

Chapter 2

Th17 Cells in Cancer

Chrystal M. Paulos, Michelle H. Nelson and Xue-Zhong Yu

Abstract T helper (Th)17 cells regulate host defense and exacerbate autoimmune diseases, yet their role in tumor immunity remains controversial with reports that Th17 cells could either promote or suppress tumor growth, depending on the type of malignancy or means of therapeutic intervention. This review discusses how inflammatory signals (such as cytokines and co-stimulatory/co-inhibitory molecules) induced in the tumor milieu regulate the functional fate of Th17 cells, which ultimately affect the cells' capacity to mount immune responses against cancer. We review recent findings regarding the factors that influence the generation, plasticity, and memory phenotype of Th17 cells and their relevance to cancer immunotherapy. Further, we discuss recent reports concerning the interaction of Th17 cells with regulatory T lymphocytes and cytotoxic cluster of differentiation 8 (CD8⁺) T cells present in tumor tissue. Unraveling the mysteries surrounding basic and translational aspects of Th17 cell biology promises to have important implications for patients with advanced malignancies.

Keywords Th17 · IL-17A · ROR γ t · Plasticity · Immunology · Cancer · Immunotherapy · Tumor microenvironment · Transplantation

1 Introduction

Cancer persists as a clinical problem not only because of the disease, in its myriad forms, but also because it remains stubbornly resistant to even some of the most advanced therapeutic regimens. Often, by the time the patient requires treatment, the

X.-Z. Yu (✉) · C. M. Paulos · M. H. Nelson
Department of Microbiology and Immunology, University of South Carolina,
Charleston, SC 29425, USA
e-mail: yux@musc.edu

Department of Medicine, University of South Carolina, Charleston, SC 29425, USA

C. M. Paulos · M. H. Nelson
Department of Surgery, University of South Carolina, Charleston, SC 29425, USA
e-mail: paulos@musc.edu

disease has already stymied the first line of defense: the immune system. Despite being exquisitely effective against disease brought about by foreign bodies, the immune system can seem impotent against cancerous self-tissue. Certainly, the immune system plays a vital role in recognizing and killing cancer cells; but, more often, the body finds itself overwhelmed by the malignancy. Under certain treasonous circumstances, the immune system can even promote the growth and spread of tumor tissue in the patient.

These facts may paint the immune system as at best neutral, at worst a foe in the treatment of cancer. However, the burgeoning field of immunotherapy still sees a promise in harnessing the immune system to arrest the advance of tumor malignancies in patients. Understanding the conditions necessary to coax the patient's own immune elements into halting or even turning back the spread of cancer provides the primary impetus for a flurry of current research into the role of T cells in tumor immunity. This review focuses on the exciting discoveries concerning the recently discovered (2005) cluster of differentiation 4 (CD4)⁺ T-cell subset called Th17, and its potential role in tumor immunity.

CD4⁺ T cells are among the chief regulators of the immune system. These cells can differentiate into different lineages of T helper (Th) cells with distinct biological functions [1]. In 1986, Th cells were divided into two distinct subsets: Th1 cells that produce interferon- γ (IFN- γ) promote cell-mediated immunity and Th2 cells that produce interleukin-4 (IL-4) support humoral immune responses. Both subsets were found to enhance antitumor immunity by inducing the expansion and cytotoxic function of CD8⁺ T cell (cytotoxic T lymphocytes, CTLs) responses to the tumor. In contrast, regulatory FoxP3⁺ CD4⁺ T cells (regulatory T (Treg) cells) were found to suppress antitumor immunity by inhibiting CTLs. In 2005, IL-17-expressing T cells (Th17 cells) were discovered as an independent subset. Studies on the newly described Th17 cells quickly established their contributions to inflammation, autoimmunity, and host defense, but the role of these cells in tumor immunity remains both unclear and hotly debated [2], [3]. Th17 cells have been found to eradicate tumors when adoptively transferred into their autologous host. However, naturally arising endogenous Th17 cells have also been found to promote tumor progression. In this chapter, we discuss the basic and translational properties of Th17 cells in the context of cancer. We discuss Th17 cell plasticity, enabling them to convert into other CD4⁺ T-cell subsets (such as Th1 or Treg-like cells) profoundly altering the cells' functional and phenotypic fate (specifically, their capacity to kill tumors). This chapter brings together the latest research on the disparate means by which cytokines, co-stimulation/co-inhibition, T-cell receptor (TCR) signal strength, transcriptional factors, and epigenetic mechanisms regulate Th17 cells in tumor tissue. We also highlight the critical importance of interplay between Th17 cells and other immune cells in regulating cancer growth. Finally, we discuss recent proto-clinical findings involving human Th17 cells in cancer and speculate how these results may lead to new treatments for cancer patients.

