Role of Lymphocytes in Cancer Immunity and Immune Evasion Mechanisms

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Abstract

It is well established that the immune system is involved in the initiation, development, and progression of cancer. The tumor microenvironment is highly infiltrated by a complex network of immune cells, which includes innate (macrophages, mast cells, neutrophils, dendritic cells, natural killer cells, innate lymphoid cells, and myeloid-derived suppressor cells) and adaptive T and B lymphocytes. This diverse set of cells, their interactions, and secretion of anti- or pro-inflammatory immune mediators create an immunologically active tumor microenvironment. It is the composition of immune cells, their functional phenotype, and their secretions that dictate either tumor regression or tumor progression. The CD4+ T cells are instrumental in eliminating cancer cells by secreting various pro-inflammatory cytokines that act directly and indirectly by activating and recruiting other cell types such as macrophages, and granulocytes to eliminate cancer. However, CD8+ T cells with the help of CD4+ T cells represent the major effector mechanism of anti-tumor immunity. On the other hand, regulatory T cells, a subset of CD4+ T cells, are involved in promoting tumor growth by suppressing both CD4+ and CD8+ T cells. With the advancement of high-throughput and multiplex analysis techniques, immune cells are characterized in detail with advanced functional roles in relation to cancer development and progression. In this chapter, we review and discuss the current knowledge with respect to the evolving functional role and prognostic significance of individual T cell subsets in various malignancies.

Take-Home Lessons

- Anti-tumor immunity mediated by lymphocytes is predetermined as well as adapted during the course of disease.
- Adaptive CD4+Th1 and CD8+ Tc1 cells have well-defined roles in anti-tumor immunity while CD4+ Tregs have pro-tumoral role and are tumor-antigen specific.
- CD4+ Th2, Th9, Th17, Th22, Tfh, and CD8+ Tc2 subsets can be both anti-tumoral and pro-tumoral depending on the context of the tumor microenvironment and cancer type.
- Unconventional, innate-like T cells have more potent anti-tumoral effects in a non-tumor antigen-specific manner, especially in solid tumors.

Box 10.1

- The tumor microenvironment consists of CD4 T cells, CD8 T cells, Tregs, antigen-presenting cells, unconventional T cells, stromal cells, and the tumor cells and harbors active processes of immunosurveillance and immune escape.
- CD4 T cell subtypes may, depending on the tumor immune context, act in both tumor killing and tumor promotion.

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- CD8 T cell subtypes are the primary effectors of anti-tumor immunity and eliminate tumor cells by direct killing through secretion of cytokines and cytotoxic granules.
- Tregs suppress the anti-tumor immunity by expressing immune checkpoint inhibitors and secreting immunosuppressive cytokines and inflammatory mediators.
- Unconventional, innate-like T cells have broad and nonspecific anti-tumor immunity, especially in solid cancer types.
- The type of T cells, their phenotypic plasticity, location, the niche they share with other immune cells, cancer cells, and stromal cells along with their complex interactions play a crucial role in modulating tumor progression, therapeutic response, and patient outcomes.

Cancer Immunoediting and Tumor Immune Evasion Mechanisms

While the role of the immune system in controlling microbial pathogens is well appreciated, the notion that the immune system can also control tumor initiation, development, and progression has been subject to controversy for over a century. In 1909, Paul Ehrlich was the first to suggest that the immune system could protect the host from malignancies [1]. Nearly 50 years later, Thomas and Burnet predicted that adaptive immunity is responsible for preventing tumor formation and progression in an immunocompetent host and proposed the concept of cancer immunosurveillance [2, 3]. Currently, the term immunosurveillance is used to describe the processes by which cells of the immune system look for and recognize foreign pathogens, such as bacteria and viruses, or precancerous and cancerous cells in the body. However, due to inadequate experimental support, the cancer immunosurveillance concept was abandoned at that time. This was largely due to the lack of mouse models with pure genetic backgrounds available at that time. By the 1990s, with improved genetically modified mouse models available, several seminal works have validated the role of cancer immunosurveillance in both chemically induced and spontaneous tumor models [4]. Multiple components of the immune system have been identified as having central roles in cancer immunosurveillance, such as T cells, B cells, natural killer (NK) cells, and cytokines such as interferon-gamma (INF-γ) and perforins [4, 5]. Similarly, several experimental and clinical studies have confirmed the existence of cancer immunosurveillance (T cell-mediated cancer immunosurveillance is described in detail in the following sections) [5]. These findings suggest that cancer immunosurveillance is an active process that happens in the tumor microenvironment. However, despite the presence of an active cancer immunosurveillance process, many immunocompetent individuals still develop cancer. This paradox is explained via seminal mice studies showing that the immune system not only eliminates but also reduces the immunogenicity of the tumor, thereby promoting tumor growth [4]. This led to a significant revision of the original cancer immunosurveillance concept wherein Robert Schreiber and colleagues proposed a new concept termed "cancer immunoediting," which emphasized the dual role of the cancer-promoting and suppressing role of the immune system during tumor growth [4, 6].

Cancer immunoediting consists of three phases: elimination, equilibrium, and escape, termed "the three E's of cancer immunoediting" [6]. The elimination phase represents the original concept of cancer immunosurveillance, in which the cooperative actions of the innate and adaptive immune system eliminates the tumor before it is clinically manifest. Studies suggest that the immune component required for the elimination of tumors depends on specific tumor characteristics such as origin (spontaneous vs. carcinogen-induced), anatomical location, histology, and growth rate. During the elimination phase, rare tumor cell variants may survive and enter into an equilibrium state. Generally, the equilibrium state is the longest phase and it can extend throughout the life of the host. In this period, tumor cells undergo a process called antigenicity sculpting, where the immune cells apply a selective pressure (to deplete susceptible tumor cells) leading to the survival of the fittest/fastest-growing cells that escape elimination by the immune system. This process results in reduced immunogenicity of tumors and acquired resistance to immune effector cells. At the end of the equilibrium and the antigenicity sculpting phase, several tumor clones with immune evasive mutations and epigenetic instability will survive and start to proliferate. These cells ultimately enter into the escape phase and develop into visible tumors and successfully avoid immune destruction, which is now considered an emerging hallmark of cancers as described by Hanahan and Weinberg [7].

Tumor cells may evade the protective immunity by a number of mechanisms as presented in Table 10.1, for example, by loss of human leukocyte antigen (HLA, also called as major histocompatibility complex (MHC) in mice) display of foreign peptides thereby impairing tumor immune recognition, by inhibition of mechanisms that promote immune cell trafficking into the tumor microenvironment, by promoting immune suppression or subversion, or by inducing tumor cell resistance to apoptosis by altering the expression of anti- and pro-apoptotic molecules. The array of immunosuppressive mechanisms that may be active include secretion soluble inhibitors (adenosine, prostaglandin E2 (PGE2), IL-10,

Table 10.1 Tumor immune evasion mechanisms

Evasion strategy	Mechanisms
Impaired tumor antigen presentation to immune cells	• Downregulation of tumor antigens or antigen processing machinery (e.g., lack of LMP and TAP proteins) [9] • Downregulation of HLA genes [10]
Impaired trafficking of immune cells into tumor microenvironment	• Epigenetic silencing of chemokine expression [11] • Lack of endothelial adhesion molecules [12–14] • Physical barrier by stroma [15] • Lack of tumor antigens in lymphoid organs [16]
Immune cell dysfunction or subversion	• Immune suppression is mediated by CD4+FOXP3+ regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [17–21] • Secretion of suppressive cytokines (TGFβ, IL-10, etc.) [22–24], and other soluble immunosuppressive factors (prostaglandin E2, VEGF, RCAS1, extracellular adenosine, reactive oxygen and nitrogen species, etc.) [25–29] • Expression of IDO in tumor cells leading to secretion of immunosuppressive tryptophan metabolites [30] • Induction of T cell tolerance by expressing cognate ligands for T cell checkpoint inhibitory receptors such as CTLA-4, PD-1, LAG-3, Tim-3 [31, 32] • Apoptosis of immune cells induced by tumor cell expression of CD95L (FasL) (tumor counterattack) [33] triggering CD95 (Fas)-mediated T cell apoptosis • Immune cell deviation and plasticity [34–37]
Tumor cell resistance to apoptosis	• Abnormal expression of antiapoptotic molecules (Bcl-2 and IAPs family protein) [38] • Mutations or loss of pro-apoptotic molecules (TRAIL and CD95 receptors) [38] • Interference with granzyme/perforin pathway [39, 40]

IL-35, transforming growth factor-β1 (TGF-β1), etc.), overexpression of indoleamine 2,3-Dioxygenase, activation of inhibitory immune checkpoints or migration or formation and activation of regulatory T cells (Tregs) locally in the tumor to suppress bystander tumor-infiltrating effector T cells [8].

