Metastasis-Promoting Immunity: When T Cells Turn to the Dark Side

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While the role of endogenous T cells in antitumor immunity is being debated, little is known about whether and how T cells promote tumorigenesis. In this issue of *Cancer Cell*, DeNardo and colleagues demonstrate that IL-4-producing T cells enhance metastasis by programming macrophages to produce factors that enhance tumor invasion.

For many decades, studies of T cell responses in cancer focused upon anticancer effects of tumor-specific T cells. Adoptive transfer studies in mice and humans certainly validated the capacity of T cells expanded and activated ex vivo to kill tumors upon reinfusion. However, the role of endogenous T cell responses in tumorigenesis has been less clear and downright controversial. The original immune surveillance hypothesis suggested that endogenous immune responses (likely T cell responses) serve an important role in inhibiting tumor formation based on recognition of "tumor rejection antigens." However, studies demonstrating that T-cell-deficient mice fail to display higher rates of chemically induced cancer (Stutman, 1974) questioned a role for endogenous T cell responses in tumor inhibition. More recent findings of increased tumor incidence in Rag-deficient mice (which lack T and B cells) or mice deficient in interferon signaling have resuscitated the concept of a potential antitumor role for endogenous T cell and innate immune responses (Shankaran et. al., 2001). Largely forgotten in this controversy has been the potential of T cells to *enhance* the processes of carcinogenesis and tumor dissemination.

DeNardo et al. (2009) bring into striking focus the potential role of T cells in promoting one of the most important steps in cancer progression—metastasis. Using a transgenic model of Polyoma Middle T antigen-driven breast cancer tumorigenesis (MMTV-PMT mice), they demonstrate that elimination of endogenous T cells dramatically reduces the incidence of lung metastases while not altering the rate of developing primary tumors. Further investigations revealed that metastasis rates depended specifically on CD4 T cells since their elimination *reduced* metastasis. How can these surprising findings be reconciled with earlier findings that tumors arise more frequently in Rag-deficient mice (Shankaran et. al., 2001)? One possibility could be that T cells play different roles in primary carcinogenesis versus metastasis—possibly even opposite roles. Insights into this paradox require an appreciation that T cell responses develop along distinct functional pathways that ultimately can have distinct consequences for cancer development.

The diversity of programmed T cell activation pathways is exemplified among CD4 "helper T cells." Helper T cells regulate immune responses via the production of specific factors that instruct other cellular elements of the immune system. There are now three well-defined helper T cell subsets: Th1, Th2, and Th17 (Zhou et al., 2009). Th1 effector cells are characterized by production of γ-interferon; Th2 cells are defined by production of IL-4 as well as the related cytokine, IL-13; and the recently discovered Th17 helper subset is characterized by production of the cytokine IL-17A. Immune responses induced by these various helper T cell subsets are counter-balanced by an inhibitory T cell subset termed regulatory T cells (Sakaguchi et al., 2008). The genetic programs that define each of the different T cell differentiation pathways are regulated by distinct transcription factors (Zhou et al., 2009). Beyond infection control, these distinct helper T cell subsets play varying roles in immune pathology.

The general consensus among tumor immunologists is that Th1 cells, based on their γ-interferon production, macrophage activation, and enhancement of killer CD8+ T cells, are critical elements in antitumor immune responses, but is it possible that different helper T cell subsets could promote cancer development or metastasis? DeNardo et al. indeed find this to be the case. They show that the metastasis-promoting CD4 T cell response in the MMTV-PMT model is mediated by Th2 responses that produce IL-4 and IL-13 and that in vivo blockade with anti-IL-4 antibodies significantly inhibited metastasis. This prometastatic Th2 response appears to be mediated in part by macrophages within the tumor microenvironment. As with T cells, there is great plasticity in macrophage activation programs leading to distinct effector functions (Mantovani et al., 2005). In part instructed by helper T cells, macrophage activation programs have been divided into M1 type and M2 type. M1 macrophages, which are induced by Th1-derived γ-interferon, are characterized by production of reactive oxygen species and nitric oxide (NO) and the cytokine IL-12, which further amplifies Th1 responses. Together with CD8 killer cells, M1 macrophage activation is thought to be a major mediator of Th1-orchestrated antitumor responses. DeNardo et al. found that a major effector pathway for the prometastatic Th2 responses involves M2 macrophages dependent on IL-4 and IL-13. M2 macrophages in turn produce various cytokines such as TGF-β, which suppresses antitumor immune responses, and EGFR ligands, which promote tumor growth and possibly invasiveness. While previous studies have demonstrated a role for IL-4 and IL-13 in promoting

