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THE JOURNAL OF IMMUNOLOGY

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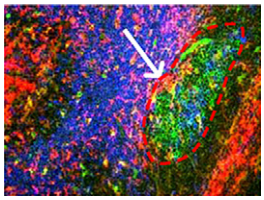
Cleaning Up for Tolerance



In the germinal centers (GCs) of secondary lymphoid tissues, clonal selection positively selects B cells with high-affinity variable regions and induces apoptosis of B cells that exhibit poor Ag affinity or autoreactivity. Studies of autoimmune diseases suggest that inefficient uptake of dead cells may play a role in the breakdown of B cell tolerance. The Mer receptor tyrosine kinase (Mer) is expressed by macrophages and facilitates their phagocytosis of apoptotic cells. In addition, Mer activation has been implicated in suppressing inflammatory responses. In this issue, Rahman et al. (p. 5859) studied T cell-dependent B cell activation in Mer-deficient mice. Mer-deficient mice developed greater numbers of Ab-forming cells and exhibited enhanced GC formation, compared with control mice. B cell development and maturation appeared to be normal in Mer-deficient mice, but serum IgG2a levels were significantly enhanced compared with those in wild-type mice. Mer-deficient mice also exhibited impaired clearance of apoptotic cells from the GC. Mer expression was largely restricted to tingible body macrophages, which were shown to play a significant role in phagocytosing dead cells within the GCs. Collectively, these results suggest an important role for Mer-mediated apoptotic cell clearance in maintaining B cell tolerance.

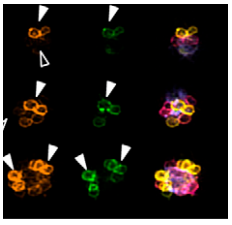
Shutting Off the NK Spigot

NK cell activity is controlled by competing positive and negative signaling pathways. To identify intracellular factors that inhibit NK cell-mediated cytolysis and cytokine production, Smith et al. (p. 6058) performed global gene expression profiling on RNA isolated from NK cells immediately or 24 hours after cytokine-induced activation. The numerous modulated transcripts identified included that of the transcriptional repressor positive domain containing 1, with zinc finger domain 1 (PRDM1; also known as BLIMP1 or PRDI-BF1). Along with the induction of IFN-γ and TNF-α expression, stimulation of NK cells with a combination of IL-2, IL-12, and IL-18 was found to markedly increase the low basal levels of PRDM1 expression. PRDMI was noted to bind regulatory sequences within *IFNG* and *TNF* loci. Correspondingly, overexpression of PRDMI blocked activation-induced transcription of *IFNG* and *TNF* genes, whereas siRNA-mediated knockdown of PRDMI expression yielded significantly elevated levels of IFN-γ and TNF-α production. Modulation of PRDMI had no effect on cytokine-induced NK cell cytolytic activity. These data define PRDMI as an inducible negative regulator of NK cell function that specifically inhibits cytokine production without affecting cytolysis.

No Clear Undoing

The Foxp3 transcription factor plays a key role in potentiating the suppressive activities of natural regulatory T cells (nTregs). Some studies have suggested that Foxp3 expression can be downregulated, whereby nTregs convert to a Th17 phenotype. To interrogate this theory, Kastner et al. (p. 5778) stimulated highly purified nTregs with anti-CD3/anti-CD28–bound beads plus various cytokines. The Th17- and Th2-polarizing cytokines IL-6 and IL-4, respectively, but not Th1-polarizing cytokines IFN-γ and IL-12, were found to induce a loss of Foxp3 expression. Moreover, the combination of IL-6 and IL-4 had synergistic effects. Attenuation of Foxp3 expression occurred independently of proliferation, but correlated with the downregulation of Treg-associated cell surface markers, such as CD25 and GITR, as well as the loss of suppressor phenotype and function. However, no clear gains of functions related to other T cell lineages occurred. Instead, low levels of both Th1- and Th2-associated transcription factors were observed, and some $Foxp3^-$ cells expressed both Th1- and Th2-associated cytokines. Notably, there was no evidence of a propensity to convert to the Th17 phenotype. Rather, in response to combined IL-6 and IL-4 treatment, both $CD25^+$ and $CD25^-$ nTregs exhibit the ability to be reprogrammed into a largely unpolarized population of $Foxp3^-$ cells.

