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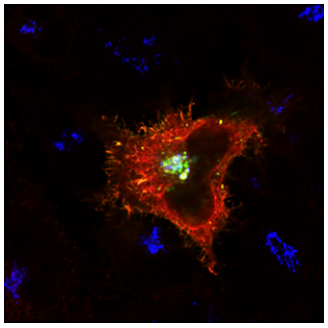
Inactivating an Activator



Human CMV (HCMV) successfully infects hosts using multiple mechanisms that modulate immune responses. One strategy employed by HCMV is the blockade of NK cell activation. Bennett et al. (p. 1093) now show that the HCMV protein UL142 can inhibit cell surface expression of the NKG2D ligand ULBP3. UL142 has been shown previously to inhibit surface expression of the full-length form of the NKG2D ligand MHC class I-related chain A. Its effect on ULBP3 during infection was identified through comparison of clinical HCMV strains that included or lacked the gene region containing ULBP3, as well as the ability of an rUL142-expressing adenovirus to inhibit ULBP3 surface expression. UL142 interacted with ULBP3 and limited its surface expression by causing its retention in the Golgi complex. Moreover, uninfected cells transfected with UL142 and ULBP3 were protected from NK cell-mediated cytolysis. These observations indicate that ULBP3 surface expression can be altered by HCMV strains expressing UL142, thus providing further evidence of the multiple evasion mechanisms employed by this virus.

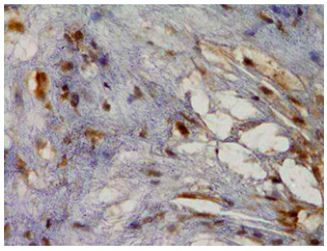
Flagellin Fires up Gut Defenses

Detection of microbial ligands by pattern recognition receptors in the mucosa sets off anti-microbial adaptive immune responses, including production of Th17-related cytokines. TLR5 is a pattern recognition receptor that detects the bacterial protein flagellin. In this article, Van Maele et al. (p. 1177) have identified a unique lymphocyte population that produces IL-17 and IL-22 in response to dendritic cell recognition of flagellin via TLR5. Greater transcription of IL-17– and IL-22–encoding genes, as well as several anti-microbial genes associated with Th17 responses, occurred rapidly and transiently in the spleen, lymph nodes, lungs, and gut of mice treated with flagellin compared with control mice. A mixed cell population of $CD3^{negative}CD127^{+}$ cells, including lymphoid tissue inducer-like $CD4^{+}$ cells, was identified as a source of Th17-related cytokine responses. Dendritic cells were required for TLR5-mediated flagellin-driven production of Th17-related cytokines but were not the primary source of these cytokines. Thus, $CD3^{negative}$ $CD127^{+}$ cells may be critical for coordinating initial responses against bacterial pathogens by producing Th17-related cytokines.

Tuberculosis Tyranny

Chronic *Mycobacterium tuberculosis* infection is established by suppression of alveolar macrophage antibacterial responses following bacterial phagocytosis. The nuclear receptor superfamily member peroxisome proliferator-activated receptor γ (PPARγ) is a transcription factor that has been shown to negatively regulate macrophage activation. Rajaram et al. (p. 929) observed that *M. tuberculosis* or mannose-capped lipoarabinomanan (ManLAM), a cell wall component, induce PPARγ expression in macrophages and modulate downstream inflammatory responses. Human macrophages infected with *M. tuberculosis* or treated with ManLAM showed a significant increase in PPARγ expression over basal levels. Infection or ManLAM treatment stimulated phosphorylation of p38 MAPK and cytosolic phospholipase 2, contributing to PPARγ-mediated IL-8 production. PPARγ-driven IL-8 production in response to ManLAM was dependent on mannose receptor signaling but did not require TLR2 or activation of NF-κB. Less PPARγ was induced by infection with the attenuated *Mycobacterium bovis* Bacillus Calmette-Guérin strain compared with *M. tuberculosis*, and *M. bovis* Bacillus Calmette-Guérin–induced IL-8 production required NF-κB and not PPARγ. Interestingly, knockdown of PPARγ in macrophages restricted intracellular replication of *M. tuberculosis* and increased TNF production. These results demonstrate that upregulation of PPARγ in macrophages may be an important response harnessed by *M. tuberculosis* to promote intracellular growth.