Targeting the immune escape mechanisms has proven to be a promising strategy for cancer treatment. The introduction of immune checkpoint inhibitors has been very successful and ICIs provide a cure or long-term remission for many patients, particularly patients with cancers with high tumor mutational burden (TMB) such as melanoma, lung, and kidney cancer [41, 42]. However, immune checkpoint inhibitors only appear to work for a subgroup (40–50%) of patients in each of these indications whereas it does not work despite high TMB in some cancers [43]. Thus, many of the other tumor immune evasion mechanisms (Table 10.1) may also be acting in parallel and have clinical importance. Therapeutic strategies for blocking these mechanisms to rescue anti-tumor immunity could add to the current repertoire of immunostimulating therapies, in a precision immune oncology approach in patients not responding to immune checkpoint inhibitors. Currently, targeting one or more of these mechanisms clinically holds the most promising approach to improving anti-tumor immunity [25].

Our group studies tumor immune evasion strategies by soluble inhibitors secreted by cancer cells (PGE2, adenosine, and cAMP), immune suppression by Tregs and interaction with immune checkpoint inhibitors [44–46]. We have studied anti-tumor immunity in colorectal cancer, pancreatic ductal adenocarcinoma, cholangiocarcinoma, ovarian cancer, and leukemias [47–53], which are discussed in detail under specific sections. In this chapter, we review and discuss the complex role of immune cells, particularly T lymphocytes and TILs in cancer immunity and tumor immune evasion mechanisms.

T Lymphocytes and Cancer Immunity

T cells are mainly classified into two lineages. CD4+ T cells and CD8+ T cells. CD4+ T cells are further subclassified into CD4+ T-helper cells (Th) that mediate tumor immunity and CD4+ forkhead protein 3+ (FOXP3) Tregs that suppress anti-tumor immunity. Naïve T cells that express a unique T cell receptor (TCR) on the surface develop through stringent positive and negative selection pathways in the thymus. T cells migrate through tissues and scan for cognate antigen peptides in the context of HLA complex on antigen-presenting cells (APCs) that activate their TCR downstream signaling, resulting in functional differentiation into a variety of T cell subsets [54]. Here we focus on conventional TCRα/β T cell subsets, unconventional T lymphocytes, and their role in tumor immunity.

CD4+ T Cells and Anti-tumor Immunity

CD4+ T cells are an important component of adaptive immune responses and are crucial in orchestrating humoral and cell-mediated immune responses [55]. However, their role in anticancer immunity is complex and reflects the diverse role of various CD4+ Th cells subsets (discussed in subsequent sections) [34]. The naïve CD4+ T cell TCR recognizes antigenic epitopes in the form of 12–20 peptide residues, presented on HLA class II expressed on professional APCs such as dendritic cells (DCs), macrophages, and B cells [56]. For a successful T cell activation, naïve CD4+ T

cells require two signals [57]. Signal-1 involves TCR recognition of antigen in the context of HLA class II expressed on the surface of APCs. Signal-2 involves an interaction of co-stimulatory receptors such as CD28 on T cells with its ligands CD80/86 on APCs, which results in clonal expansion, triggered effector functions, and subsequent memory formation. In addition, a third signal from the cytokines in the microenvironment defines the "maturation" of CD4+ T cells into its Th subtypes. The fate and functional specialization of activated CD4+ T cells are dependent on the concentration, source of antigen, type of APC, the co-stimulatory receptors, and most importantly, the polarizing cytokine milieu of the microenvironment at the time of activation [54]. Together, these polarizing factors contribute to the specific expression of key subset defining transcriptional factors and the subsequent secretion of effector cytokines that defines the functional subsets of CD4+ Th cells [54]. The cytokines secreted by CD4+ Th subsets then activate and recruit a variety of other immune effector cells that together define the type of immune response [55]. Table 10.2 summarizes the CD4+ Th cell subsets in the human and murine systems, the polarizing cytokines that drive their development, their master transcription factors, and the effector cytokines they secrete.

Conventional Role of CD4+ T Cells in Tumor Immunity

One of the important roles of CD4+ Th cells in anti-tumor immunity is to induce priming, activation, and expansion of cytotoxic T lymphocyte (CTL) responses, a concept known as CD4+ T cell help [58, 59]. CD4+ T cell help is complex and involves multiple mechanisms broadly classified into indirect and direct help. During the primary immune response to the tumor, the major indirect help from activated CD4+ Th cells comes through CD40/CD40L interaction with APCs that leads to maturation of the APCs [60–62]. This process provides all three necessary signals for CD8+ T cell activation, including antigen-mediated TCR triggering, co-stimulation, and stimulatory cytokines, most notably IL-12, that are critically important for naïve antigen-specific CD8+ T cells to differentiate into CTLs. Alternatively, CD4+ Th cells can directly activate CTLs through CD40/CD40L [63]. Activated CD4+ Th cells also directly help CTLs through the secretion of IL-2, which supports the growth and expansion of T cells [64, 65]. Furthermore, secretion of INF-γ by CD4+ Th1 cells upregulates the expression of HLA molecules on the surface of tumor cells leading to a feed-forward loop of enhanced CTL responses as well as CD4+ Th responses [66]. Recent reports also suggest the presence of cytotoxic CD4+ T cells with tumor killing by direct cytotoxicity. These cytotoxic CD4+ T cells can directly recognize tumor antigens presented in the context of HLA class II and degranulate cytotoxic compounds such as granzyme-B killing the tumor cells, for example, in melanoma and bladder cancer [67, 68].

In addition to priming the primary CTL response, CD4+ Th cells also help during the post-priming stage that takes place in the tumor microenvironment [69, 70]. Tumor-specific CD4+ T cells accelerate the recruitment of CTLs into the tumor microenvironment (TILs) by IFN-γ-dependent production of chemokines. Production of IL-2 by tumor resident CD4+ T cells enhances CD8+ T cell proliferation and upregulates the expression of granzyme-B [70]. In addition, the tumor-specific CD4+ Th cells have been shown to enhance the expansion of both low-avidity [71], and cognate [72] CTLs in the tumor microenvironment and enhance tumor killing.

Memory T cells are antigen-specific T cells that remain long-term after an infection or tumor has been eliminated. The memory T cells quickly converted into large numbers of effector T cells upon re-exposure to the specific antigen, thus providing a rapid response to past infection. In addition to their support to optimize CTL responses, CD4+ Th cells also play an essential role in the generation and maintenance of memory CD8+ T cells during active CTL responses and homeostatic proliferation [73, 74]. Hosts lacking CD4+ Th cells have been shown to have a reduced number of CD8+ memory T cells and impaired secondary CD8+ T cell responses [75]. Moreover, CTLs that develop in the absence of CD4+ T cell help are less likely to exhibit an effector-memory function and instead tend toward an exhausted phenotype [76].

Unconventional Role of CD4+ T Cells in Tumor Immunity

CD4+ Th cell-mediated anti-tumor immunity is primarily thought to be involved in activation and maintenance of CTL responses. However, recent studies have shown that CD4+ Th subsets also play independent roles in tumor immunity. Here we discuss the specific roles of different CD4+ Th cell subsets in tumor immunity.

CD4+ Th1 Cells

In 1991, *Romagnani* and colleagues discovered that human CD4+ Th clones specific for intracellular *Mycobacterium tuberculosis* were mostly Th1 type CD4+ T cells, whereas the CD4+ T clones specific for the extracellular helminth *Toxocara canis* were mainly Th2 cells [77]. The Th1 lineage is controlled by the key transcription factor T-bet and the key polarizing cytokine IL-12 [54, 78, 79]. CD4+ Th1 cells secrete a set of pro-inflammatory cytokines that includes IL-2, INF-γ, TNF-α, and the chemokines CCL2 and CCL3 that attract macrophages (Table 10.2). Th1 cells are best characterized for their role in the clearance of intracellular pathogens such as viruses and in the pathogenesis of autoim-

Table 10.2 CD4+Th cell subsets: polarizing cytokines, master transcription factors, and effector cytokines

Th subset	Polarizing cytokines	Transcription factors	Effector cytokines
Th1	IL-12, IL-18, INF-γ, IL-27	T-bet, STAT4	IL-2, IL-10, INF-γ, TNF-α, TNF-β (LT-α), CCL2, CCL3
Th2	IL-4, IL-25, IL-33, TSLP	GATA3, IRF4, STAT6	IL-4, IL-5, IL-9, IL-10, IL-13, IL-21, IL-31, TNF-α
Th9	TGF-β, IL-4	PU.1, IRF4	IL-9, IL10
Th17	TGF-β, IL-1β, IL-6, IL-21, IL-23	RORγt, RORα, IRF4 Batf, STAT3	IL-17A, IL-17F, IL-21, IL-22, IL-26 (human), CCL20
Th22	IL-6, IL-13, TNF-α	AhR, Batf, STAT3	IL-10, IL-13, IL-22, IL-21, TNF-α, IL-26 (human),
Tfh	IL-6, IL-21	Bcl6, BATF, c-MAF	IL-4, IL-10, IL-12, IL-21, INF-γ

mune conditions [80]. Th1 cells are considered to have potent anti-tumor activity due to their secretion of INF-γ, IL-2, and CD40/CD40L co-stimulation to help initiate CD8+ T cell responses as described earlier [73]. Human Th1 cells can also mediate anti-tumor immunity independently of helping CTL responses. For example, INF-γ acts directly on tumor cells and directs the immunogenic phenotype of tumors that arise in an immunocompetent host [81]. In mice, it has been demonstrated that Th1 cell-mediated INF-γ secretion in the tumor microenvironment is essential for inhibiting angiogenesis and regression of tumors that do not express HLA class II [82]. Similarly, a study of mouse B cell cancer suggests that Th1 cell-mediated INF-γ secretion in the tumor microenvironment is essential for eliminating MHC class II negative tumor cells through activation of type 1 macrophages (M1) and angiogenic inhibitors like IP-10 [83]. However, their mechanistic relevance in human cancer is yet to be determined.

