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THE JOURNAL OF IMMUNOLOGY

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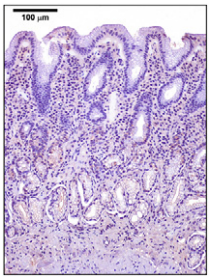
How HO-1 Helps



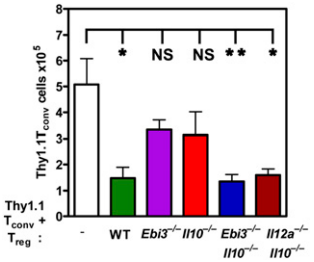
Pathogens often interfere with the host immune response to promote their own survival. Two articles in this issue implicate the anti-inflammatory molecule heme oxygenase-1 (HO-1) in bacterial and viral pathogenesis. In the first article, Gobert et al. (p. 5370) analyzed how *Helicobacter pylori*, which causes chronic inflammation in the human stomach, interacts with NO to modulate immune responses in gastric epithelial cells. In uninfected cells, NO induced HO-1 expression through NF-κB activation. *H. pylori* infection, however, inhibited NO-induced HO-1 upregulation through the virulence factor cytotoxin associated gene A (CagA). CagA, together with ERK1/2 and JNK in gastric epithelial cells, activated the transcription factor heat shock factor-1, which impaired NO-induced NF-κB activation. Supporting the relevance of this mechanism to disease, patients infected with CagA-expressing strains of *H. pylori* had lower levels of HO-1 and increased levels of gastritis than did patients infected with CagA-deficient strains. In a mouse model of *H. pylori* infection, increasing HO-1 expression reduced inflammatory chemokine expression and inhibited the development of gastritis. Taken together, these data present a mechanism by which *H. pylori* blocks an anti-inflammatory mechanism to promote persistent gastric inflammation.

In the second article, Cross et al. (p. 5015) identify a possible treatment for HIV-associated neurocognitive disorders, which often persist despite effective antiretroviral therapy. Because the reduction of peripheral inflammation might help treat these disorders, the authors assessed the effectiveness of the anti-inflammatory molecule dimethyl fumarate (DMF), which has proved to be therapeutically effective in psoriasis and multiple sclerosis. Treatment of HIV-infected monocyte-derived macrophages with DMF inhibited viral replication via impairment of NF-κB activation, which plays a major role in HIV transcription. DMF also reduced HIV-induced neurotoxicity, most likely through effects on HO-1. HIV infection significantly reduced HO-1 expression in macrophages and also interfered with other players in the antioxidant response, and DMF treatment reversed these defects. The DMF-induced upregulation of HO-1 did not affect HIV replication, but did reduce the production of neurotoxins by infected macrophages. In addition, DMF inhibited CCL2-mediated monocyte chemotaxis, suggesting that this treatment could reduce monocyte recruitment into the brain during HIV infection. Thus, the multiple effects of DMF on HIV-infected macrophages suggest its utility as adjunctive therapy for HIV-induced neurotoxicity. Both articles indicate that modulation of HO-1 expression could be an effective strategy to control inflammation.

MicroRNA Motivates Macrophages

In macrophages, several microRNAs are induced by TLR activation and mediate feedback regulation by inhibiting inflammatory signaling. In contrast, microRNA (miR)-125b is downregulated in macrophages following TLR4 activation, leading Chaudhuri et al. (p. 5062) to investigate the involvement of this microRNA in macrophage activation. miR-125b was highly expressed in macrophages, and overexpression of miR-125b induced upregulation of MHC class II and costimulatory molecules in these cells. Overexpression of miR-125b also enhanced expression of the IFN-γR and augmented the capacity of macrophages to act as APCs. In addition, both in vitro and in vivo, LPS-stimulated macrophages ectopically expressing miR-125b killed tumor cells more efficiently than did control LPS-treated macrophages. The transcription factor IFN regulatory factor 4 (IRF4) was identified as a target of miR-125b in macrophages. Knockdown of IRF4 recapitulated the enhancement of macrophage activation observed with miR-125b overexpression, suggesting that miR-125b promotes macrophage activation through the inhibition of IRF4. Thus, this microRNA plays an important role in macrophage activation, and modulation of its expression could enhance macrophage-mediated antitumor activity.

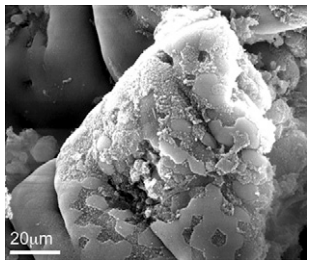
Treg Functional Flexibility



Depending on the situation, regulatory T cells (T_{regs}) can use different mechanisms to suppress the activity of diverse cell types. To better understand how specific suppressive mechanisms contribute to T_{reg} activity, Pillai et al. (p. 4987) examined mice unable to produce IL-10 and IL-35. Although mice singly deficient in either cytokine had impaired suppressive activity, T_{regs} in the doubly deficient mice suppressed conventional T cells as effectively as wild-type (WT) T_{regs}. This unexpected suppressive capacity was observed both in vitro, where it was cell-contact independent, and in several models of in vivo suppression. The gene expression profile of IL-$35^{-/-}$/IL-$10^{-/-}$ T_{regs} was generally very similar to that of WT T_{regs}. However, the doubly deficient cells had enhanced expression of cathepsin E, which has been implicated in the proteolytic release of the suppressive molecule TRAIL. Although WT T_{regs} used IL-10 and IL-35 as their primary soluble mediators, soluble TRAIL was found to be necessary and sufficient for the suppressive activity of IL-$35^{-/-}$/IL-$10^{-/-}$ T_{regs}. Interestingly, genetic background affected the preferred mechanism of T_{reg} activity, as WT BALB/c T_{regs} tended to act mainly through TRAIL, similar to the activity of IL-$35^{-/-}$/IL-$10^{-/-}$ T_{regs} on the C57BL/6 background. This

study demonstrates a surprising degree of T_{reg} functional plasticity, which may be important to maintain immune control in response to changes in the environment.