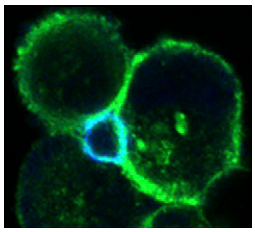
SHPing Suppression



The immunosuppressive effects of regulatory T cells (Tregs) are highly studied, but the mechanisms underlying Treg-mediated suppression are still poorly understood. To gain insights into these mechanisms, Iype et al. (p. 6115) focused on the phosphatase SHP-1, a known negative regulator of TCR-mediated signaling in conventional T cells. For their studies, Tregs were isolated from SHP-1–deficient homozygous and heterozygous *motheaten* (*me*) mice. In in vitro assays, homozygous *me* Tregs exhibited significantly increased suppressive activity compared with wild-type control Tregs, and heterozygous *me* Tregs showed intermediate activity. Treatment with a specific pharmacological inhibitor of SHP-1 increased the suppressive activity of wild-type Tregs, but not homozygous *me* Tregs. Further studies using a mouse inflammatory disease model confirmed that SHP-1 is a key regulator of TCR stimulation-induced Treg suppressor activity. SHP-1 expression levels were also found to negatively correlate with the expression of various adhesion molecules, including CD103 (αE-integrin), which is expressed on activated $CD4^+Foxp3^+$ Tregs. Furthermore, SHP-1 was observed to play an important role in regulating the conjugate formation of Treg cells with APCs. These findings demonstrate that SHP-1 is a key regulator of Treg suppressive activities

and identifies SHP-1 as a potential therapeutic target in inflammation-associated diseases.

An Unpalatable Coating for NK Cells



Immunoediting is the process by which the immune system kills tumor cells but also selects for the survival of nonimmunogenic tumors. Tumors harvested from mice with impaired immunoediting are highly immunogenic when transferred into wild-type mice and often exhibit decreased levels of surface sialylation compared with nonimmunogenic tumors. Cohen et al. (p. 5869) interrogated this observation and found that the sialylation of tumor cells directly inhibits NK cell-mediated cytotoxicity. When sialidase-treated fibrosarcoma cells were injected into immunocompetent mice, tumor growth was significantly inhibited compared with growth of untreated fibrosarcoma cells, and sialidase-treated tumors experienced enhanced leukocyte infiltration. In contrast, sialidase-treated and untreated fibrosarcoma cells exhibited similar kinetics of tumor formation in recipient immunocompromised mice. Sialidase-treated tumor cells induced higher levels of NK cell-derived IFN-γ production and NK cell-mediated cytolysis, compared with untreated cells. Antitumor NK cell activities were triggered by the engagement of the activating receptor NKG2D, and further studies revealed that NKG2D engagement of stress-induced ligands was significantly impaired by sialylation. This work reveals an important role for cell-surface sialylation in tumor immune evasion and defines a new target for antitumor therapy.

