast to controls, SIRPα-deficient mice ($SIRP\alpha^{-/-}$) displayed exacerbated and accelerated TLR9-induced sHLH. Neutralization of IFN-γ, which is largely considered a driver of HLH pathological conditions, did not prevent development of TLR9-driven sHLH in $SIRP\alpha^{-/-}$ mice. Additional studies demonstrated that SIRPα deficiency both prevented macrophages from developing a hemophagocytic phenotype and negatively regulated Erk1/2 and p38 activation downstream of TLR9, thereby reducing

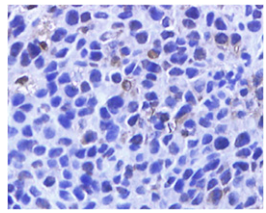
production of ferritin and proinflammatory cytokines. Collectively, these results reveal a previously unappreciated role for SIRPα in sHLH/CSS pathogenesis by preventing macrophages from becoming both hemophagocytic and hyperactivated under proinflammatory conditions.

41BB Ab Induces Tumor Regression



In this Top Read, Innamarato et al. (p. 2893) demonstrate that 41BB–41BBL bidirectional signaling between immune cells can be used to enhance expansion and function of tumor infiltrating lymphocytes (TIL). Intratumoral administration of anti-41BB resulted in tumor regression in multiple murine tumor models. Reduced tumor size correlated with increased CD8 T cell infiltration, whereas depletion of these cells prior to anti-41BB treatment abrogated the reduction in tumor growth. Additionally, TILs isolated from anti-41BB treated tumors produced IFN-γ following coculture with irradiated tumor cells, whereas isotype-treated TILs failed to produce IFN-γ, suggesting that anti-41BB may rejuvenate CD8 T cell responses. Although there were fewer classical APCs within the tumor environment after anti-41BB treatment, those present had higher levels of CD80 and CD86, which may support antitumor T cell responses. However, in humans, tumor myeloid cells and PBMCs did not express 41BB but did express 41BBL, which has been shown to promote dendritic cell maturation. Indeed, myeloid cells stimulated with 41BBL maintained cell viability and had enhanced inflammatory cytokine production compared with 41BB stimulated myeloid cells. The proliferation of TILs cultured with 41BBL-conditioned APCs was reduced when 41BBL was blocked, suggesting bidirectional signaling between myeloid cells and T cells may be responsible for enhancing the capacity of APCs to prime T cells.

Combination Therapy for Colorectal Cancer



In this Top Read, Wang et al. (p. 2905) sought to investigate the combination of anti-PD-1 and fruquitinib, a blocker of vascular endothelial growth factor receptor (VEGFR), for treatment of microsatellite-stable (MSS) colorectal cancer (CRC). Consistent with a prior report in one patient, the authors demonstrated that a combination therapy of fruquitinib and anti-PD-1 suppressed tumor growth and promoted survival time in a syngeneic murine model of MSS CRC. Furthermore, combination treatment inhibited proliferation and induced apoptosis of tumor cells and decreased angiogenesis, normalized vascular structure, and alleviated tumor hypoxia. Compared with those given single drug treatment, combination therapy reprogrammed the tumor microenvironment by enhancing release of chemotactic factors, increasing infiltration and activation of cytotoxic $CD8^+$ T cells, decreasing recruitment of regulatory T cells, and promoting polarization of tumor associated macrophages to a proinflammatory phenotype. Finally, combination treatment of CD8-deficient mice negated the antitumor effect of fruquitinib/anti-PD-1, indicating a pivotal role for these cells in the syngeneic effect of combination therapy. Thus, this study demonstrates that combination therapy for MSS CRC may be a potential strategy to broaden the benefit of anti-PD-1/PD-L1 treatment.