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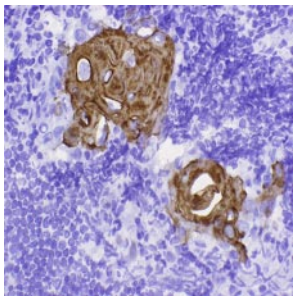
IN THIS ISSUE

Building a Better Thymus



Complete Di George anomaly is a congenital defect in which the heart and parathyroid are affected and the patient is completely athymic. This condition is fatal if untreated; one approach to treatment has consisted of an allogeneic thymic tissue transplant inserted into the quadriceps muscle. Markert, one of the researchers who pioneered this treatment, et al. (p. 6354) performed 30 biopsies and six autopsies on these patients to look for evidence of thymopoiesis in transplanted tissue and improve therapy. The transplants sampled were from 33 infants, 23 of whom survived. Of the 30 biopsies, grafted thymic tissue identified by the presence of cytokeratin was found in 25, 23 of which had evidence of thymopoiesis. They found that 19 survivors who had biopsy evidence of thymopoiesis also had naive T cells in peripheral blood samples. As well as determining the success of the graft, the results of the biopsy could be used to diagnose whether graft rejection, as seen in one autopsy, was occurring. The authors found that with the biopsy they could see the results of pulse steroids on thymopoiesis, determine whether atypical subjects needed additional immunosuppressive therapy during the engraftment process, and determine whether thymopoiesis was continuing under this immunosuppressive regimen. The data from these biopsies and autopsies will be valuable to improving the care of these vulnerable patients.

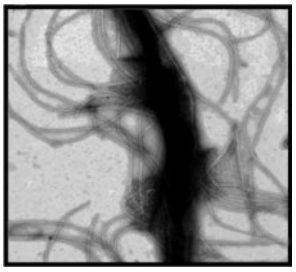
Innate IL-27

During adaptive immunity, IL-27 promotes early Th1 events but can also suppress Th1, Th2, and Th17 differentiation. However, little is known about the role of IL-27 during innate responses. Kalliolias et al. (p. 6325) set out to clarify the function of IL-27 in innate immunity by examining the effects of this cytokine on STAT1 and STAT3 tyrosine phosphorylation in resting murine macrophages and human monocytes. The authors found that treatment with IL-27 did not stimulate STAT tyrosine phosphorylation in murine bone marrow-derived macrophages (BMDMs) or in resident peritoneal macrophages. However, IL-27 treatment mediated a STAT1-dominant signaling pattern in resting human monocytes and activated the STAT1-dependent inflammatory target genes *CXCL10*, *IRF-1*, *SOCS*, and *STAT1*. IL-27 also enhanced TLR stimulation of monocytes, as IL-27 pretreatment increased IL-6 and TNF-α production in response to TLR2 ligands and did so in a STAT1-dependent manner. In addition, TLR-induced human monocyte IL-10 production was strongly suppressed by IL-27. Pretreatment of cells with LPS abrogated the proinflammatory effects of IL-27; this was mediated through a p38-MAPK mechanism. Based on these data and previous knowledge about IL-27-meditaed effects, the authors conclude that this cytokine acts to promote inflammation in monocytes in innate immunity but becomes suppressive during the adaptive response.

Novel Treg

Wakkach et al. (p. 6054) have discovered a novel population of T regulatory cells (Treg) in the intestinal lymphoid tissue that express T cell immune response cDNA7 (TIRC7). The authors subsequently defined two novel populations, $CD25^{low}TIRC7^{+}$ and $CD25^{high}TIRC7^{-}$, both of which express FoxP3 and demonstrate in vivo and in vitro suppressive activity. In a model of murine colon adenocarcinoma, $CD25^{low}TIRC7^{+}$ cells secreting IL-10 were found accumulated within the tumors. Blocking the IL-10 secreted by $CD25^{low}TIRC7^{+}$ cells with neutralizing Ab reversed their suppressive effect on CD3-stimulated $CD4^{+}$ T cells, and when $CD25^{low}TIRC7^{+}$ cells from IL-10-deficient mice were tested, they were unable to inhibit proliferation. The adoptive transfer of $CD25^{low}TIRC7^{+}$ cells into mice was also able to block pathogenesis in a well-characterized model of colitis. The $CD25^{low}TIRC7^{+}$ IL-10-secreting population was derived from the $CD25^{high}TIRC7^{-}$ subset and was stimulated to proliferate in the presence of tumoral Ags. These results led the authors to hypothesize that within a pool of natural Treg, a subset will recognize foreign Ags and that this recognition is essential to their regulatory capability.

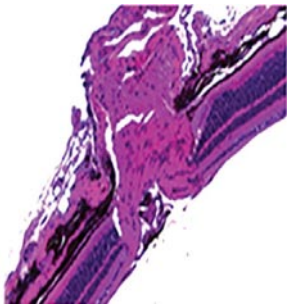
Killer Antibodies



Antibodies are the main line of defense against the *Borrelia* spirochetes that cause Lyme disease and relapsing fever. However, this defense does not require the activation of complement by Abs, as mice deficient in various complement components can clear infection. LaRocca et al. (p. 6222) have demonstrated that the variable region of a bactericidal monoclonal IgM CB515, specific for a *Borrelia* species that causes relapsing fever, is sufficient to kill the spirochete. A single-chain variable fragment of CB515 (scFv) was created that bound only to this species of spirochete and did not activate complement but retained bactericidal activity. Incubating scFv with the organism resulted in a dose-dependent bactericidal effect and preincubating scFv with *Borrelia* before injection into mice led to the growth of escape mutants, whereas preincubation with an irrelevant scFv did not. scFv incubation with *Borrelia* caused blebbing and lysis of the outer membrane, which was visualized quite elegantly

by transmission electron microscopy. The authors demonstrate that the bactericidal effect of Abs can be independent of complement activation.