A key function of Th1-derived INF-γ in tumor-bearing hosts is to substantially increase the IL-12 secretion by DCs, which serves to further polarize the naïve CD4+T cells into a Th1 phenotype thereby contributing to their own development and maintenance [84]. In addition, secretion of cytokines and chemokines by Th1 cells also leads to recruitment and activation of pro-inflammatory M1 macrophages, and NK cells at the tumor site [85–87]. The cytotoxic mediators secreted from M1 and NK cells have multiple anti-tumor properties [88, 89]. In line with this, patient studies show that the presence of Th1 cells and increased levels of their associated cytokines correlate with superior anti-tumor immunity and good clinical outcome in a majority of cancers [90]. Despite their potent anti-tumor role, Th1 cell functions are efficiently hindered by tumor cells by varying suppressive factors (Table 10.1 and described later), and imbalance or alterations in Th1/Th2 ratio in many human cancers lead to poor clinical outcomes [91]. Th1 cells are an attractive treatment option in cancer cell therapies. Adoptive transfer of tumor antigen-specific Th1 cells in patients with metastatic melanoma [92] and metastatic cholangiocarcinoma [93] was shown to induce regression of the tumor for prolonged periods. In contrast, responses in melanoma patients that received only in vitro-expanded, autologous CD8+ TILs were found to be sub-optimal in tumor clearing [94]. These findings clearly underpin the importance of inducing tumor antigen-specific Th1 cells for successful anti-tumor immunity.

CD4+ Th2 Cells

CD4+ Th2 cells are recognized for their role in the host defense against extracellular parasites and their involvement in allergy and asthma [54]. In both mice and humans, Th2 lineage commitment is controlled by the transcription factor GATA (nucleotide sequence) binding protein 3 (GATA3) and the polarizing cytokine IL-4 in the microenvironment [54, 95]. Activated Th2 cells produce their signature cytokines such as IL-4, IL-5, IL-13, and IL-10 (Table 10.2). Initial studies from murine models and in vitro studies showed that IL-4 secreted from Th2 cells has a direct antiangiogenic and tumoricidal activity [96–98]. Both IL-4 and IL-13 bind to type-II IL-4 receptor alpha (IL-4RA) and signals through signal transducer and activator 6 (Stat6) [99]. IL-4 and IL-13 are critical for the recruitment of eosinophils, macrophages, neutrophils, and CD8+ T cells to the tumor site and result in regression of the tumor [100–104]. Conversely, Th2 cytokines also interfere with anti-tumor activity, which is largely attributed to cytokines that antagonize the development of INF-γ secreting Th1 and CTLs at the tumor site. IL-4 and IL-13 have an anti-apoptotic role [99, 105–107] and IL-13 has a pro-fibrotic role [108, 109] that may affect anti-tumor activity. Activating polymorphisms in IL-4, IL-13, and STAT6 genes have been implicated in a higher risk of developing Hodgkin lymphoma [110].

Numerous studies indicate altered Th1/Th2 ratio in a variety of cancers [90, 91]. Th2 cytokines mutually antagonize the development of Th1 cells [54, 111]. This hypothesis was demonstrated using Th2-deficient Stat6-KO mice which rejected tumors through the action of tumor-specific CD8+ CTLs [99]. Immune deviation toward Th2 suppresses Th1 development, and it has been thought that induction affecting a Th2 immune response is one of the mechanisms that downregulate effective tumor immune responses. Initial murine studies suggested that both Th1 and Th2 cells contribute to anti-tumor immunity [87, 112, 113]. However, the increased presence of Th2 cells was found to be pro-carcinogenic in many human cancers [34, 90, 114, 115]. These pro-tumorigenic roles of Th2 cells were proposed to be cancer-specific rather than constituting a global effect, as the Th1 response in these patients was not impaired [116, 117]. Multiple tumor-derived factors may favor the development

of Th2 cells. Tumor cell-derived IL-10 induces skewing toward Th2 cells and inhibits the maturation of DCs, which effectively reduces the secretion of INF-γ and IL-12 from T cells resulting in impaired Th1 anti-tumor activity [118, 119]. Early reports demonstrated that human renal cell carcinoma and non-small cell lung cancer actively produced Th2 polarizing cytokines [120, 121]. Pancreatic cancer, an aggressive malignancy, is typically infiltrated by Th2 cells [122]. A clinical study from pancreatic cancer patients showed that the skewing toward Th2 was primarily due to the secretion of thymic stromal lymphopoietin from cancer-associated fibroblasts that activate DCs to produce Th2-associated cytokines and polarize T cells toward Th2 cells [123]. A similar mechanism was observed in mouse models of breast cancer [124], and chronic gastritis [125], which is the causative factor for gastric cancer. Studies in mice have shown that expression of the human tumor antigen, epithelial cell adhesion molecule (EpCAM), strongly promotes Th2 skewing despite the presence of strong Th1 polarizing conditions [126]. Moreover, Th2 cells are capable of clearing established lung and visceral metastases of a CTL-resistant melanoma [104]. Clearance of lung metastases by the Th2 cells was found to be dependent on the eosinophil chemokine, eotaxin, and Stat6, with degranulating eosinophils within the tumors inducing tumor regression. In contrast, tumor-specific CD4+ Th1 cells, that recruited macrophages into the tumors, had no effect on tumor growth. Thus, the involvement of Th2 cells in anti-tumor immunity is evolving, but still controversial, and their effect may be context-dependent.

CD4+ Th17 Cells

In 2005, the third subset of CD4+ Th cells was identified in mice as Th17 cells based on the production of the key cytokine IL-17 [127, 128]. Two years later, the existence of Th17 cells was confirmed in the human immune system [129]. The development of Th17 cells is controlled by the master transcription factor RAR-related orphan receptor gamma t (RORγt) and multiple polarizing cytokines [130–132] (Table 10.2). Th17 cells play an important inflammatory role in the host defense against extracellular bacteria and fungi, but are pathogenic in many inflammatory and autoimmune diseases [35, 130, 133–135]. Th17 cells are shown to infiltrate several cancer types in both mice and humans [35]. However, their exact role in anti-tumor immunity is controversial and still elusive. Contradictory findings with respect to their role in anti-tumor versus pro-tumoral role may be due to the existence of multiple flavors of Th17 cells that are fostered by different cancerous cell types and mediators in the tumor microenvironment. Depending on the type of cancer encountered, a number of factors could alter the effect of Th17 cells on tumor pathology, including the source of the Th17 cells (arising naturally via tumor growth or adoptively transferred following ex vivo manipulation), the functional phenotype of the cells and/or exposure to therapeutic interventions such as chemotherapy [35].

To understand the dual role of Th17 cells in promoting and antagonizing tumors, studies were conducted using a variety of mouse tumor models. Evidence for the role of Th17 cells in anti-tumor immunity came from studies with established murine models of B16 melanoma [136], and B16/F10 lung metastatic melanoma [137], in which adoptive transfer of in vitro-expanded, tumor antigen-specific Th17 cells induced regression of cancer to a larger extent than Th1 cells transferred in a parallel experiment. The transfused Th17 cells were found to promote the infiltration of DCs and enhanced cross-antigen presentation to naïve CD8+ T cells, as well as to induce the secretion of CCL20 from cancer residing lung cells to further recruit CD8+ CTLs into the tumor site [137]. Therefore, the Th17 cells were proposed to have a synergistic function with CD8+ CTLs. In contrast, other tumor models in mice, including leukemia [138], cervical cancer [139], non-small cell lung cancer [140], lung cancer [141], and colon cancer [142], suggested that Th17 cell-secreted inflammatory cytokines in the tumor microenvironment promoted neutrophil recruitment and secretion of elastase, a pro-tumorigenic factor [143]. Th17 cells also promoted the secretion of pro-angiogenic factors and pro-inflammatory cytokines from tumor cells, which promote angiogenesis and cancer progression [143]. Studies with genetically modified mice with colon cancer [144] and pancreatic cancer [145] showed that the preinvasive epithelial layer expressed large amounts of IL-17R that facilitated the infiltration of Th17 cells further substantiating the above findings. Subsequently, IL-17A derived from Th17 cells triggered the oncogenic signal through the IL-17R-STAT3 pathway and accelerated the transformation of epithelial cells into invasive neoplasia. β-catenin signaling is also implicated in the development of Th17 cells in colon cancer [146]. Similar dichotomous findings were observed in human cancers where infiltration of Th17 cells was positively associated with CD8+ T cell count and better survival in ovarian cancer [147] and esophageal cancer [148], but associated with poor prognosis in colon or pancreatic cancer [35, 90].