2 Cd4 T Cell Subsets in Tumor Immunity

2.1 *Th17 Cells: The Th1/Th2 Paradigm Demystified*

Twenty-eight years ago, Mosmann and Coffman introduced the Th1/Th2 paradigm of T helper cell differentiation to explain the adaptive immune system's mode of clearing intracellular and extracellular pathogens [4]. Subsequent investigation revealed that the Th1/Th2 paradigm could not fully account for the development of inflammatory responses to self-tissue or tumor tissue [5], [6]. The hunt was on for the T-cell subset(s) responsible for driving inflammation to fill this knowledge gap [7]. Eight years ago, a new effector CD4⁺ T helper cell subset that produces IL-17A was discovered: Th17 cells [8]–[10]. The cytokines and transcription factors that promote Th17 cell generation were soon identified, and it became clear that Th17 cells represent an independent subset of T helper cells with distinct functions in regulating inflammation—functionally divergent from that possessed by Th1 or Th2 cells. The discovery of Th17 cells thus expanded the Th1/Th2 paradigm and provided a clearer picture of the immune system's agent responsible for tissue inflammation, autoimmunity, and tumor immunity.

2.2 *T Helper Subsets in Tumor Immunity*

CD4⁺ T cells localized in tumor tissue take immunological cues from the tumor milieu (Fig. 2.1), leading to differentiation into one of several T helper (Th) subsets (Th1, Th2, Th17) [6], [11] or into a suppressive subset (Tregs) [12]. The cellular effect on cancer development will depend on the phenotypic outcome of CD4⁺ T-cell differentiation. Th1 and Th2 cells are the effector cells that express T-bet and GATA-3 [13], [14], respectively. Both subsets elicit antitumor effects, with Th1-polarized cells traditionally regarded as the more effective tumor killers. In contrast, Treg cells are believed to impair antitumor immunity by suppressing cytotoxic CD8⁺ T-cell responses [15], [16]. (For further information on Treg cells in cancer, we refer the reader to Chap. 1 of this book.) The effect of Th17 cells on cancer is more ambiguous: Some investigators have reported Th17 cell acceleration of tumor growth, while others report that Th17 prompted eradication of established tumors [2], [3]. A satisfying, all-encompassing explanation for these conflicting results has not been forthcoming, but recent results have provided a clue: Th17 cell form and function are uniquely sensitive to a host of factors in the context of tumor. The type of cancer tissue (e.g., prostate versus pancreatic), the therapeutic approach (e.g., vaccine versus adoptive cell transfer therapy; *vide infra*), and the stimuli to which the cells are exposed during activation (e.g., cytokines, co-stimulatory molecules, TCR signal strength) all significantly impact the development of Th17 cells, providing the cells with an apparently broad range of phenotypic and functional prospects. Thus, understanding the nature of Th17 cell responses in the tumor microenvironment will be essential for advancing efficacious cancer therapies. Herein, we review recent findings concerning the means by which cytokines and other signals modulate Th17 cell development, and their consequences for regulation of tumor immunity.