STAT3, IL-17, and the Eye



Central nervous system autoimmune diseases such as autoimmune uveitis require a Th17 response for progression. STAT3 has been implicated in naive T cell commitment to Th17 development. Liu et al. (p. 6070) created mice whose $CD4^+$ T cells lack STAT3 ($CD4^{Stat3-/-}$) and demonstrated that they develop neither experimental autoimmune uveitis (EAU) induced with interphotoreceptor retinoid-binding protein (IRBP) nor experimental autoimmune encephalomyelitis (EAE). The numbers of IL-17-expressing cells were reduced in the spleen and lymph nodes of EAU-resistant $CD4^{Stat3-/-}$ mice and T cells that express both IFN-γ and IL-17, normally found in mice with EAU, were absent in the $CD4^{Stat3-/-}$ mice. $CD4^{Stat3-/-}$ mice also had increases in the number of FoxP3-, IL-10-, IL-4-, and IFN-γ-expressing T cells compared with wild-type mice, suggesting that STAT3 has a role in determining the $CD4^+$ T cell repertoire. Reduced expression of $\alpha_4\beta_1$ integrins on T cells in these mice explained why fewer Th17 and Th1 cells were able to enter the eyes and brain of the treated animals and why autoimmune pathology never developed. When IRBP-specific uveitogenic T cells from wild-type mice were adoptively transferred into $CD4^{Stat3-/-}$ recipients, they developed EAU. Taken together, the data indicate that STAT3 is necessary for development of a Th17 response and trafficking of Ag-specific T cells into the CNS and that STAT3 may be considered a potential therapeutic target for treatments of uveitis and multiple sclerosis.

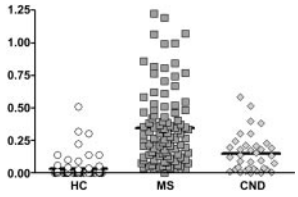
More Avid, More Active

T cell receptor affinity is the primary determinant in T cell avidity and the ability to respond to antigenic stimulation. Robbins et al. (p. 6116) have developed a rapid RNA-based transfection system that can be used to modify existing TCRs and screen for their activity. Using the 1G4 TCR, previously characterized by this group, they introduced individual amino acid substitutions in the CDR3α and CDR2β regions that enhanced the recognition of NY-ESO-1^+/HLA-A*02^+ tumor cell lines by modified $CD4^+$ T cells. Substituting two amino acids in the CDR3α region of the 1G4 TCR increased the ability of both modified $CD4^+$ and $CD8^+$ T cells to specifically recognize Ag. The authors then applied this knowledge to an unmodified TCR that recognized the MART-1_{27-35} peptide and substituted amino acids in the CDR2 and CDR3 regions to create higher-affinity TCRs and enhance $CD4^+$ T cell Ag reactivity. Not only have the authors developed a quick method to screen and test TCR affinity, but they have potentially provided an approach to generation of high-affinity, specific T cells for adoptive immunotherapy.

Transcriptional Complexities in Lupus

Patients with lupus have increased expression of IFN-inducible gene mRNAs, and the lupus-susceptible congenic mouse B6.Nba2 has increased expression of IFN-inducible *Ifi202*. Panchanathan et al. (p. 5927) found that steady-state levels of *Ifi202* were elevated in mouse embryonic fibroblasts deficient in the transcription factor E2F1 ($E2F1^{-/-}$) and that overexpression of E2F1 led to decreased amounts of p202, the protein encoded by *Ifi202.* Transcriptional repression of *Ifi202* by E2F1 was independent of p53 and pRb, proteins with which E2F1 often complexes, but required DNA binding. Mutating a predicted E2F1 binding site in the *Ifi202* gene reduced transcriptional repression. As p202 itself inhibits the transcriptional activation of E2F1 target genes, the authors examined the transcriptional profile of splenic cells from B6.Nba2 congenic mice as compared with age-matched C57BL/6. Increased expression of *Ifi202*, inhibition of E2F1-mediated transcription, and decreased levels of E2F1 and transcriptional targets such as the proapoptotic *PUMA* and *Bim* were found in these cells as compared with controls. Thus, disruption of a mutual negative transcriptional regulation loop leads to increased *Ifi202* expression, which, in turn, leads to increased lupus susceptibility.

Where Is the Lesion?



Although many studies have examined T cell responses in multiple sclerosis (MS), very few have attempted to correlate these data with demyelinated lesion localization. To bridge this gap, Greer et al. (p. 6402) tested T cell reactivity to myelin proteins and looked for the presence of anti-myelin Abs in the peripheral blood of 100 MS patients and then compared these data to lesion localization. Localization of lesions was determined by a combination of magnetic resonance imaging and clinical examination. Forty of these patients had strong $CD4^+$ T cell reactivity to myelin Ags, but those with specific reactivity to myelin proteolipid protein residues 184–209 ($PLP_{184-209}$) had a significant correlation with lesions in the brainstem and cerebellum. Expression of HLA-DR4, HLA-DR7, or HLA-DR13 molecules in patients correlated with increased T cell reactivity to $PLP_{184-209}$ and developing lesions in the cerebellum and brainstem. Cerebellar lesions correlated only with those patients who had $PLP_{190-209}$-specific Abs. Using immune responses that can be measured from the peripheral blood, the authors demonstrated that the localization of demyelinated lesions can be predicted in MS.

Summaries written by Kira R. Gantt, Ph.D.