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THE JOURNAL OF IMMUNOLOGY

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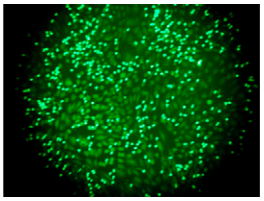
Sepsis Saps Endothelium



Dysregulation of endothelial cell function during sepsis, which can be triggered by TLR stimulation, contributes to excessive inflammation and organ failure. Shin et al. (p. 1119) now describe a multitude of damaging effects that TLR2 stimulation inflicts on endothelial cells. TLR2 agonists induced IL-6 and IL-8 secretion and E-selectin expression in a variety of primary human endothelial cells, including those from the umbilical vein, lung, and coronary artery. IL-6 responses to TLR2 agonist treatment were TLR2 dependent, as IL-6 secretion increased significantly in endothelial cells from wild-type but not $TLR2^{-/-}$ mice. Human umbilical vein endothelial cells treated with TLR2 agonist showed increased membrane permeability and dysregulation of multiple coagulation factors, as well as upregulation of TLR2 expression. Increased expression of E-selectin, P-selectin, and MCP-1 mRNAs and greater neutrophil infiltration, indicated by increased myeloperoxidase levels, were observed in the lungs of wild-type but not $TLR2^{-/-}$ mice upon systemic TLR2 agonist treatment. Lung fibrin also increased significantly in mice treated intratracheally with a TLR2 agonist compared with carrier-treated mice. These results highlight the extent to which TLR2 agonists affect endothelial cells, supporting the notion that TLR2 activation may be a major cause of endothelial damage during sepsis.

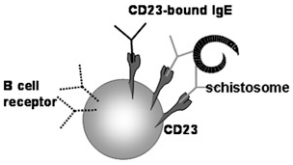
Host Seeking Long-Term IgM

IgM secretion is commonly considered an early immune response to infection, which is typically followed by the development of a longer lasting IgG response. Racine et al. (p. 1011) show that a long-lasting IgM response against the intracellular bacterium *Ehrlichia muris* is sufficient to protect mice against lethal infection. Previous work has shown that *E. muris* infection is associated with a strong IgM response. In this study, a population of $CD138^{high}IgM^{high}$ cells in the bone marrow was linked to the generation of a protective IgM response against a chronic, lethal *E. muris* infection in mice. This unique Ag-specific cell population had phenotypic features of both plasmablasts and plasma cells. Ag-specific $CD138^{high}IgM^{high}$ cells were found in the bone marrow, even in the absence of detectable infection following antibiotic treatment, and these cells could be reactivated to produce a protective IgM response upon reinfection. Moreover, IgM responses were shown to be sufficient to protect activation-induced cytidine deaminase-deficient mice, which produce only IgM and not IgG, against lethal *E. muris* infection. These findings define a unique role for the IgM response in protection against a chronic intracellular bacterial infection, and may offer a new approach for designing antibacterial therapies.

Igniting Tumor Inflammation

IL-12 immunotherapy has shown limited efficacy in anticancer clinical trials, which may be due in part to immunosuppressive mechanisms acting within tumors. Medina-Echeverz et al. (p. 807) successfully eliminated established tumors in a murine colon cancer model by combining IL-12 therapy with depletion of immunosuppressive cells, using anti-CD25 mAb or cyclophosphamide (CPA). Both of these combination therapies reduced the frequency of intratumoral regulatory T cells (Tregs) and myeloid-derived suppressor cells. Nonetheless, only IL-12 plus CPA treatment significantly reduced tumor growth and improved survival. Regressing tumors from IL-12 plus CPA-treated mice were enriched with a heterogeneous population of $Ly6C^{high}$ $Ly6G^{low}$ monocytes and $Ly6C^{+}Ly6G^{high}$ neutrophils that were termed inflammatory myeloid cells (IMCs). IMCs did not induce conversion of $CD4^{+}$ T cells into Tregs but promoted intratumoral infiltration of tumor Ag-specific $CD8^{+}$ effector T cells. Tumor regression halted upon depletion of IMCs via anti-Gr1 mAb during IL-12 plus CPA treatment, which confirmed that IMCs were required for the antitumor effects of this therapy. Taken together, IL-12 plus CPA is a potent combination for shutting down immunosuppressive mechanisms within colon tumors and activating antitumor defenses, and may lead to new strategies for formulating effective cancer therapies.

CD23 and IgE Pulverize Parasites



$BCR\mu^{+}$ B cells express CD23, a low-affinity IgE receptor, and these B cells can present Ag and activate T cells upon endocytosis of CD23 molecules bound by IgE cross-linked with Ag. Protection against infection with *Schistosoma mansoni* is associated with high *S. mansoni*-specific serum IgE levels and an increase in $CD23^{+}$ B cells in humans. Griffith et al. (p. 1060) sought to understand if IgE-mediated resistance to *S. mansoni* involved CD23-bound IgE on B cells. CD23 cross-linking induced signaling events in naïve B cells similar to those caused by BCR stimulation, including Syk and ERK1/2 phosphorylation. $CD23^{+}$ B cells from individuals chronically exposed to *S. mansoni* showed a decrease in basal B cell activation upon ex vivo stimulation with crude *S. mansoni* Ag, compared with stimulation with TLR agonists or anti-CD3/CD28 Abs. The addition of CD23-bound *S. mansoni*-specific IgE restored B cell responses to *S. mansoni* Ag.