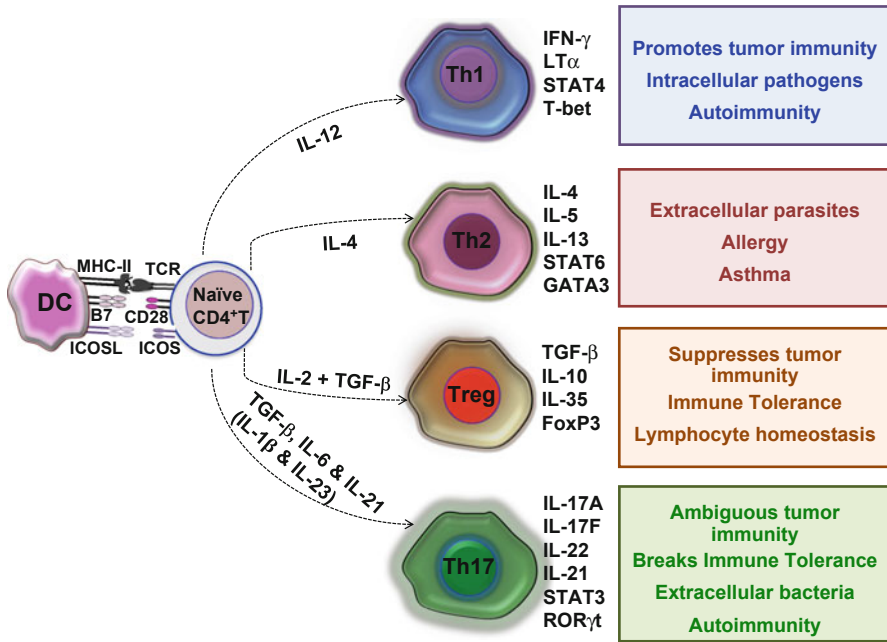


Fig. 2.1 Differentiation of helper T cell subsets. Post activation of CD4⁺ T cells with antigen presenting cells, e.g. with dendritic cells that present peptide via MHCII and costimulation with CD28 and ICOS, these cells can differentiate into various effector (Th1, Th2 or Th17 cells) or regulatory subsets (Treg cells). Their differentiation depends on the local cytokines environment they encounter during activation. The differentiation of each of these effector T cell subsets is controlled by distinct sets of transcription factors. In the presence on interleukin-6 (IL-6) and transforming growth factor-beta (TGF- β), naïve CD4⁺ T cells differentiate into a Th17 cell phenotype, which are characterized by expression of transcription factors retinoic acid receptor-related orphan receptor-gt (ROR γ t) and signal transducer and activator of transcription 3 (STAT3). IL-21 and IL-23 cytokines can promote and stabilize this phenotype during their expansion. Once programmed, these cells secrete IL-17A, IL-17F, IL-21 and IL-22. While the role of Th17 cells is controversial in tumor immunity, they play a key role in enhancing autoimmunity and host defense. The cytokines and transcription factors that control the development of Th1, Th2 and Treg cells are also shown herein and they also distinctly regulate immune response to foreign, self and tumor antigens

3 TH17 Cells in Cancer: Basic Th17 Biology and Interaction with Other Immune Cells in the Body

3.1 Cytokines, Transcription Factors, and Extracellular Markers

Th17 cell development is distinct from the development of Th1, Th2, and Treg cells and is characterized by unique transcription factors and cytokine requirements [8]. As shown in Fig. 2.1, naïve CD4⁺ T cells undergo differentiation into Th17 cells when exposed to transforming growth factor beta (TGF- β), IL-6, IL-1- β , and IL-21