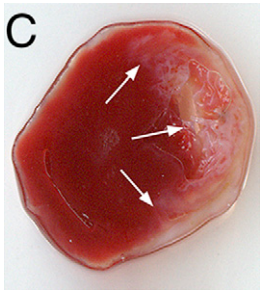
Overstimulation Can Be Degrading

Deficient T cell and NK cell activities associated with cancer and autoimmune diseases are believed to be caused in part by the impairment of CD3ζ-associated immune receptor signaling due to decreased levels of CD3ζ expression. These diseases also commonly induce chronic expression of the stress-induced MHC class I-related chains A and B (MICA and MICB) that, in turn, induce downregulation of the stimulatory receptor NKG2D on T cells and NK cells. In this issue, Hanaoka et al. (p. 5732) define a causal link between chronic NKG2D stimulation and decreased CD3ζ expression. IL-2–stimulated (licensed) NKG2D$^+$ peripheral blood CD8$^+$ T cells exhibited decreased expression of both NKG2D and CD3ζ when cultured on MICA- and MICB-expressing adherent fibroblast cells. Treatment with an anti-NKG2D masking mAb or withdrawal of MICA abrogated soluble MICA-induced downregulation of both NKG2D and CD3ζ expression and rescued CD3ζ-associated receptor functions. Costimulation of T cells by NKG2D engagement of MIC ligands was found to induce increased levels of Fas death receptor ligand (FasL) expression. In turn, the activation of caspase 3 and caspase 7 by FasL engagement of Fas could not be inhibited by NKG2D$^{low/-}$-expressing T cells or NK cells, thereby allowing the cleavage of CD3ζ. Taken together, these results show that chronic stimulation-induced downregulation of NKG2D in T cells and NK cells initiates a chain of events that ultimately leads to deficient CD3ζ-associated immune receptor signaling.

Suppressing the Suppressor

Viral infection of mammalian cells triggers an antiviral response that includes the upregulation of various microRNAs (miRNAs). One such miRNA, miR-155, is induced in macrophages in response to RNA virus infection. To investigate the relevance of miR-155 to the antiviral response, Wang et al. (p. 6226) focused on RNA virus-induced type 1 IFN responses. Vesicular stomatitis virus (VSV)- and sendai virus-induced upregulation of miR-155 expression in macrophages occurred within 24 h of infection. MiR-155 upregulation was independent of TLR/MyD88-dependent signaling pathways, as VSV-induced miR-155 expression levels in macrophages from TLR3-, TLR4-, TLR9-, and MyD88-deficient mice were similar to those harvested from wild-type control mice. In contrast, virus-induced miR-155 expression levels were markedly impaired in RIG-I–deficient macrophages and splenocytes, and by the inhibition of JNK and NF-κB activation. In culture, inhibition of miR-155 expression improved VSV replication, whereas overexpression of miR-155 was suppressive. These suppressive effects were found to be due to enhanced type 1 IFN signaling that resulted from miR-155 inhibiting the translation of suppressor of cytokine signaling 1, SOCS1. Collectively, these results ascribe a new role to miR-155 in the RNA virus-induced antiviral response.

Heart-Felt T Cells



The hormone angiotensin II (AT2) induces vasoconstriction and increased blood salt levels; thus AT2R blockers are used clinically to treat high blood pressure and cardiac failure. In recent years, however, there has been growing evidence that increased levels of AT2R expression in the heart correlate with cardioprotection following acute myocardial infarction (MI). To better understand the role of AT2, Curato et al. (p. 6286) studied the functional role of CD8$^+$AT2R$^+$ T cells following acute MI. Seven days post-MI, the numbers of CD8$^+$AT2R$^+$ T cells were increased significantly in the hearts and spleens of coronary ligated rats, compared with sham-operated rats. Unlike CD8$^+$AT2R$^-$ T cells, post-MI CD8$^+$AT2R$^+$ T cells did not exhibit cytotoxicity toward cardiomyocytes in coculture and were instead found to secrete cardioprotective IL-10 in response to AT2-mediated stimulation. In vivo treatment of rats with an AT2R agonist, compound 21, was found to increase the numbers of IL-10–expressing CD8$^+$AT2R$^+$ T cells in the infarcted myocardium relative to untreated rats. Furthermore, the transplantation of postinfarct splenic CD8$^+$AT2R$^+$ T cells into rats immediately following MI increased survival and significantly reduced the infarct volume, compared with rats that had received CD8$^+$AT2R$^-$ T cells. As CD8$^+$AT2R$^+$ T cells were also found in healthy human donors, these results have implications for AT2R-based clinical treatments of acute MI.

Summaries written by Meredith G. Safford, Ph.D.