Th17 cells are a major fraction of TILs in human cancers, attracted by tumor-derived CCL5 and monocyte chemoattractant protein-1 (MCP-1) [149, 150]. Human Th17 cells also undergo functional plasticity, secreting cytokines of other Th lineages [131, 134]. Interestingly, in vitro-expanded, tumor antigen-specific Th17 clones from melanoma, breast, and colon cancer produced large amounts of polyfunctional cytokines including IL-8 and TNF-α, but not IL-2, IL-4, IL-12, or IL-23 [149]. Furthermore, it is also suggested that Th17 cells can be converted into FOXP3 expressing Tregs that produce IL-10 and TGF-β1, indicating a possible regulatory function [151]. In contrast, other studies suggest that

in vitro-expanded, tumor antigen-specific Th17 clones from colon cancer and ulcerative colitis mainly produce IL-2, TNF-α, INF-γ, GM-CSF, and exhibite plasticity to convert into both FOXP3- and INF-γ expressing cells with suppressive properties [143, 147, 152]. These findings were contrasted by the proposed cytokine signature of freshly isolated Th17 cells from healthy donors [153] and argue that these differences may arise from in vitro induced changes or may reflect their actual function in the tumor microenvironment.

The conversion of Th17 cells into Th1 cells is well documented in autoimmune diseases and cancer [131, 134]. Additionally, studies have also shown that ex vivo isolated Th17 cells from peripheral blood mononuclear cells of human pancreatic cancer patients can also produce Th2 and Th17 cytokines [154]. Notably, these findings demonstrate that Th17 cells from human cancers not only correlate with IL-17 secretion but can also acquire Th1- or Th2-associated features. To summarize, Th17 cell-mediated anti-tumor immunity is due to the enhancement of DC and CD8+ CTL functions. However, Th17 cells also contribute to cancer-promoting inflammation and angiogenesis. Further, their plasticity-associated complexity in the tumor microenvironment may determine their pro-tumorigenic, suppressive, or anti-tumorigenic role that may influence cancer prognosis.

CD4+ Th9 Cells

In 2008, Th9 cells, a novel subset of CD4+ Th cells characterized by the secretion of IL-9 and IL-10 were reported for the first time [155]. Although the role of the IL-9 cytokine in cancer has previously been explored [156, 157], the role of Th9-derived IL-9 in effective anti-tumor responses came from a study on melanoma that exhibited superior anti-tumor properties over Th1 and Th17 cells [158, 159]. However, recent advancements in the biology of Th9 cells have resulted in a dual role, both anti-tumor and pro-tumor effects in tumor progression.

In most solid tumors such as melanoma, lung adenocarcinoma, colon cancer, and breast cancer Th9 has anti-tumor effects. Growth of B16F10 melanomas was inhibited in RORγ-deficient mice, which presented a greater number of infiltrating CD4+ and CD8+ T cells at tumor sites and secreted a high level of IL-9. The neutralization of IL-9 successfully reversed this effect, suggesting an anti-tumor role of IL-9 against melanoma [159]. The same study also revealed that the Th9 anti-tumor effect was superior compared to Th1, Th2, or Th17. In lung and colon cancer models the anti-tumor effects of IL-9 depended on mast cells [147, 148]. Inhibiting the activity of mast cells with cromoglycate or depleting mast cells with anti-CD117 antibodies reversed the anti-tumor efficacy. DC-based immunotherapy has great promise for cancer treatment. Studies have demonstrated that dectin-1-activated DCs triggers potent anti-tumor Th9 cells in vivo [160].

In contrast to its effect in most solid tumors, Th9 has pro-tumoral effects in hematological malignancies such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, adult T cell leukemia, Hodgkin's lymphoma, cutaneous T cell lymphoma, anaplastic large-cell lymphoma, and NKT cell lymphoma. It has been reported that IL-9 promotes the immunosuppression mediated by Tregs in B cell non-Hodgkin's lymphoma [161]. Overexpression of IL-9 has shown a direct contribution to the development of chronic lymphocytic leukemia in the presence of the transcription factor STAT6 [162]. High expression of IL-9 was also detected in adult T cell leukemia, Hodgkin's lymphoma, anaplastic large-cell lymphoma, and NKT cell lymphoma suggesting that IL-9 might be a potential target for the development of novel therapeutic strategies against hematological malignancies [163–166].

Intriguingly, a tumor-promoting role for Th9 cells was also suggested in hepatocellular carcinoma through CCL20 and STAT3 pathways [167]. Frequencies of Th9 cells were higher in peri-tumor and tumor tissues compared to unaffected tissues and patients with higher Th9 infiltrates appeared to exhibit shorter disease-free survival [167]. Moreover, Th17/IL-17 and Th9/IL-9 exhibit critical, but often opposing, roles in tumor progression. A recent study shows that while IL-17 and IL-9 induced distinct but complementary molecular pathways, both cytokines also induced epithelial–mesenchymal transition (EMT) in lung cancer cells and promoted metastatic spreading [168]. Overall, important progress has recently been made in understanding the role of Th9 in both pro- and anti-tumor immunity. However, the complex differentiation process and high plasticity of the Th9 subset make it difficult to pinpoint and target the Th9 cells for cancer treatment.

CD4+ Th22 Cells

Like Th9 cells, Th22 cells have only gained recognition as a distinct CD4+ T cell lineage within the past decade. Th22 cells compose another novel T cell subset with polarizing transcription factors such as aryl hydrocarbon receptor (AhR), basic leucine zipper transcription factor (BATF), and STAT3 characterized to produce IL-22, IL-26, and IL-33 [169] (Table 10.2). Expression of IL-22 is not restricted to the Th22 subsets, as Th17 cells and NK cells are also capable of IL-22 production. However, Th22 T cells are unique in their expression of IL-22 in the absence of IL-17 and IFN-γ [169].

Early studies revealed that IL-22 promotes the growth of tumor cells in many types of cancers, including lung adenocarcinoma and hepatocellular carcinoma [170, 171]. Studies have shown that IL-22 has a direct proliferative effect on colonic epithelial cells thereby modulating the tumorigenesis in the intestine [172, 173]. Furthermore, IL-22 potentially stimulates intestinal epithelial cells to secrete IL-10, the

main contributor to the formation of an immunosuppressive milieu in colorectal cancer [174]. In addition, IL-22 genetic polymorphisms have shown to be a risk factor for colon cancer and elevated serum IL-22 levels correlate with chemoresistance in patients with colorectal cancer [175, 176]. Using both murine and human breast and lung cancer models, Voigt et al. demonstrated that cancer cells directly induce IL-22 production from memory CD4+ T cells via IL-1 to promote tumor growth [177]. In addition, the authors show the existence of IL-22-producing Th1, Th17, and Th22 cells in tumor tissue of patients. Use of the clinically approved IL-1 receptor antagonist anakinra in vivo reduced IL-22 production and reduced tumor growth in a breast cancer model [177]. A recent study showed that the prevalence of Th22 cells was gradually increased in normal, para-tumor, and tumor tissues of triple-negative breast cancer, promoting migration and paclitaxel resistance through JAK-STAT3/MAPKs/AKT signaling pathways [178]. Taken together, most current data suggest a promoting effect of Th22/IL-22 on the development of various cancers making it an attractive target for anticancer therapy.

CD4+ T Follicular Helper Cells

T follicular helper (Tfh) cells are a subset of activated CD4+ Th cells characterized by expression of CXCR5, PD-1, BCL-6, and ICOS. Tfh cells are specialized in promoting germinal center reactions that support B cell proliferation and maturation, and in the development of humoral immunity [179, 180]. Evidence of Tfh in cancer came from a study of angioimmunoblastic T cell lymphoma, where the tumors phenotypically resemble the Tfh cells by the expression of CXCL13, ICOS, CD154, CD40L, and NFATC1 [181]. A mutated Rho GTPase protein (RHOA G17V) is shown to induce Tfh cell specification and promotes lymphomagenesis [182]. In follicular T cell lymphomas, TILs resemble the phenotype of Tfh cells and play a role in the regulation of Treg and Th2 cell migration into the tumor site [183]. Additionally, FOXP3+ Tfr cells are also found within tumor follicles and the number of Tfr cells is elevated during lymphomagenesis. However, in nonlymphoid tumors, Tfh cells appear to have protective roles. Higher levels of Tfh cell infiltrates and tertiary lymphoid structures within tumors have been associated with increased survival and reduced immunosuppression in breast cancer [184]. It was suggested that IL-21 and CXCL13 might play a key role in the protective functions of Tfh cells via the modulation of local leukocyte recruitment. Infiltrating Tfh cells have also been reported in chronic lymphocytic leukemia, non-small cell lung cancer, osteosarcoma, and colorectal cancer, where they positively correlated with patient survival [185–188]. To date, there is limited understanding in the functions of Tfh and Tfr subsets in lymphomagenesis further studies will be important for a better understanding of their role in cancer.