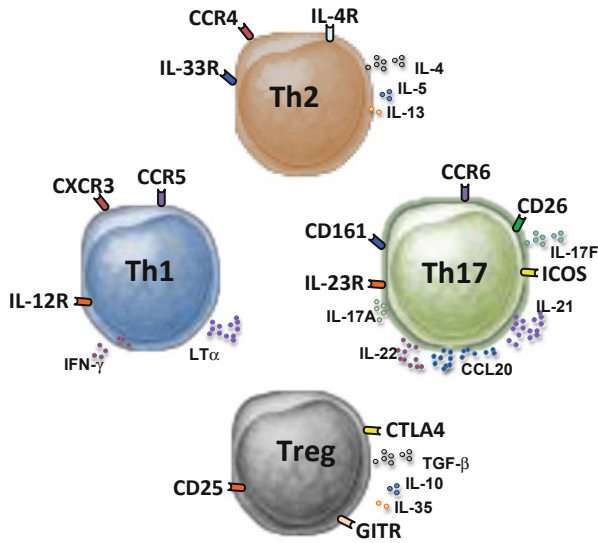


Fig. 2.2 Extracellular markers on Th1, Th2, Th17, and Treg cell subsets. Th17 cells can be distinguished from Th1, Th2 and Treg cells in the peripheral blood CD4⁺ T cells of healthy and diseased human donors by their expression of chemokine receptors and other cell surface molecules. As depicted, Th1 express CXCR3, CCR5, IL-12R but not CCR4 or CCR6 on their cell surface; and Th2 express CCR4, IL-33R and IL-4R but not CXCR3 or CCR6 on their surface; and Th17 express a number of different markers on their cell surface, including CCR6, CD161, IL-23R, ICOS and CD26. Finally, Treg cells have been found to express a high level on CD25, CTLA4 and express a low level of CD127 on their cell surface

via signal transducer and activator of transcription 3 (STAT-3)-dependent signaling [17], [18]. Th17 cells are maintained long term in the presence of IL-23 [19]. Conversely, IL-12 supports Th1 development and suppresses Th17 generation or converts them to a Th1 phenotype. Likewise, IL-4 promotes Th2 and suppresses Th17 development. TGF-β and IL-2 support Treg cell generation [2], [6] but differentially regulate whether a Th17 cells will possess inflammatory or regulatory functions (*vide infra*). As depicted in Fig. 2.1, Th17 cells are characterized by their capacity to secrete IL-17A, IL-17F, IL-21, IL-22, and chemokine (C-C motif) ligand 20 (CCL20) [20]–[22]. Moreover, the Th17 phenotype is controlled by the master transcription factors retinoic acid-related orphan receptors (RORs)γt, RORα, aryl hydrocarbon receptor (AHR), and IFN-regulatory factor 4 (IRF4) [18], [23]–[26]. In addition to these cytokines and transcription factors, Th17 cells can be identified by their surface expression of the chemokine receptor (CCR6), the IL-23 receptor (IL-23R), the inducible costimulator (ICOS), and the lectin-like receptor (CD161) (Fig. 2.2) [27]–[30]. Quite recently, human Th17 cells were found to express high levels of the dipeptidyl peptidase IV called CD26 on the cellular surface; CD26 is a multifunctional ectoenzyme involved in T cell activation and has been implicated in autoimmune pathophysiology [31]. In contrast, Treg cells express low levels of

CD26 and high levels of ectonucleotidases CD39 and CD73 [32]. CD26 expression has previously been reported to crop up in multiple inflammatory conditions. Originally linked to Th1 cells prior to the discovery of Th17 [33], in fact CD26^{bright} Th17 cells are enriched in the inflamed tissue of patients with inflammatory bowel disease [31]. Further, CD26 upregulation correlates with disease activity in human autoimmune manifestations linked to the presence of pathogenic Th17 cells, such as rheumatoid arthritis (RA). Elevated CD26 expression as well as the high expression of ICOS, IL-23R, CCR6, and CD161 allow Th17 cells to be distinguished from other T cell counterparts (Th1, Th2, and Treg) in patients with cancer as well. Please refer to additional references [27], [34] and Fig. 2.2 for a detailed description of the markers on Th1, Th2, Th17, and Treg cells. Importantly, these phenotypic markers permit the determination of Th17 distribution and functionality in tumor tissue—a prerequisite for elucidating the still murky role of Th17 cells in either promotion or suppression of tumor growth.