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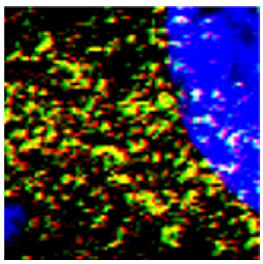
BCR signaling was reduced in naïve B cells cross-linked with both anti-CD23 and anti-BCRμ Abs, suggesting that CD23-bound IgE signaling can overpower BCR signaling. Thus, the antiparasitic attributes of IgE may be due in part to its influence on B cell activation and subsequent Ag-specific T cell activation.

Autophagy Keeps Skin Cool



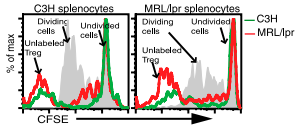
Emerging evidence suggests that intracellular degradation processes defined as autophagy may influence inflammatory responses. The scaffolding adapter protein p62, a putative autophagy receptor, can interact with polyubiquitinated proteins and target them for autophagic degradation. In this issue, Lee et al. (p. 1248) observed that inflammation in human keratinocytes is influenced by autophagy-driven suppression of p62. Treatment of keratinocytes with TLR2/6 or TLR4 agonist induced autophagy and p62 expression by stimulating NADPH oxidase-dependent reactive oxygen species generation. Keratinocytes treated with autophagy inhibitors exhibited a significant increase in p62 expression and inflammatory cytokine secretion compared with untreated or negative control keratinocytes. Conversely, RNA interference-mediated silencing of p62 caused a decrease in NF-κB–associated responses and inflammatory cytokine secretion. These data support other findings indicating that autophagy preserves cellular homeostasis by regulating p62 expression in response to inflammatory stimuli. p62 expression was significantly higher in epidermal samples from psoriatic skin than in atopic dermatitis or healthy control samples. Thus, autophagy appears to be a regulator of keratinocyte inflammation through its effect on p62 expression, and the autophagy pathway may potentially be exploited for the development of novel psoriasis therapies.

Ornery Old Myeloid Cells

Numerous defects in the immune system emerge in aging animals, but the primary causes of these defects remain poorly defined. Enioutina et al. (p. 697) previously observed that immature $Gr1^+CD11b^+$ myeloid cells accumulated in the spleens of aged mice and have now expanded this observation by characterizing attributes of these cells that influence immune senescence. An elevated number of immature $Gr1^+CD11b^+$ myeloid cells bearing phenotypic similarity to myeloid-derived suppressor cells were observed in the peripheral blood, lymph nodes, and bone marrow, as well as the spleens, of aged mice compared with young mice. Relative to comparable cells from young mice, a significantly higher percentage of both $CD4^+$ T cells and $Gr1^+CD11b^+$ myeloid cells from aged mice produced proinflammatory cytokines constitutively or upon stimulation. $Gr1^+CD11b^+$ myeloid cells from aged mice suppressed adaptive immune responses, but this effect was reversed by depletion of $Gr1^+$ cells such that Ag-specific $CD4^+$ T cell proliferation and Ab responses were similar to those of young mice. $Gr1^+CD11b^+$ myeloid cells had a defect in PI3K-Akt signaling, thus leading to uncontrolled GSK3β activity that promoted proinflammatory responses. The aberrant functions of $Gr1^+CD11b^+$ myeloid cells in aged mice suggest that these cells are influential in the events surrounding immune senescence, and further study is needed to better define their impact.

In the Transcription Trenches

Two papers in this issue feature the critical role of transcriptional regulation in T cell function. The first paper explores the influence of the transcription factor Kruppel-like factor 2 (KLF2) on T cell trafficking and cell cycle regulation by using novel knockout mice. KLF2 has been described as a transcriptional regulator in T cells, and its re-expression in T cells following activation is affected in different ways by IL-2 or IL-15 exposure. Using conditional and inducible KLF2 knockout mouse models, Takada et al. (p. 775) determined that KLF2 expression in post-activated $CD8^+$ T cells was required for transcription of the trafficking molecules CD62L and $S1P_1$. Transcription of cell cycle regulatory genes was affected differently by treatment with IL-2 or IL-15, as described previously, but this differential regulation did not require endogenous KLF2 expression. Moreover, KLF2 deficiency altered Ag-specific $CD8^+$ T cell migration in vivo but did not affect their proliferation or quiescence. Overall, these findings do not support a direct effect of KLF2 expression on cell cycle regulation, but do clarify how KLF2 expression affects activated $CD8^+$ T cell trafficking by influencing the transcription of cell surface molecules.



Irregularities in regulatory T cell (Treg) function have been observed in mice and humans with systemic lupus erythematosus, but the mechanisms behind these defects are not well understood. In the second paper, Divekar et al. (p. 924) observed aberrations in the microRNA (miRNA) pathway of Tregs from lupus-prone MRL-*Fas*$^{lpr/lpr}$ (MRL/lpr) mice. MRL/lpr mice with lupus symptoms had significantly more Tregs in their spleens, compared with control C3H mice. These Tregs had altered functional and phenotypic characteristics, including increased CD69 and reduced CD62L expression and a diminished suppressive capability relative to Tregs from C3H mice. Further examination of these abnormal Tregs revealed a significant reduction in the expression of the endoribonuclease Dicer, which is involved in miRNA generation. A number of miRNAs, including miR-155, were overexpressed in these Tregs, in spite of the Dicer deficiency. miR-155 was identified as a target of CD62L, and otherwise normal Tregs from C3H mice transfected with miR-155 showed reduced CD62L expression, compared with controls. These data suggest that abnormalities in the Tregs of lupus-prone MRL/lpr mice may be caused by multiple defects in miRNA regulation that influence transcription of genes essential to Treg function.

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