CD8+ T Cells and Cancer Immunity

CD8+ CTLs recognize their cognate antigen through binding of their TCR to antigen-HLA class I complex expressed on the surface of tumor cells. CD4+Th cells also provide help to CTL responses (section "Conventional Role of CD4+ T Cells in Tumor Immunity"). CTLs are considered as the primary effectors of anti-tumor immunity and potentially eliminate the tumor cells and are shown to correlate with a good prognosis in almost every type of human malignancy (Table 10.3). CTLs use multiple mechanisms to kill tumor cells mediated by granzyme-B, perforin, and the triggering

Table 10.3 The association of tumor-infiltrating T cell subsets and prognosis (indicated as good or poor)

Cancer types	CD8+ T cells	CD4+ Th1 cells	CD4+ Th2 cells	CD4+ Th17 cells	CD4+ Treg cells
Head and neck cancers	Good [192, 193]				Good [193]
Esophageal cancer	Good [194, 195]	Good [196]		Good [148]	
Lung cancer	Good [197]	Good [197]		Poor [198]	Poor [199]
Pancreatic cancer	Good [200, 201]		Poor [123]	Poor [202]	Poor [202, 203]
Distal bile cancer	Good [204]				Good [204]
Breast cancer	Good [205]	Good [206]	Good [207]	Poor [208]	Poor [209, 210] Good [211]
Gastric cancer	Poor [212, 213]	Good [214]	Poor [214]	Good [215] Poor [216]	Good [216] Poor [217]
Hepatocellular carcinoma	Good [218, 219] Poor [219]	Good [220]		Poor [221]	Poor [219, 222]
Colon cancer	Good [223–229]	Good [223–225]	None [224]	Poor [224, 230, 231]	Good [224, 231–233] Poor [234] None [227]
Ovarian cancer	Good [235]	Good [236, 237]	Poor [237]	Good [147]	Good [238, 239] Poor [240]
Renal cell carcinoma	Good [241]	Good [242]			Poor [242]

Table 10.3 (continued)

Cancer types	CD8+ T cells	CD4+ Th1 cells	CD4+ Th2 cells	CD4+ Th17 cells	CD4+ Treg cells
Prostate cancer	Good [243]				
Urothelial carcinoma	Good [244]				
Endometrial cancer	Good [245]				
Cervical cancer	Good [246] Poor [247]				
Melanoma	Good [248, 249]				None [250] Poor [251, 252]
Follicular and Hodgkin's lymphoma			Good [253]		Good [254, 255] Poor [253]

of the Fas signaling pathway through Fas ligand (FasL). Major CTL activities are mediated either directly, through synaptic exocytosis of cytotoxic granules containing perforin and granzymes into the target, resulting in cancer cell destruction, or indirectly, through secretion of pro-inflammatory cytokines. CTLs and target cell interactions are characterized by sustained motility of the CD8+ T cell on the target cell [189]. FasL expressed on CTLs binds to its Fas receptor on the tumor cell surface activates death domains, which, in turn, activates caspases and endonucleases, leading to the fragmentation of target cell DNA [190]. In parallel, perforin secreted by activated CTLs forms pores on the surface of tumor cells that aid in the directed delivery of granzyme-B into the tumor cell cytoplasm subsequently inducing apoptosis. Alternatively, a complex of granulysin, perforin, and granzymes are ingested by target cells through endocytosis of CTL membranes. Granulysin and perforin subsequently create pores in the endosomal membrane and release several granzymes into the cytoplasm [191].

Similar to CD4+ T cells subset differentiation (Th1, Th2, and Th17), after antigen recognition, the naïve CD8+ T cells also differentiate into different T cell cytotoxic (Tc) subsets. The CD8+ T cells differentiation is controlled by the master regulator transcription factors and cytokines, such as Tc1 (T-bet+ Eomes+ INF-γ+), Tc2 (GATA3+ IL4+), and Tc17 (RORγt+ T-bet+ IL17+) cells (Table 10.2 and Fig. 10.1). Since type 1, 2, and 17 related cytokines are primarily produced by Th subsets rather than Tc subsets in the tumor microenvironment, their functional relevance is not yet clearly known. Studies in mice suggest that T cells secrete INF-γ and IL-2 directly into the immune synapse targeting antigen-presenting tumor cells, whereas TNF-α and CCL3 were released multidirectional [256]. It is possible that INF-γ secreted by tumor-infiltrating Tc1 cells can have direct anti-tumor activity by enhancing HLA expression on cancer cells, inducing angiostatic effects, and also recruiting macrophages [85]. IFN-γ produced by CTLs supports their further differentiation to effector CTLs [257]. IFN-γ is responsible for the induction of the CD8+ T cells into being antigen-specific CTLs, which leads to the expansion of immunological memory cells for combatting tumors. The role of IL-4 secreting Tc2 cells in the tumor microenvironment is largely unknown, although a study from breast cancer [258] showed their association with cancer progression. In contrast to Tc1 cells, IL-17 secreting Tc17 cells were found to be impaired in their cytotoxic activity [259, 260]. However, adoptive transfer studies in mouse tumor models have shown that Tc17 cells inhibited tumor growth, which was primarily associated with their plasticity to convert into Tc17/Tc1 cells that produced INF-γ along with IL-17A [261]. Moreover, Tc17 cells were identified in gastric cancer [212], hepatocellular carcinoma [262], cervical cancer [247], breast cancer [258], and endometrial carcinoma [263], primarily found to be less cytotoxic and rather promoted cancer. Especially, in gastric cancer [212] and cervical cancer [247], Tc17 cells are shown to promote angiogenesis and recruit immune suppressor cells, including myeloid-derived suppressor cells (MSDCs) and Tregs. In addition, our study on CD8+ T Cells that co-express RORγt and T-bet were functionally impaired in Distal Bile Duct Cancer [51]. Therefore, emerging results suggest that the cytotoxic activity of CTL secreted cytokines is context-dependent, and under specific polarizing conditions, they may potentially lose their cytotoxic activity. Continued activation of CTLs can cause expression of co-inhibitory receptors on them restricting priming of newly recruited CD8+ T cells to the tumor stroma or their exhaustion, predominantly dampening immune-activating signals within the tumor microenvironment, all of which are in favor of tumor progression and invasiveness. Additionally, cancer cells can also develop defense mechanisms by downregulating the expression of surface HLA molecules, secreting perforin-degrading enzymes, as seen in melanoma cells [264] or by upregulation of checkpoint inhibitors (discussed below).

Regulatory T Cells and Cancer Immunity

Tregs are a highly immune-suppressive fraction of CD4+ T cells, which were originally reported as CD4+ T cells expressing the IL-2 receptor alpha chain (CD25) by Sakaguchi et al. in 1995 [265]. Tregs are a dynamic subset of CD4+ T lymphocytes that modulate physiological (peripheral tolerance) and pathological (autoimmunity) responses thereby maintaining immune homeostasis [266]. Tregs can