3.2 Th17 Cell Distribution and Impact on Tumor Immunity

While Th17 cells are abundant in the mucosal tissues and support gut-related homeostasis, few Th17 cells ($\sim 0.1\%$) reside in the peripheral blood of healthy individuals or cancer patients [3], [35], [36]. However, significantly greater numbers of Th17 cells infiltrate tumors, especially as compared to Th17 density in the adjacent, non-tumor tissues of patients. This heightened presence of Th17 cells in tumor tissue holds true for a vast range of malignancies, including melanoma, ovarian, pancreatic, colon, and prostate cancer (Table 2.1) [37]–[55]. These observations imply that tumors produce factors that promote Th17 cell trafficking to the diseased site; the responsible parties include factors such as monocyte chemotactic protein 1 (MCP-1), regulated on activation, normal T cell expressed and secreted (RANTES), and tumor-secreted prostaglandin E2 [40], [56]. Tumor-associated fibroblasts, monocytes, and macrophages also promote Th17 cell infiltration and expansion in hepatocellular carcinomas [54]. Nitric oxide (NO)-producing myeloid-derived suppressor cells from patients with ovarian cancer were also recently found to support the Th17 cell development [57]. Collectively, these data suggest that new targets can be manipulated to modulate Th17 responses in cancer.

Murine tumors similarly house large Th17 cell populations [58], permitting researchers to examine Th17 capacity to either promote tumor growth or enhance antitumor immunity. The results have added to the confusion concerning Th17 cells and cancer. Proinflammatory cytokines secreted by Th17 cells *in vivo*, such as IL-17A, have been reported to impair immune surveillance and promote tumor growth [59], [60]. In contrast, other studies reported that Th17 cells mediate the regression of large, established, and poorly immunogenic melanoma tumors in mice to a greater extent than Th1 cells [61], [62]. Those studies followed an adoptive T cell transfer (ACT) therapy approach, which takes advantage of CD4⁺ T lymphocytes that express a TCR recognizing tyrosinase tumor antigen. Exploitation of the TCR

leads to rapid expansion of Th17 populations to large numbers *ex vivo* for reinfusion into the autologous tumor-bearing host mouse [62], [63]. This approach effectively parallels ACT trials in human patients, and has allowed investigators to examine how infused TCR-specific CD4⁺ (or CD8⁺) T cells interact with other immune cells in the body—interactions that may either enhance or impair treatment outcome, and may hold the key to understanding the Janus-faced effects of either protumor or antitumor Th17 cells.

3.3 *Interplay Between Th17 Cells and Other Immune Cells in the Tumor*

Until recently, CD4⁺ T cells had been regarded as mere suppliers of growth factors in support of CD8⁺ effector T cells. CD8⁺ T cells, believed to be the more important antitumor immune actors, kill tumors by direct cytotoxicity. However, mounting evidence has revealed that CD4⁺ Th cells—particularly Th17 cells—are capable of mediating tumor regression, not in an ancillary role but as the primary cytotoxic agents [62], [64]. In fact, in some cases the ability of CD4⁺ T cells to reject tumor significantly improves on the antitumor capacity of CD8⁺ T cells. This result has sparked heated debate, fueled by reports suggesting an indirect regulatory—as opposed to direct cytotoxic—role for Th17 cells in tumor destruction, via interaction with Treg and CD8⁺ T cells [61], [65]. The following sections address this debate.

