Cancer Cell International

REVIEW Open Access

Th17 cell function in cancers: immunosuppressive agents or anti-tumor allies?

Milad Taghizadeh Anvar[1†], Kimiya Rashidan[1†], Nima Arsam[2†], Ashkan Rasouli-Saravani[1†], Hamidreza Yadegari[1†], Ali Ahmadi[3], Zeynab Asgari[4], Ahmad Ghorbani Vanan[1*], Farid Ghorbaninezhad[1*] and Safa Tahmasebi[1*]

Abstract

T helper (Th) 17 cells, a distinct subset of Th lymphocytes, are known for their prominent interleukin (IL)-17 production and other pro-inflammatory cytokines. These cells exhibit remarkable plasticity, allowing them to exhibit different phenotypes in the cancer microenvironment. This adaptability enables Th17 cells to promote tumor progression by immunosuppressive activities and angiogenesis, but also mediate anti-tumor immune responses through employing immune cells in tumor setting or even by directly converting toward Th1 phenotype and producing interferon-gamma (IFN-γ). This dual role of Th17 cells in cancer makes it a double-edged sword in encountering cancer. In this review, we aim to elucidate the complexities of Th17 cell function in cancer by summarizing recent studies and, ultimately, to design novel therapeutic strategies, especially targeting Th17 cells in the tumor milieu, which could pave the way for more effective cancer treatments.

Keywords Th17 cells, Cancer milieu, Anti-tumor activity, Immunosuppression, Plasticity

Introduction

Numerous immune cell types are involved in the intricate process of identifying and killing cancer cells, which is mainly dependent on the immune system. Researching on the immunological components of the tumor microenvironment (TME) is crucial for both cancer immunotherapy and understanding the developmental paths of tumors [1, 2]. Since cancers originate from normal cells, it can be difficult for the immune system to identify and react to self-derived tumor cells [3]. Both innate and adaptive immune responses may be triggered by malignant cellular change [4]. Since discovery of T helper (Th) 17 cells in 2005 and after being thoroughly examined in the context of autoimmune disorders [5], Th17 cells are now understood to be a crucial cell type that promotes inflammation in a variety of pathophysiologic situations, including infections [6], autoimmunities [5], and cancer [7, 8]. These cells are a subset of $CD4^+$ T cells which

†Milad Taghizadeh Anvar, Kimiya Rashidan and Nima Arsam contributed equally to this work and should be considered co-first authors.

†Ashkan Rasouli-Saravani and Hamidreza Yadegari contributed equally to this work.

*Correspondence:
Ahmad Ghorbani Vanan
ghorbanivanan@sbmu.ac.ir
Farid Ghorbaninezhad
ghorbaninezhadfarid@gmail.com
Safa Tahmasebi
safa.tahmasebi@sbmu.ac.ir
[1]Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[3]Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

produce interleukin (IL)-17 (also known as IL-17 A), IL-17 F, IL-21, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-22 [9]. Engagement of naive $CD4^+$ T cells into the Th17 subset relies on various cytokine cocktails including transforming growth factor beta (TGF-β), IL-6, IL-1β, or IL-21 [10]. IL-23 has been demonstrated to preserve Th17 cells' pathogenic phenotype and survival, while not being necessary for their differentiation [11]. Upon steady state, Th17 cells are located in lamina propria of the small intestine but can be induced in any other tissues (more precisely in mucosal and epithelial barriers) to fight extracellular bacteria, viruses, and fungi [12]. Their primary physiological role of Th17 cells is to protect the host against extracellular pathogens at the mucosal surfaces [13]. The involvement of these factors extends to tissue inflammation and the development of several autoimmune conditions, including multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease (IBD) [14]. Although Th1 and Th2 subsets are considered definitive and mutually exclusive lineages, it seems that Th17 and regulatory T cells (Tregs) subsets do not represent stable differentiation processes and retain plasticity allowing them to adapt to different environments [12]. Th17 presence in the TME has unveiled a complex dichotomy; on the one hand, Th17 cells have been shown to facilitate tumor growth by inducing angiogenesis and promoting the survival of cancer cells [15]. On the other hand, they have a role in tumor elimination by releasing interferon-gamma (IFN-γ) and recruiting dendritic cells (DCs), $CD8^+$ T cells, and natural killer (NK) cells to the tumor site [15]. This duality underscores the need for a deeper understanding of the factors that govern the behavior of Th17 cells in cancer. By summarizing the studies of previous scholars, we found that this high degree of plasticity is also imperative for the anti-tumor activity defined for Th17 cells in the development of autoimmunity because Th17 cells can even directly convert to the Th1 phenotype and produce IFN-γ to exert anti-tumor effects. To date, studies strongly indicate that Th17 cells influence the prognosis of cancer patients through their high plasticity and the secretion of inflammatory cytokines like IL-17. In this paper, we aim to explore the intriguing dichotomy of Th17 cells, examining the mechanisms behind their conflicting roles and discussing the potential implications of this cells in various cancers. By navigating through their immunosuppressive and anti-tumor activities, we seek to shed light on how these cells can be targeted or modulated for improved cancer treatment outcomes.