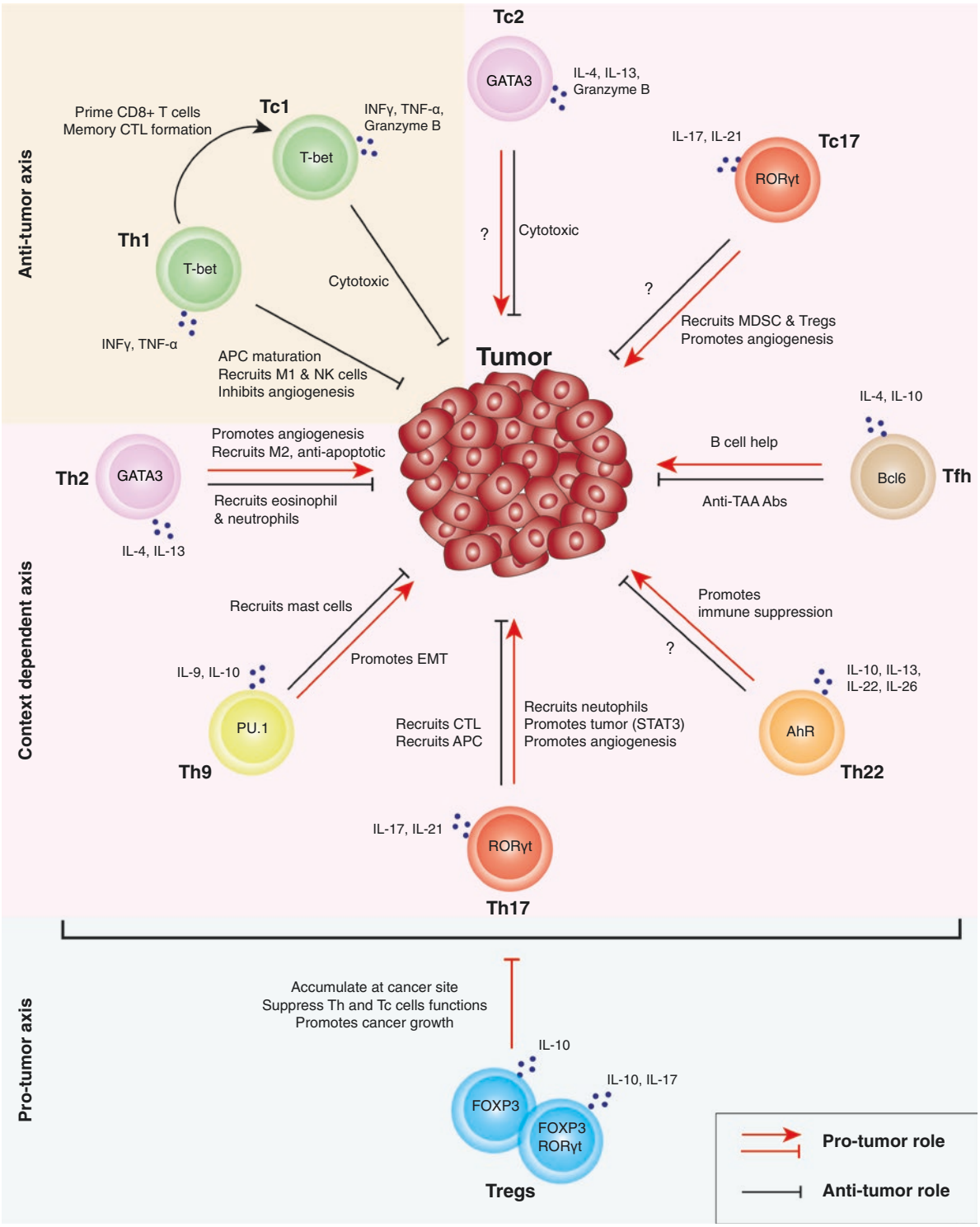

Fig. 10.1 Role of T cell subsets in anti-tumor immunity. Th1 cells express T-bet, INFγ, and IL-12. Th1 cells are superior in anti-tumor activity primarily due to their activation of APC, recruitment of M1 macrophages and NK cells, and their priming of the CTL (Tc1 cells) response. Both Th1 cells and Tc2 cells associate with good prognosis in many cancers and form a prominent anti-tumor axis in humans. Th2 cells express GATA3, IL-4, and IL-13 and contribute to cancer regression via recruiting eosinophils and neutrophils. Furthermore, cytokines produced by Th2 cells also contribute to angiogenesis, recruit M2 macrophages, and have an anti-apoptotic role. Their counterpart the Tc2 cells contribute to cancer regression through their cytotoxic activity but their possible cancer-promoting features are not clearly known. Th17 cells contribute to cancer regression via activating APC and CTL. However, they may also contribute to cancer progression by various mechanisms. Similarly, their counterpart Tc17 also primarily contributes to cancer progression by recruiting suppressor cells into cancer stroma, mainly Treg and MDSC. Both Th17 and Tc17 cells contribute to angiogenesis. Tregs contribute to cancer progression by suppressing effector functions of Th and Tc subsets. Tregs also largely accumulate at the cancer site and their phenotypic heterogeneity and plasticity also contribute to pro-carcinogenic inflammation and cancer progression. Therefore, Th2, Th17, Tc17, and Treg subsets form a context-dependent axis in anti-tumor immunity in human malignancies

be broadly divided into natural or thymus-derived (nTregs or tTregs), which are TCR reactive to self-peptides presented on HLA molecules and peripherally induced Tregs (pTregs or iTregs) in response to TCR stimulation with retinoic acid or TGF-β [267]. The master transcription factor FOXP3 is essential for the development and function of Tregs [266]. In humans, FOXP3 expression alone cannot delineate the suppressive function of Tregs, since FOXP3 is also upregulated following the activation of naive T cells. Based on expression levels of FOXP3 and the naive T cell marker CD45RA, Tregs can be functionally classified into naive Tregs (nTregs: CD45RA+ FOXP3low CD4+ cells), effector Tregs (eTregs: CD45RA-FOXP3high CD4+cells), and non-Tregs (CD45RA– FOXP3low CD4+ cells) [268]. The essential function of Tregs is to suppress the activation, clonal expansion, and effector functions of various immune cells including CD4+ T cells, CD8+ T cells, NKT cells, and APCs through a myriad of mechanisms [269, 270].

The role of Tregs in tumor immunity was first established by animal studies where Treg depletion by anti-CD25 depleting antibody or CD4 depletion in mice prevented the tumor growth [271]. In human tumor biopsies, the proportion of Tregs was significantly higher in tumor sites (i.e., TILs) than in peripheral blood (also see the section below) [272]. Accumulating evidence suggests that naturally occurring Tregs are specifically attracted to the tumor site by chemokines or their receptors expressed by tumor cells [17]. Several chemokines and their cognate receptors are involved in the recruitment of Tregs into TILs, such as CCR4 with CCL22, CCR4 with CCL17, CCR10 with CCL28, and CXCR4 with CXCL1 [209, 273–275]. Tumors may establish resistance to immunotherapy by regulating Treg recruitment via CCR4 [276]. The tumor microenvironment provides a niche to strongly expand Tregs [277] and the Tregs next contribute to the suppression of anti-tumor immunity initiated by Th cells, CTLs and other innate immune cells tumor [18]. In addition, the conversion of Th cells into Tregs also contributes to the presence of Tregs in tumor tissue [278]. Within the tumor, Tregs exhibit highly activated phenotypes, such as high expression of suppressive immune checkpoint molecules like CTLA-4, TIGIT, ICOS, and GITR [279–281]. It is critical to decipher their role in the immune response in order to fully utilize the potential of immune checkpoint inhibitors and other immune-modulating agents. Moreover, tumor-infiltrating Tregs can also be activated by a large number of self-antigens released from tumor cells, because Tregs usually harbor high-affinity TCRs against self-antigens, compared to conventional T cells [282].

Apart from their suppressive function through the surface expression of checkpoint inhibitors, cytokines such as IL-10 secreted by Tregs can also skew Th subsets in the tumor into a Th2 phenotype, which is associated with poor prognosis in many tumor types (Table 10.3). Tregs are known to produce TGF-β, which can promote differentiation of naive CD4+ T cells into Treg cells via FOXP3 expression [283]. Further, TGF-β is also known to dampen effector T cells and APCs [284]. Findings from many solid tumors such as colon cancer [285], pancreatic cancer [154], and breast cancer [286] suggest that IL17+FOXP3+ Tregs retain their suppressive function, but also contribute to Th17 associated inflammation, which is associated with poor prognosis in these tumor types (Table 10.3).

Several immune escape mechanisms involving Tregs rely on cAMP-dependent pathways to suppress Teffs [287]. Tregs may utilize a COX-2-dependent mechanism of suppression [48, 288] where PGE2 is produced by Tregs and can bind to its cognate receptors (EP1-EP4) on effector T cells, thus inhibiting their activation through the TCR [44–46]. In particular, EP2 and EP4 signal through a cAMP inhibitory pathway (cAMP-PKA-Csk-Lck) that was identified in the Taskén laboratory [45, 289–292]. A parallel mechanism that also turns on cAMP is the production of adenosine from ATP via the exoenzymes CD73 and CD39 expressed on Tregs. Adenosine signals through adenosine A2A receptors (A2AR) on Teffs and signaling converges on the inhibitory cAMP pathway [48, 288, 293–295]. Yet another mechanism involves direct transfer of cAMP from Tregs to Teffs through gap junctions [296, 297]. Monocyte-mediated PGE_2 production is also a significant source of cAMP in Teff [298]. Furthermore, antagonists targeting PGE_2 signaling through its EP4 receptor (Grapiprant, E7046, and ONO-4578/BMS-986310), adenosine A2a receptor (A2AR) antagonists (Ciforadenant), and CD73 and CD39 blocking antibodies (CPI-006, TTX-030) are in clinical use or under development reviewed in [299–301].