Th17–CD8⁺ T cell dynamics. Th17 cells mount antitumor immune responses not merely in experimental models of cancer that involve ACT therapy; in some studies, vaccines have successfully induced endogenous antitumor effects. A positive example involved forming a vaccine from pancreatic cancer cells (Pan02). Pan02 cells, which normally secrete TGF- β but not IL-6, were transduced to secrete IL-6 and transplanted into syngeneic mice [66]. As expected, an increase in host tumor-infiltrating Th17 cells was observed in mice with IL-6-transduced tumors. This is not surprising given that TGF- β and IL-6 are critical cytokines for promoting Th17 cell generation. In this model, vaccinated mice displayed a significant delay in tumor growth and enhanced survival prospects compared to mice treated with wild-type, untransduced Pan02 tumor cells. Additional investigation revealed results with interesting implications for the species responsible for the antitumor response: Murine Pan02 tumors transduced to secrete IL-6 not only induced host Th17 cells but also drove concomitant recruitment of IFN- γ -producing CD8⁺ T cells to the tumor, which enhance antitumor activity of Th17 cells.

This discovery—bolstering of CD8⁺ T cell activation by endogenous Th17 cells in mice with IL-6-transduced pancreatic cancer—complements recent findings in the context of adoptively transferred Th17 cells (Fig. 2.3a). Restifo, Dong, and colleagues found that adoptively transferred tyrosinase-related protein-1 (TRP-1) Th17 cells elicited activation of endogenous CD8⁺ T cells in mice with melanoma. CD8⁺ activation was crucial for the observed antitumor effect [61]. Subsequent studies revealed that Th17 cells promoted CD8 α ⁺ dendritic cell recruitment into the tumor

Effector versus regulatory Th17 cells in tumor immunity

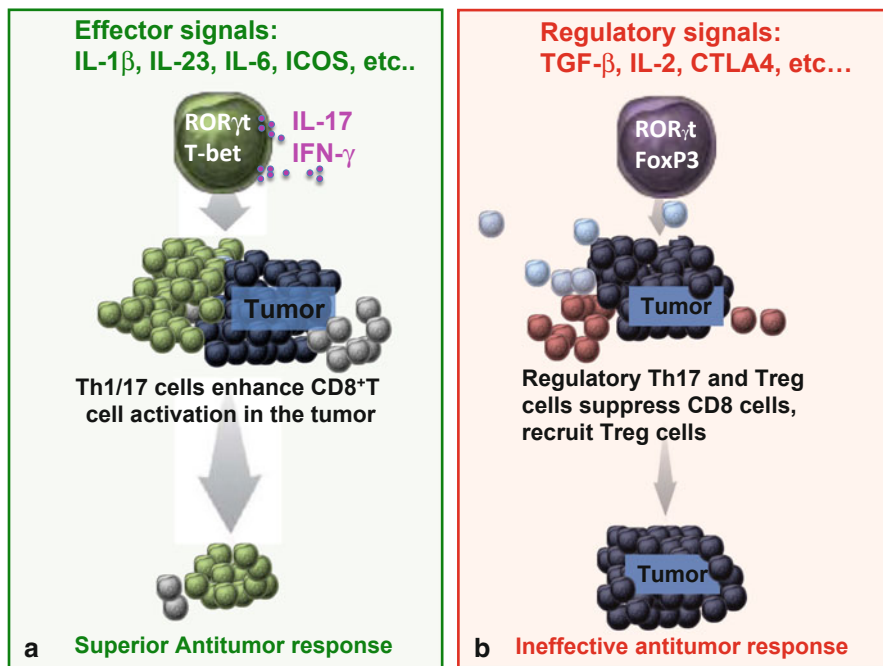


Fig. 2.3 Effector (a) versus regulatory (b) Th17 cells in tumor immunity. Depending on the cytokine or other signals that Th17 cells encounter during tumor progression, they can transform into either effector or regulatory Th17 lymphocytes that either enhance or suppress tumor regression. **a)** Th17 cells (effectors) activated with IL-1 β , IL-23, IL-6 and/or ICOS agonist are poly-functional and capable of mediating potent tumor regression in solid tumors. **b)** Th17 cells (regulatory) programmed with cytokines such as TGF- β , IL-2 and or CTLA4 can dampen their function and persistence, thereby potentially reducing their capability to kill tumors. Regulatory Th17 cells likely do not foster the induction or cooperation of CTLs to the malignant site

