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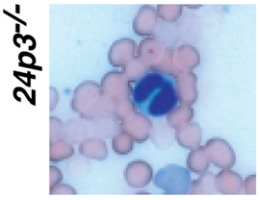
THE JOURNAL OF IMMUNOLOGY

In This Issue

24p3: More than Just a Siderocalin?



The neutrophil secondary granule protein lipocalin 24p3 is a siderocalin, sequestering iron-rich bacterial siderophores to hinder bacterial growth. 24p3 is released by both macrophages and neutrophils, and mice deficient in this molecule are susceptible to bacterial pathogens that have siderophores sequestered by 24p3. This siderocalin has been shown to have a number of functions beyond siderophore sequestration, and Liu et al. (p. 4692) found that neutrophils from 24p3-deficient (*24p3*$^{-/-}$) mice lost chemotactic function and were unable to extravasate to infection sites. Transcripts controlling cytoskeletal reorganization were suppressed in *24p3*$^{-/-}$ neutrophils and these cells could no longer phagocytose bacteria. Compared with wild-type mice, *24p3*$^{-/-}$ mice demonstrated increased susceptibility to intracellular *Listeria moncytogenes* and extracellular *Staphylococcus aureus* bacteria, as well as the extracellular fungus, *Candida albicans.* Neither *L. moncytogenes* nor *C. albicans* have siderophores that are sequestered by 24p3. The data indicate that 24p3 plays a unique role in neutrophil cytoskeletal rearrangement and chemotaxis necessary to host protection from pathogens.

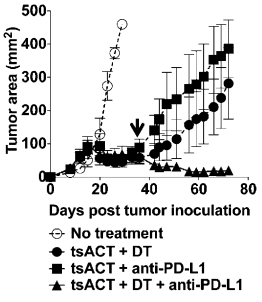
Dual Regulation by Id2

The differentiation of effector and memory CD8$^+$ T cells is controlled by a network of transcription factors acting through mechanisms that remain poorly understood. Inhibitor of DNA binding 2 (Id2) is a basic helix-loop-helix protein upregulated in effector T cells that is capable of binding to E protein transcription factors and antagonizing their binding to DNA. To elucidate the role of Id2 in peripheral CD8$^+$ T cell differentiation, Masson et al. (p. 4585) assessed the T cell responses of mice bearing an Id2-GFP reporter allele or specifically lacking Id2 in T cells. Id2-deficient CD8$^+$ T cells failed to form a short-lived effector population in response to influenza or *Listeria* infection. In contrast, memory CD8$^+$ T cells from these mice had an enhanced recall capacity relative to wild-type cells. Id2 expression was found to impair memory T cell activity and modulate the CD8$^+$ T cell transcriptional program in a dose-dependent manner. Id2 blocked memory differentiation by inhibiting the transcription factor E2A and its direct activation of the expression of *Tcf7*, a transcription factor critical for memory CD8$^+$ T cell development. In an apparently E2A-independent manner, Id2 also induced expression of the gene encoding T-bet, which is important for the development of short-lived effector CD8$^+$ T cells. Taken together, these data provide important insights into how Id2 modulates peripheral CD8$^+$ T cell fate.

TNFR p55 versus TNFR p75

To develop into effector CTL, CD8$^+$ T cells need TCR- and CD28-mediated signals. However, for full maturation they also require a third signal, which can come from the IL-2 and IFN-α produced during some infections but must come from another source in pathogen-free settings. Soloviova et al. (p. 4562) used an alloantigen-driven parent-into F1 model that develops acute graft-versus-host disease (GVHD) to test if TNF could function as a third signal for CD8$^+$ CTL maturation. The model is characterized by a TNF-dependent donor antihost CD8$^+$ CTL response, and the authors examined which TNF receptor, p55 or p75, was responsible for the third signal leading to CD8$^+$ CTL maturation. In this model, p75 knockout (KO) donor T cells induced a lupus-like chronic GVHD and p55 KO donor T cells induced the typical acute GVHD. Donor T cells from p75 KO had defects including reduced perforin, IFN-γ, and TNF production. Adoptive transfer experiments revealed that CTL maturation required signaling through p75 in both CD4$^+$ and CD8$^+$ T cells. While CD4$^+$ p75 KO T cell help resulted in defective CD8$^+$ CTLs, B cell responses were intact. Thus, the authors have shown that in vivo maturation of CD8$^+$ CTL is dependent on signaling through the TNF p75 receptor but not p55, suggesting intriguing possibilities for therapies that could reduce inflammation but retain CD8$^+$ CTL effector responses.

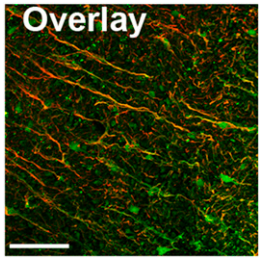
Targeting Recurrent Tumors



Adoptive cell transfer therapy is a promising treatment for melanoma; however, tumors often recur and become more difficult to combat. Goding et al. (p. 4899) have developed a strategy to successfully treat recurring tumors in a mouse model of B16.F10 melanoma. Naive tumor Ag-specific CD4$^+$ T cells transferred into tumor-bearing lymphopenic hosts differentiated into cytotoxic Th1 cells and mediated tumor regression, which was frequently followed by tumor relapse. Relapsing mice had very high numbers of tumor-specific regulatory T cells (Tregs) relative to nonrelapsing mice. However, depletion of Tregs neither protected against nor treated tumor recurrence. Tumor-specific effector CD4$^+$ T cells in relapsing mice were chronically exhausted, as characterized by elevated expression of inhibitory receptors, including PD-1, which was also upregulated on Tregs in these mice. Blockade of the PD-1 ligand PD-L1 combined with Treg depletion, but neither treatment alone, effectively mediated regression of

recurrent tumors and reversed effector T cell exhaustion. In contrast, either treatment alone led to regression when used on primary tumors. Because Treg depletion is not a practical clinical treatment, the authors assessed other options and found that anti–PD-L1 and anti–LAG-3 Abs in combination (but again, neither alone) mediated recurrent tumor regression. These data characterize differences in immunity to primary and recurrent tumors and illustrate the potential of combinatorial immunotherapy for controlling recurrent melanoma.

