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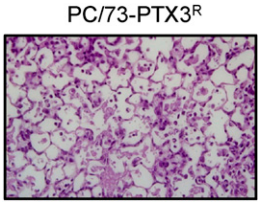
Influenza Gives Pentraxin the Slip



Pentraxin 3 (PTX3) is a sialylated glycoprotein that is produced by innate immune cells and airway epithelial cells and can inhibit infection with influenza A viruses (IAV). PTX3 and the short pentraxin serum amyloid P (SAP) both inhibit H3N2 IAV by acting as receptor decoys through the binding of their sialic acid residues to viral hemagglutinin (HA). In this issue, Job et al. (p. 271) identified viral determinants of sensitivity to PTX3 by isolating H3N2 viral mutants that were resistant to PTX3 but maintained sensitivity to SAP. Analysis of these pentraxin 3 resistant ($PTX3^R$) mutants, combined with sequence analysis of H3N2 strains in public databases and confirmation via reverse genetics, revealed the critical importance of residue 145 of HA in determining viral sensitivity to PTX3 inhibition. $PTX3^R$ viruses did not differ from wild-type (wt) viruses in the specificity of their HA for sialic acid, nor in their ability to productively infect cells in vitro. However, $PTX3^R$ viruses demonstrated increased virulence in vivo, causing both more severe airway inflammation and increased systemic disease in comparison to wt viruses. At day 7 following infection, the bronchoalveolar lavage fluids (BALF) from mice infected with $PTX3^R$ virus contained higher levels of PTX3 than BALF from wt virus-infected mice, and this PTX3 could neutralize wt H3N2 IAV. Viral titers in the lungs of mice infected with wt IAV were reduced by PTX3 treatment, but this was not effective in mice infected with $PTX3^R$ IAV, which differed from wt viruses only at HA residue 145. Very minor variations in IAV may therefore determine whether an infection is subject to control by PTX3.

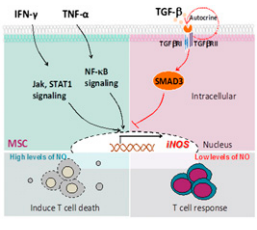
Etoposide Topples Autoimmune T Cells

Multiple sclerosis (MS) is characterized by encephalitogenic T cells that attack the myelin sheath surrounding nerve fibers in the CNS and cause brain pathology. Current MS therapies often broadly dampen immune cell responses, which minimizes the autoimmune activity of pathogenic T cells but also adversely affects protective immunity against pathogens and tumors. In an effort to specifically target disease-causing encephalitogenic T cells without reducing beneficial immune responses, McNally et al. (p. 73) induced the MS-like disease experimental autoimmune encephalomyelitis (EAE) in mice, and then treated them with etoposide, a topoisomerase inhibitor used clinically to combat cancer. They found that providing etoposide after EAE induction delayed the onset and reduced the severity of autoimmunity, preventing EAE incidence in 60% of mice, relative to EAE-induced mice treated with a vehicle control. Etoposide administration caused selective apoptosis, dampened cytokine production, and reduced Ag spread in myelin-specific T cells without hindering naive and memory T cell responses to viral pathogens, indicating that etoposide solely affected autoreactive T cells. These results suggest that etoposide may specifically eliminate encephalitogenic T cells without compromising protective immune responses and that this inhibitor may be a viable treatment option for MS patients.

TRAF5 Keeps TABs on TLR Signaling

The TNFR-associated factor (TRAF) cytoplasmic adaptor proteins mediate signaling through receptors of the TNFR and IL-1R/TLR superfamilies. Roles for TRAF3 and TRAF6 in TLR signaling have been defined, but it is not known whether TRAF5, which is structurally similar to TRAF3, is involved in TLR activity. Buchta and Bishop (p. 145) assessed TRAF5 activity following TLR stimulation using both TRAF5-deficient mice and B cells overexpressing TRAF5. $TRAF5^{-/-}$ B cells produced significantly higher levels of IL-6, IL-10, TNF-α, and IL-12p40 than did wild-type B cells but did not differ in proliferation or survival following stimulation with TLR4, TLR7, or TLR9. Overexpression of TRAF5 in B cells further supported its inhibitory role in B cell cytokine production, which also extended to inhibition of Ab production in response to TLR stimulation. TRAF5 deficiency did not dramatically affect cytokine production in dendritic cells or macrophages, suggesting B cell-specific activity. TRAF5 inhibited the phosphorylation of ERK1/2 and JNK in B cells but did not affect NF-κB activation. Deficiency in TAB2, another adaptor protein involved in TLR signaling, has been shown to result in a phenotype directly opposite to that of $TRAF5^{-/-}$ mice, suggesting that the two adaptors might be related. Indeed, TRAF5 was found to form a complex with TAB2 and MyD88 and to inhibit the association of TAB2 with TRAF6. TRAF5 thus emerges as an important negative regulator of TLR-mediated B cell stimulation.