A Mosaic of M Cells



M cells are specialized epithelial cells that act in mucosal immune surveillance by transcytosing Ags from the lumen to underlying dendritic cells. These cells are found in follicle-associated epithelium overlying Peyer's patches and nasal-associated lymphoid tissue, in inducible lymphoid aggregates including isolated lymphoid follicles, and in an inducible fashion at the tips of intestinal villi (villous M cells). Wang et al. (p. 5277) have undertaken a comprehensive study of the different types of M cells in an attempt to understand their development and specific roles in different locations. Expression of the peptidoglycan recognition protein-S (PGRP-S) was found on Peyer's patches, nasal-associated lymphoid tissue, and isolated lymphoid follicle M cells, but not on villous M cells. Although M cell function required B cells and CD137 expression, commitment to the M cell lineage and associated expression of PGRP-S were B cell and CD137 independent. Interestingly, cholera toxin induced M cell differentiation from mature epithelial cells in both the intestine and the airways. Despite many similarities in origin and development among the different M cell types, their functional phenotypes were found to be quite distinct. By defining characteristics of several specific M cell subsets, this study provides a framework to study the specialized roles these cells may play in mucosal immunity.

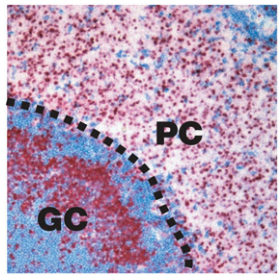
Klf3 Calls the Shots

Krüppel-like factor 3 (Klf3) is a member of a family of zinc finger-containing transcription factors and generally acts as a transcriptional repressor. Because Klf3 has been implicated in B cell activation and function, Vu et al. (p. 5032) analyzed Klf3-deficient mice to investigate its role in B cell development. In the absence of Klf3, cell-autonomous defects in B cell differentiation were observed in the bone marrow, spleen, and peritoneal cavity. Compared with wild-type mice, $Klf3^{-/-}$ mice had fewer pro-B and immature B cells in the bone marrow, but increased numbers of mature B cells in both the bone marrow and the peripheral blood. In the spleen, Klf3 was found to be important for the differentiation and proper localization of marginal zone (MZ) B cells. When compared with wild-type MZ B cells, the $Klf3^{-/-}$ MZ B cells had defects in BCR signaling and activation in response to TLR stimulation. In addition, Klf3 was required for proper development of B1 B cells in the peritoneal cavity. Finally, B cells lacking Klf3 upregulated closely related Klf family members, suggesting the existence of a regulatory network of Klf transcription factors that control B cell activity. This demonstration that Klf3 is broadly involved in B cell differentiation is important for the full understanding of the effective generation and regulation of a B cell response.

Platypus Ponders TCR Ancestry

Placental mammals assemble genes encoding their TCRs through V(D)J recombination of four loci: α, β, γ, and δ. Recently, a fifth locus, designated TCRμ, was identified in marsupials. Wang et al. (p. 5246) have now found that, although TCRμ is absent from the genomes of placental mammals, an orthologous TCRμ locus is present in a monotreme, the duckbill platypus. Analysis of platypus TCRμ transcripts indicated that, like marsupial TCRμ, they consisted of two V domains, designated V1 and V2, followed by a C domain. Both V1 and V2 appeared to be assembled through RAG-mediated recombination; however, V1 had longer CDR3 regions and contained Dμ segments, whereas V2 seemed to result mainly from direct joining of Vμ and Jμ segments. The TCRμ V gene segments were more similar to the V regions of Abs than to those of conventional TCRs, and the TCRμ genomic locus, like that of the marsupial TCRμ locus, appeared to be organized in tandem clusters. The discovery of a monotreme TCRμ suggests that the TCRμ locus was present in a common ancestor of all mammals and was lost in placental mammals during evolution. Future studies of cells bearing TCRμ receptors may provide a deeper understanding of T cell Ag recognition and of the reasons this locus was retained or lost during evolution.

Skewing Skin Susceptibility



Epidermolysis bullosa acquisita (EBA) is an autoimmune skin disease characterized by autoantibodies to type VII collagen. In mice, disease is linked to the MHC haplotype $H2^s$ and is associated with IgG2 complement-fixing Abs. These data led Hammers et al. (p. 5043) to hypothesize that a predominant Th1 response would lead to EBA susceptibility, whereas a Th2 response would be linked to resistance. In support of this idea, SJL/J mice were susceptible to EBA induction and Th2-prone BALB/c mice were resistant. In SJL/J mice, autoantibodies bound to the dermal–epidermal junction were dominated by complement-fixing IgG2c Abs, whereas those in the resistant BALB/c mice were mainly of the IgG1 isotype. In draining lymph nodes, SJL/J mice demonstrated Th1 skewing, increased T cell proliferation, and increased production of plasma cells compared with BALB/c mice, which had a Th2-dominated response. C57BL/6 mice were also resistant to EBA induction, showing a phenotype similar to that in BALB/c mice. However, congenic C57BL/6 mice bearing the $H2^s$ haplotype became susceptible to disease. Analysis of FcR expression in these mouse strains revealed that peripheral leukocytes in susceptible mice had higher FcγRIV expression than did cells of resistant mice. These insights into the contributions of both innate and adaptive immunity to EBA susceptibility may help lead to new treatments for blistering skin diseases.

Summaries written by Jennifer Hartt Meyers, Ph.D.