IL-7's Effects on EAE

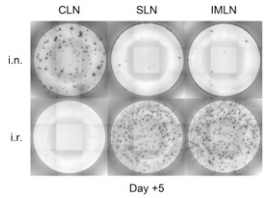


Mutations in the gene encoding IL-7Rα, which plays important roles in T cell development and homeostasis, may predispose individuals to multiple sclerosis (MS). To determine how IL-7Rα might be involved in MS pathogenesis, Ashbaugh et al. (p. 4525) investigated the contributions of IL-7Rα expression on different cell types to the development of experimental autoimmune encephalomyelitis (EAE), the mouse model of MS. Mice with thymus-restricted IL-7Rα expression ($IL7RTg^{IL7R-/-}$) developed significantly less severe EAE than wild-type (WT) mice, suggesting the involvement of IL-7Rα expression on non-T cells in disease pathogenesis. Treatment of WT mice with a neutralizing anti–IL-7Rα Ab during peak EAE promoted recovery, supporting the pathogenic role of IL-7Rα signaling. During acute EAE, dramatic changes from WT were seen in T cell subsets in the spleens and spinal cords of $IL7RTg^{IL7R-/-}$ mice, including a marked reduction in TNF-producing $CD4^+$ T cells. Chimeric mice expressing IL-7Rα only on nonhematopoietic cells were not protected from EAE, nor were mice expressing the receptor only on hematopoietic cells. In contrast, chimeric mice completely lacking IL-7Rα were almost completely protected from disease. In WT mice, IL-7Rα expression was observed on oligodendrocytes and astrocytes. This study suggests that IL-7Rα could be an attractive target for MS therapeutics because of its involvement in EAE pathogenesis, both through modulation of T cell effector function and signaling in nonhematopoietic cells such as astrocytes.

Foreboding Fibrocytes

Fibrocytes are circulating hematopoetic cells derived from $CD14^+$ monocytes. Discovered in 1994, fibrocytes are known to contribute to wound healing and fibrosing disorders, but much remains to be learned about these cells. In this issue, van Deventer et al. (p. 4861) found that fibrocytes, through the action of chemokines, were responsible for early events leading to tumorigenesis in a B16-F10 metastasis model. They isolated $CD45^+$, $CD11b^+$, $CD13^+$, and $Col1a1^+$ fibrocytes from both wild-type (WT) and *Ccr5*$^{-/-}$ mice and injected them into *Ccr5*$^{-/-}$ mice prior to administration of B16-F10 cells. The WT fibrocytes, but not *Ccr5*$^{-/-}$ fibrocytes, increased metastatic foci, and the increase was dependent on matrix metalloprotease-9 (MMP9). The injection of WT fibrocytes caused recruitment of $Gr\text{-}1^{Int}CD11b^+Ly\text{-}6C^+CD117^+CD45^+$ monocytes, which presented a similar profile to monocytes found in premetastatic niches. Transfer of these monocytes increased metastases in *Ccr5*$^{-/-}$ mice. Both WT and *Ccl2*$^{-/-}$ fibrocytes increased *Ccl2* expression in the lung, relative to *Ccr5*$^{-/-}$ fibrocytes. In addition, WT fibrocytes did not promote metastasis in either *Ccr2*$^{-/-}$ or *Ccl2*$^{-/-}$ mice. These data show that fibrocytes contribute to metastasis in a MMP9-dependent manner, recruiting $Ly\text{-}6C^+$ monocytes through the action of CCL2, the predominant ligand of CCR2. Thus, events that stimulate fibrocytic activity, such as inflammation and tissue damage, could increase metastatic risk.

GPS for the Gut



Vaccine-induced mucosal immunity requires direct delivery of immunogens to mucosal surfaces, and different routes of immunization can elicit responses in specific mucosal tissues. In this issue, Agnello et al. (p. 4836) compared the migration of IgA-producing Ab-secreting cells (IgA ASCs) following intrarectal (i.r.) immunization to that elicited by other routes of mucosal immunization. I.r. immunization with rotavirus viral-like particles induced Ag-specific IgA ASCs in the colon, cecum, and small intestine, whereas intranasal (i.n.) immunization induced IgA ASCs in the lung and bone marrow. Although i.r. immunization–induced IgA ASCs were found in the small intestine, they were unable to migrate toward the small intestinal chemokine CCL25. These ASCs did migrate toward CCL28, but CCL28 was dispensable for their localization to the small intestine. In contrast, IgA ASCs elicited via oral immunization migrated in response to both CCL25 and CCL28. Immunization via the i.r. route, but not the i.n. route, induced the expression of $\alpha_4\beta_7$ integrin on Ag-specific IgA ASCs, which was important for their migration to the small intestine. Interestingly, this integrin also appeared to play a role in excluding i.n. immunization–induced ASCs from the small intestine. This study suggests a mechanism responsible for the differential homing observed by IgA ASCs elicited via different routes of vaccination.