Our studies on Tregs reveal their complex nature in the tumor microenvironment. Tregs contribute to an immunosuppressive microenvironment in colorectal cancer and inhibit effector T cells by a COX-2-PGE2-dependent mechanism and thereby facilitating tumor growth. Thus targeting Tregs and the PGE2-cAMP pathway may enhance the anti-tumor immune activity in colorectal carcinoma patients [49, 302]. Intriguingly, in human pancreatic cancer Tregs that co-express RORγt and FOXP3 are both pro-inflammatory and immunosuppressive [50]. Due to the anti-tumor activity of Tregs through various mechanisms, anticancer drugs often fail to activate the endogenous immune cells against cancer. Currently, there are several strategies to enhance the specificity of Treg targeting, especially checkpoint inhibitors like CTLA-4, PD1, LAG3, and TIGIT either alone or in combination for cancer immunotherapy are underway [303].

Unconventional T Cells and Cancer Immunity

T cells make up a central part of the adaptive immune system. Certain T cell populations, frequently referred to as unconventional T cells, share functional profiles of both innate and adaptive immunity. The unconventional, innate-like T cell population consists 20–50% of CD3+ T cells such as mucosal-associated invariant T cells (MAIT), TCR γδ T cells, and innate lymphoid cells (ILCs) and invariant NKT (iNKT). Broadly, unconventional T cells comprise cells with invariant TCRs, different from conventional TCR αβ T cells that most commonly reside in an epithelial environment such as the skin, gastrointestinal tract, or genitourinary tract. Their role is to recognize infections and cancer cells and regulate inflammatory responses that arise in these tissues [304]. These innate-like T cells have the capacity to rapidly respond to non-cognate stimulation by releasing large amounts of cytokines. Use of unconventional T cells have certain advantages in anticancer treatment compared to conventional Th1 and Th17 cells. These cells are non-HLA restricted, meaning that they can have off-the-shelf applicability irrespective of an individual's genotype without HLA-dependent graft versus host disease [305]. While most conventional T cells are rather ineffective in solid tumors, unconventional T cells have the advantage of being tissue resident in most cases [305]. Here we summarize the role of iNKT cells, MAIT cells, and γδ T cells in cancer.

Invariant NKT Cells

Invariant NKT cells are characterized by their semi-invariant Vα24Jα18 and TCRβ chains, which recognize glycolipid antigen in the context of the nonclassical HLA molecule CD1d [306]. Several studies have demonstrated the anti-tumor potential for iNKT cells in mice [307]. Activated iNKT cells also express cytotoxic factors such as perforin, granzymes, FasL, and TNF-related apoptosis-inducing ligand (TRAIL), and are capable of directly lysing tumors [308, 309]. Activated iNKT cells in turn activate many other cells of the immune system and in particular DCs where multifactorial crosstalk involving CD40L-CD40, IFN-γ, and IL-12 production leads to increased expression of CD80, CD86, CD70, and IL-12 production by the DCs. This translates to more potent activation of conventional CD4 and CD8 T cells [310]. In addition, other bystander cells are activated in this environment that contribute to tumor rejection, including NK cells [308] and γδ T cells [311], leading to enhanced effector function at many levels. Studies have shown that low iNKT cell frequencies are associated with poor prognosis in head and neck carcinoma, acute myeloid leukemia, neuroblastoma, and chronic lymphocytic leukemia [312–314]. Overall, targeting iNKT cells appears to engage several arms of the immune system at once, reducing the potential for tumor escape from a more focused immune response.

Mucosal-Associated Invariant T Cells

MAIT cells reside, as their name implies, in the mucosa, but they are also found in the peripheral blood, lymphoid tissues, and organs such as the liver. MAIT cells can be activated by viruses in a TCR-independent manner, or through the MAIT TCR-MR1 axis and are thought to play a role in protection against bacteria [315, 316]. In addition, MAIT cells are also implicated in several autoimmune disorders including diabetes [317, 318]. MAIT cells are reminiscent of type I NKT cells, rapidly secreting cytokines including IFN-γ, TNF, and, in some situations IL-17, following TCR-mediated activation [319]. While there are no defined MR1-binding tumor antigens that activate MAIT cells, it is conceivable that MAIT cells may encounter microbial antigens in tumor types, such as mucosal cancers, where bacterial infiltrates are likely to be present. MAIT cells can be activated in the presence of virus-induced inflammatory cytokines, such as IL-12 and IL-18, without specific antigen stimulation [320]. The first report to document the role of MAIT cells in human cancers is in brain and kidney tumors [321]. More recently MAIT cells were found to be diminished in the circulation of mucosal-associated cancers (gastric, colon, and lung), but not in association with non-mucosal cancers (breast, liver, and thyroid) [322]. MAIT cells are highly abundant in the human liver. In hepatocellular carcinoma patients' liver samples, MAIT cells were found to be abundant in healthy liver tissue, but diminished in number in the tumor site correlating with poor prognosis [323]. In multiple myeloma patients, MAIT cells are also numerically and functionally diminished in blood and bone marrow [324]. These studies suggest that inhibition of MAIT cell infiltration and/or function may be important for tumor survival.

Gamma Delta T Cells

In humans, γδ T cells represent approximately 1–5% of circulating T cells, also localized in peripheral sites such as skin and large intestine. The γδ T cells are Th1-type cytokine bias with strong IFN-γ production and potent cytotoxicity that are closely correlated with tumor destruction. Many γδ T cells have unique homing properties compared to αβ T cells, typically migrating to peripheral sites, such as epithelial tissues and solid tumors. While the major focus for the function of γδ T cells has been their role in homeostasis, wound repair, and infection [325], there is also a great interest in the role that these cells play in cancer, especially as intra-tumoral γδ T cells represent the most favorable prognostic indicator across different cancers [326]. Evidence for the role of γδ T cells in cancer surveillance first came from studies using γδ T cell-deficient mice showing a significantly elevated incidence of tumors of skin and prostate adenocarcinoma [327, 328]. Human γδ T cells can also elicit strong anti-tumor responses in vitro. Activated γδ T cells recognize and kill a broad range of tumor target cells in vitro [329–331].

However, the association between γδ T cells and tumor progression and/or patient survival is still controversial. In melanoma patients, an abundance of γδ T cells in TILs was positively associated with survival [332]. In several leukemias, patients receiving allogenic bone marrow transplantation revealed a strong correlation between γδ T cell abundance and overall survival or disease-free survival [333, 334]. In contrast, γδ T cells also have been shown to be associated with poor outcomes or high tumor burden, indicative of a pro-tumorigenic role. A study in rectal cancer showed the γδ T cells among TILs to positively correlate with tumor burden [335]. Another study also found an association between IL-17-producing γδ T cells and poor survival in gall bladder patients [336]. In primary breast cancer patients, γδ T cells were associated with more severe disease and reduced overall survival, indicating a pro-tumor role [337]. Peng et al. isolated regulatory γδ T cells from breast cancer TILs that specifically recognized a tumor epitope via the γδ TCR and exhibited immune-suppressive functions [338]. Collectively these studies highlight the importance of further research to understand the key factors involved in driving pro- versus anti-tumor immunity by γδ T cells.

Tumor-Infiltrating Lymphocytes and Cancer Prognosis

The tumor microenvironment plays a crucial role in tumor progression, therapeutic response, and patient outcomes. The tumor microenvironment primarily includes TILs, blood, and lymphatic vessels [7]. There are anticancer and pro-cancer immune cells. In general, infiltration of anticancer immune cells, such as CTLs, is associated with a favorable patient prognosis. In contrast, infiltration of pro-cancer immune cells, such as Tregs, TAMs, and MDSCs is associated with a poor prognosis. These characteristics of T cell subtype distribution are incorporated for example in IMMUNOSCORE, a test used in clinics to measure the response of a patient's immune system to a tumor [339].

Despite the importance of TIL characteristics described above, phenotyping of tumor-infiltrating T cell subsets as a prognostic marker is a complicated endeavor. In addition to the complex interactions in the tumor microenvironment, CD4+ Th cells in the tumor are found in different maturation states such as activated, exhausted, or regulatory. Moreover, they may share phenotypic markers with other immune cells adding more complexity to the analyses and interpretations of individual patient TIL profiles. Conflicting conclusions with respect to TIL phenotype could also potentially be due to differences in methodologies used, such as polymerase chain reaction, immunohistochemistry, multicolor flow cytometry, and CyTOF. Nonetheless, similar conclusions drawn for a particular cancer type by several groups substantiate the need for studying the link between Th cell subsets and prognosis and/or response to therapy. Here, we summarize the prognostic value of analyzing the abundance of Th subsets, Tc subsets, and Tregs in several human malignancies (Table 10.3).