Different th cell subsets in cancer immunity

The process by which naive CD4+T cells differentiate into distinct subpopulations of helper T cells is contingent upon the cytokines released by antigen presenting cells (APCs) and various precursor cells. These cytokines initiate a cascade of downstream signaling pathways that facilitate the initial activation, proliferation, and subsequent differentiation of naive T cells into specific effector cells [16]. Different T cell populations that have been characterized, are tightly involved in several cancers and inflammatory diseases [11]. In the tumor microenvironment (TME), a diverse array of cytokines seems to facilitate the differentiation of naive CD4+T cells into various functionally specialized T helper (Th) subsets [17]. Each of these subsets subsequently influences the immune system's capacity to combat tumors in distinct ways [12]. Interestingly, these Th subsets demonstrate a remarkable degree of plasticity, indicating their ability to modify their functional roles from one type to another in response to environmental signals [13] (Fig. 1).

Th1

Research shows that Th1 cells are essential for promoting positive patient outcomes in different cancer types [18]. The cytokines IFN-γ and IL-12 are the main factors that stimulate the production of these powerful anti-tumor T cells [19]. IL-12 stimulates NK cells to produce IFN-γ, triggering the STAT1 and STAT4 signaling pathways in $CD4^+$ T cells [19]. T-bet, also known as T-box expressed in T cells, is a crucial transcription factor that stimulates Th1 differentiation while inhibiting the growth of Th2 and Th17 cells as a result of this coordinated activation [9, 20]. Moreover, the secretion of IFN-γ by these developing Th1 cells generates a positive feedback loop that enhances Th1 differentiation even more [21]. Th1 cells employ multiple anti-tumor mechanisms, including the inhibition of angiogenesis and metastasis, as well as the induction of programmed cell death, or apoptosis, in cancer cells. Additionally, interferon-gamma (IFN-γ) promotes the activation of M1 macrophages, disrupts the function of regulatory T cells (Tregs), and triggers tumor dormancy and senescence [22]. These results are corroborated by clinical observations, which show that increased Th1 cell levels in the TME are associated with a favorable prognosis in a number of cancers, including laryngeal carcinoma, ovarian cancer, breast cancer (BC), melanoma, glioblastoma, colorectal cancer (CRC), and non-small cell lung cancer (NSCLC) [23–28]. It's crucial to recognize that IFN-γ could have effects that vary depending on the situation. IFN-γ has been demonstrated to promote tumor spread and immune evasion in chronic inflammation [22]. To completely understand the intricate interactions between Th1 cells and the TME, more investigation is required.

Th2

Th2 cells are essential in mediating type 2 immune responses, orchestrating the removal of pathogens,