Healthier Arteries with IL-33



Atherosclerosis is a chronic inflammatory condition associated with fibrotic plaque formation in arteries. Plaque formation is driven by multiple mechanisms, including IFN-γ–mediated recruitment of macrophage-derived foam cells to inflamed vessels. IL-33 is a member of the IL-1 cytokine family that induces production of Th2 cytokines and has been shown to inhibit atherosclerosis development. In this issue, McLaren et al. (p. 1222) show that IL-33 blocks plaque development by inhibiting foam cell formation. IL-33 treatment of atherosclerosis-prone apolipoprotein $E^{-/-}$ mice reduced both the percentage of foam cells in atherosclerotic plaques and the frequency of foam cells being converted from macrophages compared with control mice. In vitro IL-33 treatment of human macrophages decreased their low-density lipoprotein uptake and promoted cholesterol efflux. IL-33–mediated changes in macrophage gene expression were dependent on signaling via its receptor, ST2, as IL-33 did not reduce foam cell formation in $ST2^{-/-}$ murine bone marrow-derived macrophages. Collectively, these data clarify the mechanisms by which

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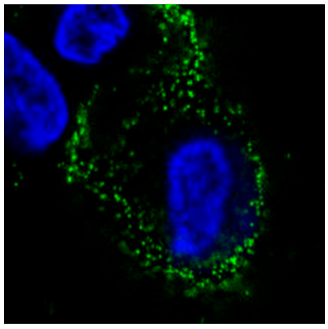
IL-33 reduces atherosclerosis and support further investigation into the use of IL-33 in anti-atherosclerosis therapy.

A New View of Endothelial Glue



Inflammation-induced upregulation of adhesion molecules on the endothelial cell surface is critical for the recruitment of leukocytes from the bloodstream to damaged tissues. Activation of endothelial cells has been shown to be promoted by TNF and IL-1β, and Cheng et al. (p. 1238) now show that macrophage migration inhibitory factor (MIF) also boosts adhesion molecule expression and leukocyte recruitment. Small-interfering RNA-mediated suppression of MIF in HUVECs significantly reduced their ability to interact with and adhere to leukocytes following TNF treatment compared with control TNF-treated HUVECs. In addition, these TNF-treated MIF-depleted HUVECs expressed significantly lower levels of the adhesion molecules E-selectin, ICAM-1, and VCAM-1 on the cell surface. MIF-depleted HUVECs also produced significantly lower levels of the inflammatory mediators IL-6, IL-8, and MCP-1 upon TNF treatment compared with the control MIF-expressing HUVECs. Adhesion molecule expression was linked to a role for MIF in TNF-induced p38 MAPK phosphorylation. Exogenous treatment of HUVECs with MIF in combination with TNF significantly enhanced leukocyte adhesion compared with TNF alone and correlated with increased surface expression of P-selectin, but not E-selectin, ICAM-1, or VCAM-1. Thus, MIF is able to promote endothelial adhesion functions, but different mechanisms may be enlisted depending on the route of MIF exposure.