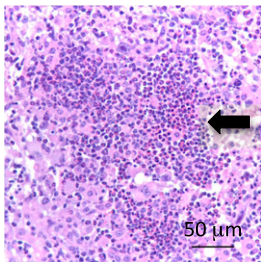
The Other Side of TGF-β



The therapeutic utility of mesenchymal stem cells (MSCs) in treating inflammatory diseases is attributed to their potent suppression of T, B, dendritic, and NK cell maturation and function. MSCs are not innately immunosuppressive, but rather, acquire this property upon activation with inflammatory cytokines, which leads to the production of inducible NO synthase (iNOS) by mouse MSCs. To further elucidate the immunosuppressive mechanisms employed by MSCs, Xu et al. (p. 103) evaluated the role of TGF-β1, a prototypic immunosuppressive cytokine, in this process.

Contrary to the authors' original hypothesis, the addition of TGF-β1 to cocultures of MSCs and splenocytes reversed MSC-induced inhibition of T cell proliferation. Similar coculture experiments with MSCs expressing a dominant negative form of the TGF-β receptor II, which abolishes TGF-β signaling, demonstrated that TGF-β1 acted directly on MSCs. iNOS production in MSCs after inflammatory cytokine stimulation was blocked by TGF-β1, and this inhibition was reversed in small interfering RNA knockdowns of SMAD3, demonstrating that TGF-β1 inhibited MSC iNOS production through a SMAD-dependent pathway. Furthermore, MSCs also produced TGF-β that inhibited iNOS in an autocrine manner and blocking TGF-β signaling in these cells restored iNOS expression. In this study, the authors demonstrate a unique role for TGF-β in blocking immunosuppression by MSCs.

Challenging the Canonical CD8$^+$ Antitumor Response



Current cancer immunotherapy largely focuses on the role of CD8$^+$ T cells as mediators of antitumor immunity despite a multitude of studies supporting the antitumor capabilities of other immune cell populations. Immunotherapy for brain malignancies, such as glioblastoma multiforme (GBM), is uniquely challenging due to the immunosuppressive nature of the brain. In this article, Murphy et al. (p. 224) elucidate the mechanism responsible for the efficacy of their previously reported vaccine/Fc-OX40L therapy for GBM. Elimination of CD4$^+$ or CD8$^+$ T cells, B cells, or NK cells in vaccine/Fc-OX40L–treated tumor-bearing mice demonstrated that the enhanced survival and tumor regression resulting from vaccine/Fc-OX40L treatment was CD8$^+$ T cell independent, but CD4$^+$ T cell, NK cell, and B cell dependent. A trend toward increasing tumor-reactive IgG, but not IgM, was observed in the serum of vaccine/Fc-OX40L–treated tumor-bearing mice. Vaccine/Fc-OX40L treatment of gliomas in FcRγ- or plasma cell–deficient mice demonstrated an intermediate tumor growth phenotype, suggesting that Ab-dependent tumor regression is mediated through an FcR-based mechanism. Interestingly, analysis of tumor-infiltrating cells in vaccine/Fc-OX40L–treated mice showed an increase in CD4$^+$ and CD8$^+$ T cells (including Foxp3$^+$ regulatory T cells), CD11b$^+$ MHC II^{neg} neutrophils, and CD3^{neg}NK1.1$^+$perforin$^+$ cell populations, suggestive of active NK cells. This study highlights a CD8$^+$ T cell–independent antitumor response and suggests alternate mechanisms of tumor eradication in the therapeutic treatment of GBM.

Heterozygous Harm to Hematopoiesis

Self-renewing long-term hematopoietic stem cells (LT-HSCs) differentiate along lymphoid or myeloid lineages to replenish cells as needed in vivo. The transcription factor E47 is an important regulator of hematopoiesis that activates the major cyclin-dependent kinase inhibitor p21 in vitro. To address the potential biological relevance of an E47–p21 pathway, Santos et al. (p. 160) generated mice haploinsufficient for the genes encoding these factors, either individually or in combination, and analyzed hematopoiesis under steady-state or repopulation stress conditions. Compared with cells from singly heterozygous mice (E47^{het} or p21^{het}), LT-HSCs from the bone marrow of E47^{het}p21^{het} doubly heterozygous mice showed increased proliferation under steady-state conditions in vivo. E47^{het}p21^{het} LT-HSCs did not show defects when subjected to acute stress but were dramatically depleted, while continuing to proliferate at a higher rate than controls, in a serial adoptive transfer model of chronic stress. Thus, the E47–p21 interaction was important, in a cell-intrinsic manner, for the control of LT-HSC proliferation and associated maintenance of these cells during long-term repopulation stress. Analysis of downstream cellular compartments revealed that the effects of a defect in the E47–p21 pathway on LT-HSCs could be compensated for in the development of myeloid cells but not lymphoid cells. The observed developmental defects caused by the combined heterozygosity of genes encoding E47 and p21 both advance our understanding of lymphoid development and have clinical implications for the study of lymphoid malignancies linked to E47 loss of heterozygosity.