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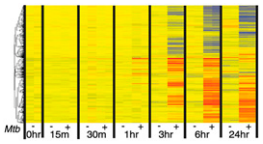
Signaling To Balance IFNs



Intracellular bacteria, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*, are controlled by the immune system through a variety of responses including cytokine production. If control of one of these responses is dysregulated, host defense suffers and pathogenesis occurs. The host can be protected during *M. tuberculosis* and *L. monocytogenes* infection by a classical Th1 response, characterized by the production of IL-12, TNF-α, IL-1, and IFN-γ, along with IL-12–activated $CD4^+$ T cells. However, overproduction of type I IFN leads to a level of IL-10 release that is detrimental to the host and exacerbates disease in both mice and humans. McNab et al. (p. 1732) performed microarray analysis on the transcripts of *M. tuberculosis*–infected macrophages and found that the tumor progression locus-2 (TPL-2)–ERK1/2 signaling pathway was activated. The TPL-2–ERK1/2 signaling pathway was important for regulation of type I IFNs, and deletion of TPL-2 in vivo caused overproduction of type I IFN–driven IL-10. TPL-2–deficient mice were also more susceptible to *L. monocytogenes* infection, and carried a 10-fold greater bacterial burden than wild-type controls. Thus, the authors have pinpointed an important signaling mechanism by which TPL-2–ERK1/2 can control type I IFNs and susceptibility to intracellular bacterial infection.

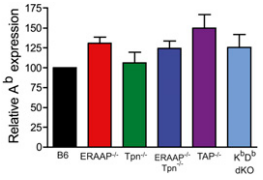
Taking Harmful T Cells Down a Notch

Inhibiting Notch, a widely expressed receptor important in many cellular processes, in experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis that causes myelin degeneration, drastically reduces disease-associated symptoms. However, the mechanism by which Notch inhibition ameliorates EAE has not been well defined because of variability in inhibitor efficacy and affected cell types in several studies. Sandy et al. (p. 1606) set out to determine the importance of Notch inhibition in pathogenic $CD4^+$ T cells in EAE by targeting a Cre-inducible pan-Notch inhibitor, dominant negative form of Mastermind-like 1 (DNMAML), to the T cell lineage in myelin-specific 2D2 TCR transgenic mice. They found that DNMAML expressed in myelin-specific T cells led to decreased EAE incidence and severity, reduced accumulation of myelin-specific T cells in the CNS, and lower IFN-γ and IL-17 production by CNS-infiltrating T cells compared with controls. Conversely, DNMAML-expressing T cells in the draining lymph nodes maintained the capacity to produce these cytokines, indicating a CNS-specific function for Notch in $CD4^+$ effector cells. However, WT and DNMAML 2D2 TCR transgenic mixed bone marrow (BM) chimeras demonstrated EAE incidence similar to control BM chimeras, which suggested that DNMAML-expressing T cells did not have dominant suppressive functions. These results indicate an essential role for Notch signaling in CNS-restricted $CD4^+$ effector T cells in EAE.

B Cells Play Nice with Siglec-G

CD22 and Siglec-G are inhibitory coreceptors expressed on B cells and have been implicated in the maintenance of self-tolerance and the prevention of autoimmunity. In a recent hemophilic mouse model study, B cell treatment with liposomes bearing CD22-specific ligands and Ag demonstrated CD22's importance in the induction of B cell tolerance. However, because a highly specific ligand for Siglec-G does not exist, the role of Siglec-G in B cell tolerance induction was not explored. This prompted Pfrengle et al. (p. 1724) to formulate a glycan ligand, called 3′-^{BPA}NeuGc, that binds Siglec-G with high specificity. They created Siglec-engaging tolerance-inducing antigenic liposomes (STALs) that contain this ligand and Ag to determine the importance of Siglec-G in B cell tolerance. The authors found that treating B1a or B2 cells ex vivo with STALs containing 3′-^{BPA}NeuGc and anti-IgM caused colocalization of Siglec-G and the BCR, reduced B cell calcium flux, and suppressed B cell activation in a Shp-1–dependent manner. Injecting STALs containing 3′-^{BPA}NeuGc and classical T-independent (nitrophenyl) or T-dependent (hen egg lysozyme) Ags into mice also induced B cell tolerance, whereas administering liposomes containing only Ag resulted in a robust Ag-specific Ab response. These results suggest that Siglec-G colocalization with the BCR in the presence of ligand and Ag can regulate B cell signaling and contribute to B cell tolerance induction.