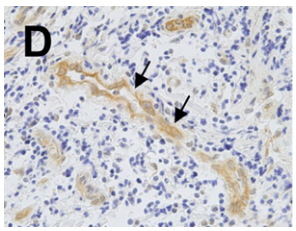
Awakening NK Cells

NK cells initiate maximal effector responses upon receiving stimulatory as well as additional priming signals. Lee et al. (p. 917) now show that suppressor of cytokine signaling 2 (SOCS2), a regulator of receptor-mediated signaling, plays a critical role in NK cell priming by IL-15. SOCS2, but no other SOCS family members, was specifically upregulated during in vitro differentiation of human NK cells treated with IL-15. SOCS2 was required for IL-15–mediated priming of NK cell cytotoxicity and IFN-γ expression, as these functions were absent in IL-15–treated NK cells in which SOCS2 expression had been silenced by RNA interference. SOCS2 has been shown previously to regulate other cytokine signaling pathways by binding to phosphorylated intracellular proteins and targeting them for proteosome-mediated degradation. Along these lines, IL-15 priming promoted SOCS2 interactions with proline-rich tyrosine kinase 2 phosphorylated at tyrosine 402 (p-Pyk2^{Tyr402}), which resulted in ubiquitination and proteosomal degradation of p-Pyk2^{Tyr402}. Furthermore, SOCS2 silencing correlated with an accumulation of p-Pyk2^{Tyr402} and inhibition of NK cell effector functions. Taken together, these data indicate that IL-15 priming contributes to activation of NK cell effector functions by upregulating SOCS2 and limiting the accumulation of p-Pyk2^{Tyr402}.

A Fresh Look at Allelic Exclusion

Most lymphocytes in jawed vertebrates rely on allelic exclusion as a strategy to ensure that Ag receptor expression originates from a single allele, and several mechanisms have been suggested for driving allelic exclusion. Steinel et al. (p. 1055) provide data supporting a process of posttranscriptional silencing of endogenous VβDJβCβ genes to impose TCRβ allelic exclusion. Vβ segment expression was assessed in mice expressing a single copy of a preassembled functional endogenous Vβ14DJβ1.5Cβ1 gene (Vβ14^{NT}) and/or transgenic mice carrying a preassembled Vβ8.2DJβ1.1Cβ1 transgene (Vβ8^{Tg}). Most αβ T cells from these Vβ14^{NT} or Vβ8^{Tg} mice exclusively expressed Vβ14^{+} or Vβ8^{+} TCR β-chains, respectively. Other endogenous rearranged Vβ segments that originated from wild-type alleles were also expressed in some αβ T cells from both of these mice strains. Interestingly, the majority of thymocytes from Vβ8^{Tg}:Vβ14$^{NT/+}$ mice generated by a cross between Vβ14$^{NT/+}$ and Vβ8^{Tg} mice expressed Vβ8^{+} TCRβ on the cell surface, but approximately half expressed Vβ14^{+} TCRβ in spite of similar levels of Vβ14^{NT} mRNA in Vβ8^{+}Vβ14^{+} and Vβ8^{+}Vβ14^{-} cells. These data suggested a mechanism of posttranscriptional silencing of functionally assembled endogenous VβDJβCβ genes, thus revealing another potential strategy used by lymphocytes to promote TCRβ allelic exclusion.

A Parallel Path to Inflammation



Wnt signaling is known to play roles in development and cancer, and recent evidence indicates its involvement in inflammation. Kim et al (p. 1274) have defined a role for Wnt5a in inducing endothelial cell inflammation that is independent of TNF-α–induced signaling. In vitro treatment of human aortic endothelial cells with rWnt5a induced a rapid and significant increase in genes expressing inflammatory cytokines, especially cyclooxygenase-2, compared with untreated cells. Wnt3a treatment induced less inflammation compared with Wnt5a, which suggested that Wnt-induced inflammation was β-catenin independent. TNF-α treatment induced inflammatory cytokine gene expression, but was less effective at inducing cyclooxygenase-2 compared with Wnt5a treatment, suggesting Wnt5a and TNF-α differentially regulate downstream inflammatory genes. Wnt5a-induced inflammatory responses required Ca^{2+} signaling and protein kinase C activity, as well as NK-κB signaling. Wnt5a was nearly undetectable in normal tissues but was expressed in a variety of inflamed tissues, including endothelial cells and histocytes associated with atherosclerotic vessels and activated synoviocytes from rheumatoid arthritis-affected tissues. Thus, Wnt5a appears to stimulate inflammatory endothelial responses independent of TNF-α–induced signaling and may provide a novel route of therapeutic intervention for conditions involving endothelial inflammation.

Summaries written by Christiana N. Fogg, Ph.D.