tissues as well as the draining lymph nodes, likely inducing the activation and expansion of cytotoxic CD8⁺ T cells. Th17 cells promoted CCL20 chemokine production by tumor tissues, thereby recruiting CD8⁺ T cells to the malignant site. Additionally, tumor-bearing CCR6-deficient mice did not respond to Th17 cell therapy. Th17 cells, thus, elicited a protective inflammatory response that promoted the activation of tumor-specific CD8⁺ T cells perhaps via CCL20/CCR6 homing mechanisms.

A picture of synergistic interaction between Th17 and CD8⁺ T cells emerges from these antitumor studies; yet recent work from the Antony laboratory suggests caution against overemphasizing this interplay of immune cells. Antony and coworkers reported that tumor-specific TRP-1 CD4⁺ T cells can eradicate large tumors directly and without the need for endogenous CD8⁺ T cells or natural killer (NK) cells [67]. These contrasting results highlight the need for follow-up investigations of the role of antitumor CD4⁺ T cells (as well as Th1 and Th17 cells) on host or infused CD8⁺

T cells. CD4⁺ T cell cooperation with cytotoxic CD8⁺ T cells in tumor immunity is currently under investigation in the laboratories of the authors as well as others.

Th17–Treg dynamics. What remains clear, however, is that Th17 cells—under the right conditions—have positive antitumor effects. For example, adoptively transferred Th17 cells can mediate potent tumor regression in irradiated mice bearing the established B16F10 tumor. Interactions between the Th17 and CD8⁺ T cells may have certain consequences for the treatment outcome; however, another important question, with ramifications for the efficacy and persistence of these treatments, concerns the proportion and effects of Th17 and Treg cells on each other and on tumor regression. The influence of host Treg cells on either endogenous or infused Th17 cells is unclear, though the potential role of Tregs in dampening antitumor responses (*vide supra*) has been mentioned herein (Fig. 2.3b).

Discussion of the effect of IL-2—often administered to mice in ACT experiments to support the expansion of transferred Th17 cells—on either Th17 or Treg or both cell subsets suffices to exemplify the current lack of conceptual clarity concerning Th17–Treg interactions and their role in antitumor immunity. The Zou group first reported that IL-2 signaling exerts significant but divergent regulatory effects on Th17 and Treg cells in the tumor microenvironment [68]. In other words, while IL-2 bolsters Th17 cell populations, which subsequently—by an unknown mechanism—appear to dampen host Treg populations in the tumor tissue. These findings would suggest that infused Th17 cells may reduce the number and the suppressive function of host Treg cells; abrogation of Treg suppressor function offers one explanation for why the therapeutic outcome in these ACT-treated mice is curative (Fig. 2.3a). However, once again, alternate explanations for conflicting data in the literature may be preferred. For example, Treg cells require IL-2 for their *in vivo* maintenance and outcompete other cell subsets (including Th17) for the molecule via a high-affinity IL-2 receptor (67). Thus, it is conceivable that Treg cells impair the engraftment of infused Th17 cells by depriving the infused cells of the beneficial cytokine, a situation that would certainly hamper treatment efficacy, as seen in some literature reports (Fig. 2.3b). On the other hand, given that high concentrations of IL-2 impair the expansion and function of Th17 cells, Treg cells may actually support the engraftment and function of adoptively transferred Th17 cells (at least, in the B16F10 model; see below for the discussion of different tumor tissues) by functioning as an IL-2 cytokine sink. If so, then depletion of host Treg cells would impair the persistence and antitumor activity of donor Th17 cells. These conjectural scenarios suggest that experiments with Treg-depleted FoxP3-DTR mice would go a long way toward elucidating the Th17–Treg dynamics in melanoma-bearing mice that are infused with TRP-1 Th17 cells. Such studies are currently underway in several laboratories. Questions concerning the interplay of host Th17 and Treg cells with endogenous CD8⁺ T cells also need to be addressed. However, as will become evident in the following sections of this chapter, Th17 interactions with other T cell subsets do not present the only riddles surrounding T cell tumor immunity; the incompletely characterized roles of subcellular molecular species (e.g., cytokines and co-stimulatory molecules) in activating or pacifying Th17 cells—whether in isolation or in interaction with other cell subsets—requires comment and further study.