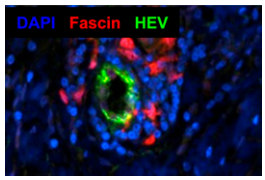
Peptide Editing Collaborators



The stable presentation of peptides within MHC class I (MHC I) molecules is necessary for recognition and effective responses by $CD8^+$ T cells. The correct peptide motif must be chosen and loaded onto the histocompatability molecules to form the peptide–MHC I complex (pMHC I), a process that is incompletely understood. Kanaseki et al. (p. 1547) demonstrated that tapasin of the peptide-loading complex and the endoplasmic reticulum aminopeptidase associated with Ag processing (ERAAP) act to edit which peptides are loaded onto MHC I. Loss of either of these molecules changed the peptide profile that was presented to $CD8^+$ T cells. T cell lines generated from WT mice following immunization with either ERAAP- or tapasin-deficient cells demonstrated that different peptide profiles were expressed depending on which peptide editor was deleted. In addition, immunization experiments revealed

no overlap in the distinct peptide profiles controlled by ERAAP versus tapasin activity. Changing the sequences of peptides bound to MHC I indicated that tapasin defined the carboxyl termini of canonical MHC I peptides, whereas ERAAP was responsible for influencing the amino termini. Thus, these two molecules act in concert to edit and select a pMHC I repertoire capable of stable presentation to $CD8^+$ T cells.

Cancer-Fighting Conduits



Tumor vascularization is associated with poor clinical prognosis for cancer patients. However, one recently discovered type of blood vessel, the tumor high endothelial venule (HEV), acts as a conduit to allow cancer-killing lymphocytes and dendritic cells (DCs) access to the tumor environment and is associated with positive prognosis for cancer patients. In this issue, Martinet et al. (p. 2001) characterized HEVs in human breast cancer using freshly resected and cryopreserved breast tumor samples. They found that tumors with a high density of HEVs (HEV^{high}) had increased mRNA expression of lymphotoxin β (LTβ), a molecule important for lymphocyte egress from HEVs in the lymph node. HEV^{high} tumors also contained mature DCs that clustered near HEVs and expressed DC-LAMP, fascin, and membrane-bound LTβ. In turn, highly dense clusters of DC-$LAMP^+$ DCs were associated with increased tumor HEV density, high levels of $CD3^+$ T cell tumor infiltration and favorable clinical outcome in a cohort of 146 breast cancer patients. Regulatory T cells (Tregs) also infiltrated HEV^{high} tumors, but the ratio of $FoxP3^+$ Treg to other $CD3^+$ T cells was lower in HEV^{high} tumors than in HEV^{low} tumors, indicating that having a high density of HEVs in tumors may depend on maintaining a low Treg: non-Treg T cell ratio. Together, these data suggest that DC-derived LTβ is important in the generation of HEVs in tumors and offer the hope that further study of tumor HEVs will aid the development of more effective therapies for solid tumors.

14-3-3γ/NF-κB Switch Up Recombination

Class switch DNA recombination (CSR) allows the B cell to achieve a wide variety of biologic effector functions while maintaining the Ag specificity gained through positive selection. In studying this process, Mai et al. (p. 1895) have focused on the 14-3-3 adaptor proteins, which recruit and stabilize the activation-induced cytidine deaminase (AID) during CSR. The 14-3-3γ isoform specifically targets AID to switch (S) region DNA, where, as its name suggests, this enzyme deaminates deoxycytosines. Deletion of 14-3-3γ leads to a significant reduction in CSR. The authors demonstrated that 14-3-3γ was expressed in germinal center B cells in vivo, and both protein and message were produced in cultured human and mouse cells in response to T-dependent and -independent CSR-inducing stimuli. Measurements of expression kinetics indicated that 14-3-3γ was produced rapidly in response to LPS, peaked at 3 h after LPS administration, and then was maintained throughout the expression of AID and induction of CSR. NF-κB recruitment to the 14-3-3γ promoter enhanced CpG island-binding of CFP1 (component of the COMPASS histone methyltransferase complex) and enrichment of histone 3 lysine 4 trimethylation, thus enhancing transcription through epigenetic modifications. NF-κB also sustained 14-3-3γ expression and CSR by promoting binding of the B cell lineage–specific factor E2A to an E-box motif found after two transcription start sites (TSSs). Thus, the authors determined that 14-3-3γ expression during CSR was dependent on NF-κB, which in turn recruited promoter-associated factors that caused epigenetic modifications and sustained expression of the AID-targeting adaptor.