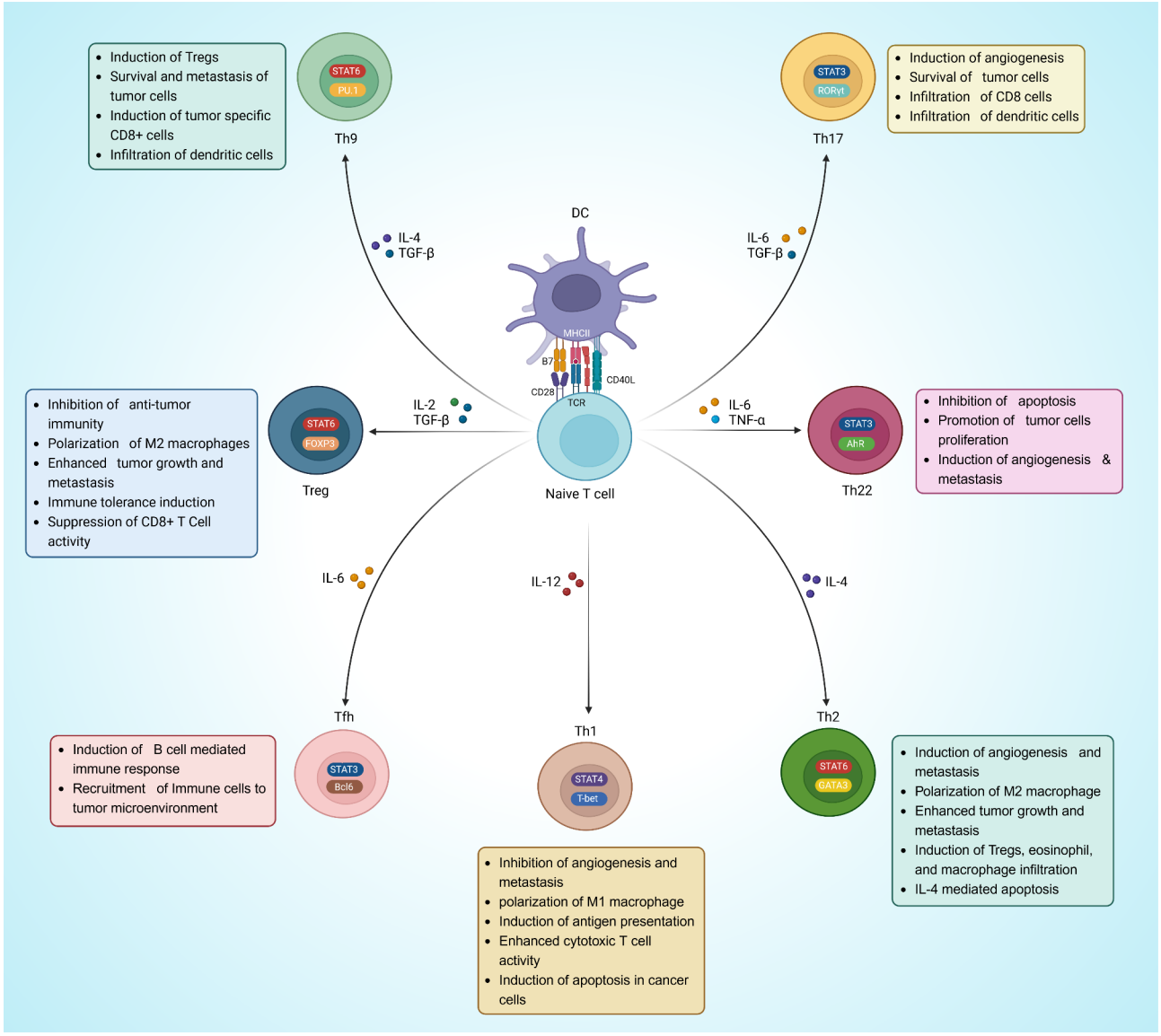

Fig. 1 Different Th cell subsets in cancer immunity. In the tumor microenvironment (TME), a wide range of cytokines appears to promote the differentiation of naive CD4 + T cells into various specialized T helper (Th) subsets. Each of these subsets plays a unique role in modulating the immune system's effectiveness against tumors. Furthermore, these Th subsets exhibit significant plasticity, reflecting their capacity to alter their functional characteristics in response to different environmental cues. *Abbreviations*: IL: interleukin, Th: T helper, Tfh: T follicular helper, TGF-β: transforming growth factor beta, TNF-α: tumor necrosis factor alpha, DCs: dendritic cells, Treg: regulatory T cell, CD40L: CD40 ligand

allergens, and extracellular microorganisms [29]. In order to do this, they secrete a specific arsenal of cytokines, including IL-4, IL-5, IL-9, IL-13, and IL-25 [29]. These cytokines operate as important modulators of humoral immune responses which attract and stimulate immune effector cells, such as mast cells and eosinophils [30]. IL-4 seems to be a key factor in Th2 differentiation. This cytokine is released by a variety of cell types, including basophils, NKT cells, and existingTh2 cells and stimulates the STAT6 signaling pathway in naive $CD4^+$ T cells [31]. The transcription factor GATA3, the main regulator of Th2 cell growth, is upregulated as a result of this activation [9, 21]. Historically, it has been believed that Th2 responses accelerate the growth of tumors by inhibiting Th1-mediated anti-tumor action and boosting angiogenesis. Nevertheless, new data points to a more complex function for Th2 cells, with certain elements perhaps aiding in the eliminating tumors [32]. The existence of Th2 cells and their secreted cytokines are linked to a poor prognosis in a number of malignancies, including melanoma, gastric, ovarian, pancreatic, and cervical cancers [33–37]. While the precise mechanisms by which Th2 cells promote tumor growth are still under investigation, several key pathways have been identified. Tumor immune escape