4 Multiple Facets of Th17 Cells in Cancer Development

4.1 Regulatory and Inflammatory Th17 Cells in Cancer

Th17 cells are not uniformly beneficial in mediating antitumor responses; one possible explanation is their inflammatory function, which has been linked to tumor growth. The Th17 cell function may depend on the type of cancer encountered by the cells; and, if so, a number of factors could alter the effect of Th17 cells on a malignancy's pathology: the source of the Th17 cells (arising naturally via tumor growth, or adoptively transferred following ex vivo manipulation); the regulatory or inflammatory functional phenotype of the cells (and what gives rise to the functionality); and/or exposure to therapeutic interventions such as chemotherapy, vaccination, cytokines, or co-inhibitory/co-stimulatory molecules. Understanding how Th17 cells cause inflammation in the context of these factors, as well as how these elements impact patient survival, is of considerable interest in the cancer immunotherapy field.

One thing remains clear: The influence of Th17 cell accumulation in murine and human tumors on cancer progression remains controversial due to the disparity of experimental results of Th17 cell interactions with cancers [2], [3]. Some small measure of consensus is arising from the controversy, however: Th17 cell subsets can possess either regulatory or inflammatory properties depending on the stimuli they encounter, which may explain why Th17 cells have potent antitumor properties in some experimental regimens but actually fosters tumor growth in others. Th17 cell responses to foreign pathogens provides some illumination of this concept, for example, the Sallusto laboratory found that different pathogens favor the generation of either regulatory or effector Th17 cells [69]. Specifically, *Candida albicans*-specific Th17 cells secreted IL-17 and IFN- γ , but no IL-10, whereas *Staphylococcus aureus*-specific Th17 cells secreted IL-17 and IL-10 (upon restimulation). At the molecular level, *C. albicans* IL-1 β was essential for differentiation of *C. albicans*-induced, IL-17/IFN- γ double-producing Th17 cells. IL-1 β inhibited IL-10 secretion; blockade of IL-1 β in vivo rescued cell capacity for IL-10 secretion. The different cytokines presented by *C. albicans* and *S. aureus* prime Th17 cells to produce either effector IFN- γ or regulatory IL-10, respectively (and further identify IL-1 β as a regulator, along with IL-2, of Th17 cell function).

An implication for Th17 functionality in the context of cancer follows from these observations with pathogen-primed cells: Different types of tumor tissue may foster the generation of Th17 cells with different phenotypes—either suppressive or inflammatory, with divergent consequences for tumor growth progression. Indeed, high-frequency Th17 cell infiltration into the tumor bed of patients with colon or pancreatic cancer strongly correlates with poor prognosis [70]. Conversely, increased Th17 cell numbers in ovarian tumors have been associated with improved patient survival rates [71]–[75]. The intrinsic properties of tumors that might regulate the anticancer activity of Th17 cells have not been fully identified, but the inconsistent success of Th17 cell-based cancer immunotherapy may arise when varying cytokines produced in tumor microenvironments or co-stimulatory and/or co-inhibitory

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Gabrilovich, D.I.; Hurwitz, A.A. (Eds.)

2014, XIV, 464 p. 38 illus., 34 illus. in color., Hardcover

ISBN: 978-1-4899-8055-7