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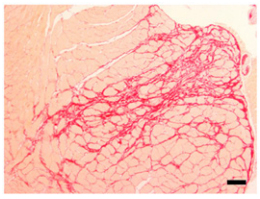
Getting to the Heart of Inflammation

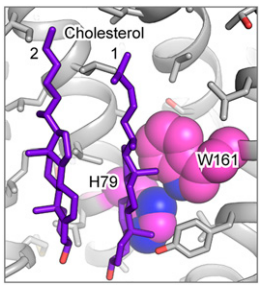


Vasoactive intestinal peptide (VIP), a neuropeptide with diverse effects on the cardiovascular system, also has anti-inflammatory properties. Because increasing evidence suggests that autoimmunity plays a role in the pathogenesis of inflammatory cardiovascular diseases, Benitez et al. (p. 3697) investigated the therapeutic effect of VIP in established murine models of experimental autoimmune myocarditis (EAM) and atherosclerosis. In addition to reducing the number of inflammatory $CD45^+$ leukocytes, $CD4^+$ lymphocytes, and $CD11b^+$ cells in the myocardium, disease prevalence and severity were reduced in mice administered VIP i.p. during the effector phase of EAM compared with untreated controls. These observations were associated with reductions in myocardial infiltrating Th17 and Th1 cells, serum levels of TNF-α, IL-6, and IL-17, and cardiomyogenic Ag–specific IgG2a and IgG1 autoantibodies. VIP treatment during the effector phase of EAM also suppressed inflammatory T cell responses and increased regulatory T (Treg) cell numbers in the draining lymph nodes (DLNs). Similar to EAM models, acute and chronic models of atherosclerosis showed reductions in the size and number of atherosclerotic plaques in the hearts of VIP-treated animals. These mice also displayed an increase in Treg cells and a reduction in IFN-γ– and IL-17–producing $CD4^+$ T cells in the arteries and the DLNs following VIP treatment. In vitro, accumulation of cholesterol in macrophages and formation of atherogenic foam cells, key events in the early stage of atherosclerosis, were significantly reduced in the presence of VIP. This effect was mediated by an increase in the expression of the membrane transporter ATP-binding cassette A1 (ABCA1) and a decrease in scavenger receptor CD36 expression, molecules known to be involved in cholesterol transport. Consistent with this, VIP also increased the expression of ABCA1 in aortas from atherogenic mice. Finally, VIP impaired proliferation and migration of smooth muscle cells, key steps in the progression of atherosclerosis, in a mouse model of complete carotid ligation. Together, these data indicate that VIP may be effective in reducing inflammation and promoting Treg cell accumulation in patients with inflammatory cardiac conditions.

NSAIDs Impact *Listeria* Immunity

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) activity and formation of proinflammatory eicosanoids, including PGE_2. Eicosanoids are implicated in immune responses to *Listeria monocytogenes,* but the mechanisms remain unknown. Thus, Theisen et al. (p. 3729) examined the effects of NSAIDs on the generation of cell-mediated immunity to *L. monocytogenes*, with a focus on COX modulation in the context of immunotherapy based on the ability of *L. monocytogenes* to generate robust T cell immunity and thereby trigger tumor-specific T cell responses. Treatment of mice with the nonspecific COX inhibitor indomethacin impaired cell-mediated immunity in response to attenuated *L. monocytogenes* (attenuated Lm), as evidenced by a decrease in Ag-specific IFN-γ–producing $CD8^+$ T cells and diminished multifunctional Ag-specific T cell responses. Mice lacking COX-1 and immunized with attenuated Lm demonstrated improved Ag-specific $CD8^+$ T cell responses and were protected from a secondary lethal challenge with virulent *L. monocytogenes*, relative to COX-1–sufficient controls. Mice treated with the COX-2–specific inhibitor celecoxib had impaired Ag-specific effector and multifunctional $CD8^+$ T cell responses. Thus, COX-2 is critical, whereas COX-1 is detrimental, for the development of immunity to *Listeria*. Mice deficient in PGE synthase displayed impaired Ag-specific IFNγ production and multifunctional $CD8^+$ T cell responses in the context of attenuated Lm infection and were unable to clear a secondary challenge of virulent *L. monocytogenes*. However, treatment of these mice with exogenous PGE_2 rescued T cell responses. Thus, PGE_2 is necessary and sufficient for generation of an optimal T cell–mediated immune response to infection. Interestingly, acetaminophen did not negatively impact cell-mediated immune response to *Listeria*. These data reveal contrasting roles for COX-1 and COX-2 in immune responses to *Listeria* and demonstrate that analgesia delivered by acetaminophen may be preferable to that mediated by NSAIDs during *L. monocytogenes* immunotherapy.