The Th1 cells and CD8+ CTLs are strongly associated with good prognosis in many human cancers including esophageal cancer [194–196], colon cancer [223–229], head and neck cancer [192, 193], lung cancer [197], pancreatic cancer [200, 201], distal bile duct cancer [204], breast cancer [205, 206], gastric cancer [214], prostate cancer [243], urothelial cancer [244], ovarian cancer [235–237], endometrial cancer [245], cervical cancer [246], hepatocellular carcinoma [218–220], melanoma [248, 249], and renal cell carcinoma [241, 242]. The CD8+ CTLs lead target cancer cells to apoptosis in a series of steps, known as the cancer-immunity cycle [340]. Neo-antigens released by tumor cells are captured and processed by DCs and presented to CTLs. The CTLs are primed and activated to cancer-specific neo-antigens. Activated CTLs are attracted by chemokines such as CCL5 and CXCL10 and infiltrated into the tumor site. Infiltrated CTLs bind to tumor cells through the TCR-HLA class I and secrete granzymes to induce apoptosis of the target cells. Dead cells release additional neo-antigens, further fueling the cancer-immunity cycle. Therefore, high infiltration of CTLs is a favorable prognostic marker in many cancers. Th1 cells produce pro-inflammatory cytokines, such as IFN-γ and IL-2, to assist CTLs. Despite this, the presence of CD8+ T cells has also been reported to associate with poor outcomes, particularly in hepatocellular carcinoma, gastric cancer, and cervical cancer (Table 10.3), which is thought primarily to be due to the conversion of CD8+ T cells into Tc17 cells [212, 247]. However, CD8+ CTLs within tumors manifest a broad spectrum of dysfunctional states, molded by multiple suppressive signals in the tumor microenvironment. The mechanisms underlying CD8+ T cell failure in the tumor microenvironment may include: (1) exclusion by stromal cells; (2) exhaustion associated with the expression of inhibitory receptors and their ligands; (3) lack of intratumoral niches which maintain CD8+ CTL functions; (4) loss of HLA class I; (5) recruitment of immunosuppressive cells; (6) direct inhibition of CD8+ CTL functions by suppressive cytokines; (7) direct suppression of CD8+ CTL functions by generated metabolites; and (8) physiological stress conditions such as hypoxia, low pH, and nutrient deprivation. One or more of these mechanisms are related to the failure of current immunotherapies. Hence, current translational research has a significant focus on how to reinvigorate the suppressed CTLs [341].

In contrast to Th1 cells and CD8+ CTL cells, Th2 and Th17 cells correlate with either good or poor prognosis (Table 10.3). Th17 cells have been associated with a good prognosis in esophageal cancer [148], ovarian cancer [147],

and gastric cancer [215], but correlated with poor prognosis in colon cancer [224, 230], lung cancer [198], pancreatic cancer [202], breast cancer [208], gastric cancer [216], and hepatocellular carcinoma [221] (Table 10.3). Whereas the presence of Th2 cells is associated with a good prognosis in breast cancer [207], follicular lymphoma, and Hodgkin's lymphoma [253], their presence associates with poor prognosis in pancreatic cancer [123], gastric cancer [214], and ovarian cancer [237], but does not appear to have an impact on colon cancer prognosis [224] (Table 10.3). Interestingly, in gastric cancer accumulation of Th17 cells has been shown to associate with either good prognosis irrespective of the cancer stage [215] or poor prognosis at an early stage of cancer [216]. These disparities could originate from differences in experimental setup and markers used to define Th17 and Th2 cells. Some of the above-mentioned studies used only IL-17 as a predictor, investigating the CD4+IL17+ T cells. This may affect the results as other immune cell types including γδ T cells, myeloid cells, and innate lymphoid cells can also produce IL-17 [55, 135]. In addition, as described earlier (section "Unconventional Role of CD4+ T Cells in Tumor Immunity"), Th17 cells also undergo plasticity and therefore the conflicting observation of Th17 cells and Th2 cells may also reflect the fundamental differences in the inflammatory tumor microenvironment and stress the importance of well-delineated Th lineage analysis in these patients. In addition, Fridman et al. proposed a concept termed "immune contexture" in which the location and density of CD8+ T cells and CD4+ Th cells in both the invasive margin and intra-tumoral region predicted a favorable outcome in colorectal cancer patients [223, 342]. Currently, this particular immune contexture has been demonstrated in other cancer types such as biliary cancer, pancreatic cancer, breast cancer, and gliomas [204, 343–346]. In our own study on ovarian cancer, TILs in malignant ascites were distinctly different from peripheral blood T cells [52]. This indicates that test systems predicting patient responsiveness to immunotherapy may need to explore both tumor-infiltrating immune cells and circulating cells. These findings provide a framework to further standardize the studies that involve T cell subset association with prognosis in human cancers.

Tumor-infiltrating Tregs have been extensively studied and the prognostic value of their presence varies in different tumors. Specific depletion of Tregs in vivo can effectively stimulate the anti-tumor immune response of cancer patients. The cytokines IL-10 and IL-35 expressed by Tregs in the tumor microenvironment promote intra-tumoral T cell exhaustion by regulating the expression of several inhibitory receptors and the exhaustion-associated transcriptomic signatures of CD8+ TILs [347]. Tregs have been reported to correlate with poor outcomes in colon cancer [234], lung cancer [199, 348], pancreas cancer [202, 203], breast cancer [209, 210], gastric cancer [217], ovarian cancer [240], renal cell carcinoma [242], and hepatocellular carcinoma [219, 222] as well as melanoma, follicular lymphoma, and Hodgkin's lymphoma [253]. In contrast, the presence of Tregs was found to be associated with a good prognosis in colon cancer [224, 232, 233], head and neck cancer [193], distal bile duct cancer [204], gastric cancer [216], ovarian cancer and breast cancer [211], as well as follicular lymphoma and Hodgkin's lymphoma [254, 255]. Intriguingly, associations with both good and poor prognoses were observed within the same cancer type for colon, breast, gastric, and ovarian cancer and Hodgkin's lymphoma. Moreover, some studies have reported that the presence of Tregs has no impact on colon cancer and melanoma (Table 10.3).

These discrepancies in prognostic value may arise from the use of different markers to define Tregs. Both CD25 and FoxP3, the bona fide Treg markers, can also be expressed by activated T cells [268]. Other factors that may contribute to these discrepancies are tumor subtypes, tumor stage and the location of the characterized Tregs (within the tumor tissue, at the margin of the tumor, or in the inflamed tissue outside the tumor). Finally, the role of Tregs in cancer progression may also be dependent on whether the cancers were preceded or stimulated by inflammation. In addition, many of these studies have not reported Treg-suppressive function or their phenotypic plasticity. The positive impact of Tregs in some tumor types may reflect their anti-inflammatory role in suppressing tumor-promoting inflammation. Discrepancies within the same tumor type such as colon, breast, and gastric cancer may indicate that Tregs may predominantly share other Th lineage phenotypes, such as IL17+FOXP3+ Treg, which have been found to be the major Treg pool in colon, breast, and pancreatic cancer patients [154, 286, 349]. Remarkably, Tregs are further categorized into type 1 (Tr1), Th3 Tregs, and CD8+ Tregs based on their mechanisms of suppression and cytokine profiles which lack FOXP3 expression [350–352]. Hence, it is imperative to add phenotypic plasticity of Tregs to characterize the immune suppression in the tumor and then draw conclusions on the prognosis of cancer patients. Nonetheless, these data suggest that the original view of Tregs suppressing anti-tumor immunity is oversimplified and that Tregs may have multiple roles in influencing inflammation and shaping the tumor microenvironment as well as in suppressing anti-tumor immunity.

Concluding Remarks/Summary

Experimental and clinical studies now indicate that T cells play a pivotal, albeit sometimes paradoxical role in shaping anti-tumor immunity (Fig. 10.1). Nonetheless, the presence of Th1 and CTL cells is strongly associated with favorable outcomes in many tumor types and indicates that active cancer immunosurveillance is an integral part of many human

malignancies. However, the potency of CTLs' function in several malignant tumors is generally compromised. The main factors contributing to tumor immune evasion include reduced HLA class I and class II expression by tumor cells to eliminate the direct detection by CTLs, along with reduced help from CD4+ Th tumor cells. In addition, the differentiation of CD8+ T cells into less cytotoxic and anti-inflammatory subsets under polarizing conditions in the tumor microenvironment together with Treg-mediated immunosuppression at the cancer site contribute to the functional defect in tumor-specific Th1 cells and CTLs that ultimately lead to tumor progression. In addition, Th2, Th17, and Tregs are largely associated with poor outcomes in many tumor types. The bifurcation of the pro- and anti-tumorigenic nature of T cell subsets is too complex to predict, as it largely depends on cytokines secreted in the cancer microenvironment. To add to this complexity, recent reports suggest that T cells share different lineage-specific transcription factors and exhibit heterogeneity and plasticity. This may explain the paradoxical role of Th2, Th17, and Treg subsets observed, as many earlier studies assessed the prognostic value of individual subsets but did not consider the potential of phenotypic plasticity. It is also inevitable that the location of T cells and the niche they share with other immune cells, cancer cells, and stromal cells along with their complex interactions dictate their functional status. An integrated picture of all these factors will shed more light on the role of T cells in cancer and enable us to better tailor T cell therapies in the future.

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