appears to be significantly facilitated by Th2-associated cytokines [38]. Moreover, IL-10 can stimulate Tregs and inhibit DCs from presenting antigens, hence reducing the anti-tumor immune response [32]. Furthermore, IL-4 potentially enhances the metastatic potential of cancer cells by altering the phenotype of tumor-associated macrophages [39]. According to some publications, Th2 cells may have an anti-tumor effect in certain situations, such as chronic lymphocytic leukemia, BC, and Hodgkin lymphoma [40–42]. In these instances, a good prognosis for the patient was correlated with the presence of Th2 cells or their secreted cytokines. It has been demonstrated that IL-4 encourages eosinophil and macrophage infiltration into the TME [43]. Moreover, research conducted in vitro has shown that IL-4 might cause BC cells to undergo programmed cell death, or apoptosis [44].

Th9

Th9 was formerly thought to be a member of the Th2 lineage but now it is identified as a separate population. An increasing amount of research focuses on the possibilities of less-studied helper T cell populations in adaptive anti-tumor immunity, in addition to the well-known Th1 and Th2 subsets. The Th9 cell is one such subgroup; it was formerly thought to be a member of the Th2 lineage but now it is identified as a separate population [45]. Th9 cells are $CD4^+$ T lymphocytes that produce IL-9 in addition to IL-10 and IL-21 [46]. Although like Th2 cells, Th9 rely on IL-4 signaling via STAT6 for their differentiation, but also TGF-β is a crucial cytokine [47]. Functionally, Th9 cells support type 2 immune responses and work with Th2 cells to eradicate extracellular parasites and trigger allergic reactions [48]. Th9 cells have different functions in hematological malignancies and solid tumors, and their effects on tumor formation are context-dependent. Numerous researches indicate that Th9 cells may have a pro-tumorigenic role in hematological malignancies [49]. Proposed mechanisms by which IL-9 may facilitate tumor promotion involve the augmentation of lymphoma cell viability through the reduction of oxidative stress levels [50] and the activation of Treg-mediated immunosuppression [51]. Clinically, aggressive lymphomas including Hodgkin's lymphoma and large-cell anaplastic lymphoma have been linked to increased IL-9 expression [52]. Additionally, compared to healthy controls, patients with nasal NK/T-cell lymphoma had higher tumor cell IL-9 mRNA levels [53]. Studies indicate that Th9 cells primarily function as anti-tumor cells in solid tumors, in contrast to hematological malignancies [54]. Notably, extensive evidence in melanoma indicates that Th9 cells induce strong anti-tumor responses which involve the recruitment of DCs to the tumor site and the subsequent differentiation of tumor-specific $CD8^+$ T cells [55–58]. In a similar vein, Th9 cells in BC facilitate anti-tumor immunity by secreting IL-9 and IL-21 [59]. But in some solid tumors, Th9 cells seem to play a more intricate function. For example, Th9 cells in hepatocellular carcinoma (HCC) have been shown to up-regulate CCL20, which has been involved in encouraging tumor growth [60]. Similarly, research on lung cancer indicates that Th9 cells may promote the migration and proliferation of cancer cells, hence aiding in the formation of tumors [61].

Th17

Th17 cells, a subset of $CD4^+$ helper T cells, have been linked to a number of inflammatory conditions and have been implicated in autoimmune diseases [8]. A particular cytokine profile, comprising IL-17 A, IL-17 F, IL-21, and IL-22, is produced by these cells [9]. Naive $CD4^+$ T cell development into Th17 cells is regulated by a specific cytokine milieu, which is mostly composed of TGF-β, IL-6, IL-1β, and IL-23 [8]. Furthermore, the Th17 cell transcriptional program is established by the master transcription factor RORγt, which is crucial [62].

A crucial element for the development of Th17 cells is HIF-1α; its deficiency leads to a reduction in the differentiation of these cells [63]. The commitment of naïve T cells into the Th17 lineage necessitates the selective control of genes associated with glycolysis, in which HIF-1 plays a crucial function in establishing the metabolic conditions necessary for Th17 development [64, 65]. This process seems to rely on mTORC1 downstream of the PI3K–Akt complex [63]. Additionally, it has been shown that mTORC1 exerts a positive control on the production of IL17 via many pathways, including STAT3, HIF-1α, and S6K2 [66].

A recent investigation has shown that humans' diverse Th17 cell subgroups may be further classified into two primary groups according to the varying expression of chemokine receptors CCR4 and CXCR3: classical immunomodulatory Th17 and non-classical pro-inflammatory Th17. Classical Th17 is characterized by ($CCR4^+CXCR3^-$); they secrete large quantities of IL-17 and a low amount of IFN-γ. However, non-classical Th17 is identified by ($CCR4^-CXCR3^+$, also known as Th17.1 or Th1/Th17) secrete low amounts of IL-17 and high levels of IFN -γ, with a phenotype comparable to the Th1 [67].