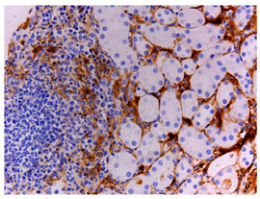
Plunging into the Depths of Chemokine Receptor Interaction Sites



The G protein–coupled receptors CXCR4 and CCR5 bind their respective ligands CXCL12 and multiple inflammatory chemokines to trigger lymphocyte trafficking and can also function as coreceptors for HIV-1 entry. Mutations that impact the interactions of these receptors with their various protein ligands remain to be elucidated. In this issue, Heredia et al. (p. 3825) used deep mutational scanning to define the sequence-activity landscapes of CXCR4 and CCR5 by using single-site saturation mutagenesis (SSM) libraries expressed in human Expi293F cells, which do not express CCR5 and were engineered to lack CXCR4. Expi293F cells expressing the CXCR4 SSM library were exposed to 12G5, an Ab that binds CXCR4 and blocks HIV-1

infection. Residues critical for 12G5 binding were found in the N terminus and solvent-exposed tips of extracellular loops 2 and 3 of CXCR4, in agreement with prior studies. Proline 27 of CXCR4 was identified as one of the most highly conserved residues for CXCL12 affinity. Furthermore, mutations on the transmembrane (TM) domains 1, 2, and 7 of CXCR4 reduced CXCL12 binding. CXCR4 mutations increasing CXCL12 interactions localized to three general regions, including a putative allosteric site, the base of the ligand-binding cavity at the receptor's center, and the cytoplasmic junction of helices TM2, TM3, TM6, and TM7. In similar studies involving CCR5, acidic amino acid substitutions in CCR5 extracellular regions enhanced binding of HIV-1 gp120, whereas mutations of residues near the extracellular loop 2–TM5 junction disrupted the CCR5–gp120 complex but had little effect on CXCR4–CXCL12 binding. Overall, this study demonstrates that deep mutational scanning has the potential to reveal residues critical for HIV pathogenesis and elucidate receptor activity and ligand interactions, beyond what is discoverable via small-scale mutagenesis studies, bioinformatics, and crystallization.

TLR4 Drives Macrophage Metabolic Reprogramming



Increasing antibiotic resistance has highlighted the need for alternative therapies to treat nosocomial infections. Although recent studies have demonstrated that treatment with the clinically approved TLR4 agonist monophosphoryl lipid A (MPLA) confers resistance to bacterial infection, the mechanisms responsible this protection are not well understood. In this issue, Fensterheim et al. (p. 3777) determined whether metabolic reprogramming of macrophages triggers TLR4-driven resistance to infection. Treatment of mice with MPLA 2 consecutive days prior to i.v. bacterial or fungal infection improved pathogen clearance and facilitated organ protection. The beneficial effect of MPLA correlated with a significant increase in the number of tissue macrophages, which also exhibited increased phagocytic and respiratory burst activity. To assess the molecular mechanisms underlying the TLR4-driven enhancement of macrophage function, bone marrow–derived macrophages (BMDM) were treated in vitro with MPLA for 24 h, washed, and cultured for an additional 3 d in the absence of MPLA (referred to as 3 d post-MPLA [3dp] macrophages). Compared with BMDM treated with MPLA for 24 h prior to examination, 3dp macrophages displayed elevated glucose intake, coupled with increases in extracellular acidification rate (a measure of glycolytic capacity) and basal oxygen consumption rate. 3dp macrophages also showed increased lactate and ATP production and an increase in mitochondrial DNA, suggesting a shift to aerobic glycolysis coupled with mitochondrial biogenesis. Consistent with these observations, 3dp macrophages displayed increased malate transport into the mitochondria, thus enabling elevated mitochondrial activity that drives ATP production. This metabolic program was dependent on MyD88- and TRIF-dependent signaling pathways, in addition to downstream mTOR activation. In vivo, blockade of mTOR in mice 3 h prior to MPLA treatment abolished the survival benefit conferred by MPLA treatment during systemic *Staphylococcus aureus* infection. Together, these findings demonstrate that TLR4 priming of macrophages improves their antimicrobial function, through a process driven by metabolic reprogramming. As MPLA has a proven safety record in humans, MPLA may be considered for use in hospitalized patients to improve immune responses to antibiotic-resistant infections.