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Supplementary Material

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Memories of the Liver

Antigen-stimulated CD8+ T cells develop into central memory T (T_CM) cells or effector memory T (T_EM) cells, which home to lymphoid and non-lymphoid tissues, respectively. Having found that the adoptive transfer of ex vivo Ag + IL-4-activated naive CD8+ T cells into histocompatible mice yielded long-lived functional memory CD8+ T cells, Su et al. (p. 7498) investigated the homing and functional characteristics of these cells. The spleen showed the highest absolute counts of donor cells, followed by the liver and bone marrow, with the lowest numbers detected in lymph nodes. Liver memory T (T_LM) cells formed large clusters that arose from in situ clonal expansion. Cluster development was IL-15/IL-15R dependent. Cluster development was IL-15/IL-15R dependent and involved close contact between T_LM cells and hepatic stellate cells. Similar to T_EM cells, T_LM cells had a CD62L-low phenotype; however, they were comparatively functionally deficient. Interestingly, secondary transfer revealed that T_LM cells could differentiate into both T_EM-like and T_CM-like cells. When mice were challenged with Listeria monocytogenes, T_LM cell clusters formed at greater numbers than were found with unimmunized mice. Collectively, these data reveal that clonally derived clusters of T_LM cells develop in discrete microenvironments within the liver under homeostatic as well as pathological conditions, and these foci may serve as an important source of peripheral memory CD8+ T cells.

Modifier Genes for Cystic Fibrosis

The fatal lung disorder cystic fibrosis (CF) stems from mutations in a chloride channel gene, but its clinical manifestations can be modified by allelic variations or mutations in unrelated genes. An increased inflammatory response to the flagellated bacterium Pseudomonas aeruginosa has been noted in CF patients; therefore, Blohmke et al. (p. 7731) sought to determine if the flagellin receptor TLR5 may be a CF modifier gene. In culture, a strain of flagellin-negative P. aeruginosa induced significantly reduced levels of IL-6 and IL-8 production by airway epithelial cells, compared with cells cultured with wild-type P. aeruginosa. Furthermore, wild-type P. aeruginosa-induced cytokine levels were significantly reduced when TLR5 activation was specifically inhibited by TLR5 activation. To test the significance of TLR5-flagellin interactions for CF patient health, CF patients homozygous for the wild-type TLR5 allele were compared with those heterozygous for a nonfunctional TLR5 truncated version, and those patients with the TLR5 truncated version were found to have a statistically significant higher body mass index. These data define TLR5 as a modifier gene of CF and show TLR5 to be a potential therapeutic target to improve the health status of CF patients.

Basal Basophil Support

Basophils have recently been revealed to play a role in supporting and directing the anti-infection humoral immune response through cytokine production. Because basophils reside at high frequency in the bone marrow (BM) and spleen alongside plasma cells, Rodriguez Gomez et al. (p. 7180) wondered if basophils played a role in maintaining plasma cell viability and Ig production. Following immunizations of mice with an Ag, plasma cells and basophils were isolated and cultured. In the absence of basophils, plasma cells produced only low levels of Ag-specific IgG1 and IgG2a that tapered off with time. In contrast, coculture with basophils resulted in high and continuous Ag-specific IgG1 and IgG2a production and significantly improved the numbers of surviving plasma cells. Basophil-derived soluble factors IL-4 and IL-6 appeared to mediate, at least in part, these supportive effects. The comparison of total BM cultures with basophil-depleted BM cultures revealed that physiological levels of basophils were sufficient to support plasma cell survival and IgG production. In vivo, the depletion of basophils after Ag immunization resulted in decreased Ig production and reduced numbers of plasma cells in the spleen. Taken together, these data ascribe a role to basophils in supporting plasma cell viability and Ig production.

A Creative GIFT to Immunotherapy

Dendritic cell (DC)-based cancer immunotherapy shows great potential but is challenged by the difficulty of obtaining large enough numbers of autologous DCs and the isolation of appropriate tumor-derived Ags for the ex vivo loading of DCs prior to injection. In this issue, Williams et al. (p. 7358) show that the treatment of blood-derived monocytes with the chimeric fusion product of GMCSF and IL-21 (termed GIFT-21) yields DCs with potent antitumor activities and characteristics that circumvent these immunotherapy challenges. Phenotypically, GIFT-21 DCs closely resembled monocyte-derived DCs generated by recombinant murine GMCSF treatment but, dissimilarly, they expressed decreased levels of CD11c and MHC II and substantially increased levels of IL-6, TNF-α, and IFN-α. When non–Ag-loaded GIFT-DCs were injected into tumor-bearing mice, they migrated to the periphery of the tumors, where they induced potent antitumor responses through cross-presentation of tumor Ags to CD8+ T cells. Importantly, analogous to mouse monocytes, GIFT-21 treatment of peripheral blood-derived CD14+ monocytes induced the
development of CCL2- and IL-6-producing cells. These data reveal a novel means to obtain ample numbers of autologous DCs for cancer immunotherapy, and because their antitumor activity does not require ex vivo Ag priming, GIFT-DCs show promise for treating tumors difficult to biopsy and/or with undefined Ags.