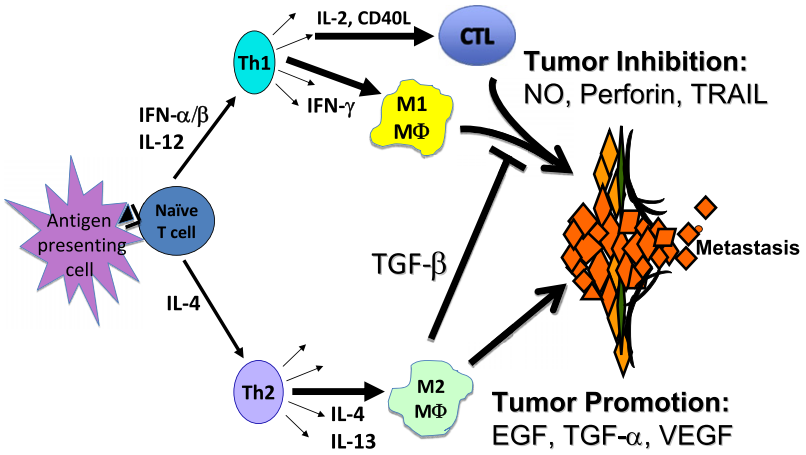

Figure 1. Two Distinct T Cell Differentiation Pathways Lead to Immune Responses that Can Inhibit or Promote Cancer Progression

The figure demonstrates the concept that the consequences of T cell activation for cancer inhibition versus promotion depend on the pathway of differentiation. T cells are activated when their T cell receptor recognizes cognate antigen on an antigen presenting cell (typically a dendritic cell, macrophage or B cell). Depending on the balance of cytokines present at the time of antigen recognition, T cells can differentiate along various pathways. Shown in the figure are two pathways of differentiation: the Th1 pathway, promoted by proinflammatory cytokines such as type 1 interferons (α and β) and IL-12 and the Th2 pathway, promoted by IL-4. Th1 cells, through production of γ-interferon, instruct macrophages toward a tumoricidal M1 program as well as providing signals to activate anti-tumor cytotoxic T cells (CTL). Thus, a Th1 diffrentiation program inhibits tumor growth and progression. Alternatively, if Th2 responses develop, macrophages are programmed via IL-4 and/or IL-13 toward a tumor-facilitating M2 differentiating program, characterized by production of growth and pro-angiogenic factors as well as TGF-β, an inhibitor of antitumor immune responses. Additional T cell differentiation programs, such as Th17 and regulatory T cells (not shown in figure), likely play distinct roles in the cancer process that is currently under investigation.

cancer growth and metastasis via Stat6 signaling in myeloid cells (Terabe et al., 2000; Ostrand-Rosenberg et al., 2000), DeNardo et al. are the first to demonstrate an example whereby this mechanism is truly T cell dependent. This work supports the notion that T cells can impact various steps of cancer development and progression but that their specific role depends on the type of T cell program initiated, which in turn determines the nature of downstream effector responses (Figure 1). Beyond Th1 and Th2, the role of Th17-type immune responses in cancer development and progression is likely to be distinct and is currently being investigated (Wang et al., 2009). While regulatory T cells are well documented to inhibit antitumor T cell responses (Yamaguchi and Sakaguchi, 2006), their role in modulating procarcinogenic or prometastatic T cell immunity remains to be defined.

A major unanswered question in this study, and all studies implicating endogenous T cell responses in cancer development, is the nature of the antigen(s) recognized. All T cells require antigen recognition via their heterodimeric αβ T cell receptor (TCR) in order to become activated. In the case of infection-induced carcinogenesis, proteins expressed by the infectious agent represent the likely antigens to engage T cells. However, in the MMTV-PMT metastasis system, there is no obvious infectious agent, so the prometastatic Th2 response is likely initiated by a self-antigen minimally expressed in normal somatic tissues and upregulated in the mammary tumors. Clues as to the identity of the self/tumor antigen(s) may be drawn from another spontaneous murine tumor model that has long been known to depend on CD4 T cells—the B cell lymphomas that arise frequently in SJL-strain mice. These lymphomas involve the activation of an endogenous mammary tumor virus encoding a superantigen that stimulates CD4 T cells to produce Th2 cytokines just as in the MMTV-PMT model (Tsiagbe et al., 1993). Each different superantigen selectively activates T cells whose TCR utilizes distinct Vβ segment. If an endogenous retroviral encoded superantigen is indeed the instigator in the MMTV-PMT system as with the SJL lymphomas, metastases would be dependent on CD4 T cells predominantly expressing a single Vβ segment.

Finally, the therapeutic relevance of these findings should not be overlooked. If distinct T cell programs selectively enhance or inhibit cancer progression, it should be possible to "redirect" tumor-specific T cell programs from procancer to anticancer. Since the cytokines, receptors, and signaling pathways responsible for initiating and maintaining each of the helper T cell programs are becoming well defined, it should indeed be possible to block certain procarcinogenic differentiation programs while promoting antitumor programs. If we look carefully, we may find that there are already antibodies and drugs on shelves able to accomplish just that.

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