Misinformed SIV-specific T Cells

Dendritic cell (DC)-expressed B7-H1 (PD-L1) inhibits T cell functions through engagement of PD-1 on T cells. Upregulation of B7-H1 on both myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) has been reported in HIV-infected individuals. To investigate the relevance of this phenomenon to SIV/HIV immune responses and disease progression, Xu et al. (p. 7340) used the SIV-infected rhesus macaque model. Whereas mDCs and pDCs isolated from the blood and the peripheral and mucosal lymphoid tissues of control macaques expressed low levels of B7-H1, these same populations in SIV-infected animals expressed substantially greater levels of B7-H1 and showed increased frequencies of B7-H1+ DCs. Similarly, T cells expressed increased levels of PD-1, and both B7-H1 and PD-1 expression levels increased with disease progression that culminated in AIDS. In comparison, SIV controllers and uninfected controls expressed comparable levels of B7-H1 and PD-1. To study the relationships between B7-H1, PD-1 expression, and SIV-specific T cell function, SIV Ag-loaded monocyte-derived DCs were cultured with SIV-primed T cells. Compared with irrelevant Ab-treated cultures, SIV-specific T cells in B7-H1–specific blocking Ab-treated cultures exhibited increased proliferation and IL-2 and IFN-γ production, but decreased IL-10 production. Thus, SIV-induced increases in B7-H1 and PD-1 expression on DCs and SIV-specific T cells, respectively, hinders T cell–mediated immune responses to SIV infection. These data support further investigations of B7-H1 as a therapeutic target.

Enabling Tregs

The induced expression of Foxp3 in CD4+CD25– T cells by TGF-β and IL-2 stimulation is considered a reliable marker of induced regulatory T cell (iTreg) function in mice but does not definitively correlate with iTreg function in humans. Recent studies have suggested that agonists of peroxisome proliferator-activated receptors (PPARs) have immunosuppressive effects. When Lei et al (p. 7186) screened libraries representing nuclear receptor ligands and bioactive lipids, they identified multiple PPARα and γ agonists that increased the expression of Foxp3 in human iTreg cells. Compared with control iTregs induced by TGF-β/IL-2 treatment alone, naïve CD4+CD25–CD45RA+ T cells also cultured with any of the PPAR agonists developed suppressive function that persisted when cells were maintained with further PPAR agonist and IL-2 treatment. The stable nature of PPAR agonist-induced Foxp3 expression was linked to the demethylation of eight key regulatory CpG sites in the Foxp3 proximal promoter. Subsequently, demethylation of these sites was linked to TGF-β– and PPAR agonist-induced downregulation of DNA methyltransferases. Thus, it appears that PPARα and PPARγ agonists, together with TGF-β, efficiently convert human CD4+CD25– T cells into functional Foxp3+ iTregs by enabling the upregulation of Foxp3 expression.

Turning the Tide on Tumors

Gr-1+ monocytes have the potential to differentiate into either inflammatory or tolerogenic dendritic cells (DCs), but predominantly become tolerogenic DCs in the tumor environment. Because of their apparent plasticity, Augier et al. (p. 7165) wondered if Gr-1+ monocytes could be induced to become immunogenic DCs in the tumor environment, instead. To create a tumor cell line with the potential to divert the differentiation pathway of Gr-1+ monocytes adaptively transferred into tumor-bearing mice, the C26 tumor cell line was transfected with a plasmid encoding IL-10 soluble receptor and IL-3 (C26-p310R). Both C26-p310R cells and control plasmid-transfected CD26 cells proliferated at the same rate in vitro and formed tumors in mice when injected subcutaneously. However, tumor growth was significantly inhibited in C26-p310R–injected mice, and these mice exhibited better survival, compared with C26 control-injected mice. Furthermore, the C26-p310R tumor environment improved host antitumor responses by inducing the generation of immunogenic Gr-1+ monocyte-derived DCs, thereby reducing the frequency of regulatory T cells within the tumor. These data identify Gr-1+ monocytes as a promising target for cancer immunotherapy.

Controlling B Cell Whereabouts

Transitional B cells enter the spleen from the blood and are believed to give rise to both naive and memory B cells, which home to lymphoid follicles and the marginal zone, respectively. To gain better insight into the regulation of follicular (FO) versus marginal zone (MZ) B cell differentiation, DeKoter et al. (p. 7374) focused on three highly related members of the Ets transcription family: PU.1, Spi-B, and Spi-C. To interrogate their relevance, experiments were conducted using mice with inactivating mutations in the genes encoding PU.1 (Sfpi1) or Spi-B (Spib). In the spleen, Sfpi1−/−/Spib−/− (PUB) mice exhibited reduced frequencies of CD23+ FO B cells, compared with wild-type mice. In contrast, the frequency of splenic CD23− MZ B cells was increased. These alterations were partially rescued by ectopic expression of Spi-C, which appeared to reduce the frequencies of MZ B cells by promoting increased CD23 expression. Furthermore, ectopic expression of Spi-C partially rescued the reduced frequency of CD23+ transitional-2 cells observed in PUB mice. Not surprisingly, further experiments revealed that PU.1, Spi-B, and Spi-C activate transcription of the gene encoding CD23, Fcer2a, thereby furthering our understanding of both FO and MZ B cell differentiation.

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