The reported variations in Th17 cells' functions within the TME are probably due to their phenotypic flexibility. Depending on the unique features of the tumor, Th17 cells may show pro- or anti-tumor traits. This complexity is further highlighted by the reciprocal and antagonistic regulation of Th17 and Treg differentiation pathways [68]. Numerous studies has investigated the relationship between the Th17/Treg ratio and patient outcomes in light of this interaction [69]. A disparity that benefits the Th17 or Treg populations may accelerate the growth

of tumors by inducing excessive inflammation or suppressing the immune system's ability to fight cancer, respectively [69]. Although a number of studies have found links between the Th17/Treg imbalance and various patient outcomes, such as survival and cancer grade [69–73], however, the nature of this imbalance appears to be significantly influenced by the specific type of tumor involved [74]. Th17 cells have the ability to both promote and prevent tumor growth. For example, they can stimulate angiogenesis and increase the survival of cancer cells, which can aid in the formation of tumor [75]. On the other hand, by producing IFN-γ and attracting immune effector cells to the tumor site, such as DCs, $CD8^+$ T cells, and NK cells, they can also assist in the tumor elimination [15]. There is ample evidence that the relationship between Th17 cells and cancer is intricate and heavily context-dependent.

Th22

Th22 cells, recently discovered $CD4^+$ Th subset, are distinguished by their production of IL-22, IL-13, and tumor necrosis factor alpha (TNF-α), but not IL-17, IFN-γ, or IL-4 [76]. Their differentiation from naive $CD4^+$ T cells is driven by a specific cytokine milieu, including IL-6, IL-23, IL-1β, and TNF-α [76, 77]. A growing body of research indicates that Th22 cells may have a role in the development of tumors in a number of malignancies, including ovarian, gastric, lung, hepatocellular, and colon cancers [78–82]. The functional characteristics of IL-22, which have been demonstrated to suppress apoptosis, enhance tumor cell proliferation, angiogenesis, migration, the shift from epithelial to mesenchymal tissue, and metastasis, are most likely responsible for this connection [83–85]. It is important to notice that Th1 and Th17 cells can also contribute in production of IL-22 that present in the TME, meaning that Th22 cells are not the only ones that can produce IL-22 [86, 87].

T follicular helper (tfh) cells

Tfhs represent a distinct lineage of $CD4^+$ Th cells, essential for the production of high-affinity antibody responses. They accomplish this by encouraging the growth of B cells and making immunoglobulin class switching easier [88]. IL-6 and IL-21 work together to drive Tfh cell differentiation by inducing the production of the transcription factor Bcl-6 and activating STAT3 signaling, which in turn polarizes the cells into Tfh effector cells [9, 88]. Tfh cells appear to have a context-dependent function in the genesis of cancer [89]. Circulating Tfh-like cells are associated with a poor prognosis in chronic lymphocytic leukemia, especially in later stages [89]. However, Tfh cell infiltration into the tumor is linked to a better prognosis and increased patient survival in non-lymphoid malignancies such as colorectal, lung, and BCs [90–92]. This implies that Tfh cells may have an anti-tumoral function in solid cancers. The creation of ectopic lymphoid tissues inside the TME is the suggested mechanism for this anti-tumor impact [93]. These organs function as centers for attracting more immune effector cells that are essential for the removal of tumors. Furthermore, Tfh cells may aid in the production of anti-tumor antibody responses by influencing B cell activity [93].

Tregs

About 10% of $CD4^+$ T cells in healthy individuals are naturally occurring Tregs, or nTreg cells [94]. These cells are characterized by the constitutive expression of the FoxP3 transcription factor in the nucleus, along with CD25 and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) surface markers, all of which are critical for their suppressive function [95]. These cells are responsible in maintaining immunological self-tolerance [95]. However, they can also impede anti-tumor immunity and accelerate the course of cancer by controlling immune surveillance and suppressing effector T-cell responses [96], . In fact, poor survival outcomes and disease progression are correlated with higher nTreg levels in individuals with different malignancies [97]. Certain immunotherapies and targeted treatments may be less effective as a result of this immunosuppressive impact [98]. One mechanism by which nTreg cells suppress anti-tumor immunity involves CTLA-4-dependent downregulation of CD80 and CD86 expression on APCs [98]. This hinders the presentation of the tumor antigen and the consequent activation of tumor-specific T cells [98]. Interestingly, studies indicate that Treg cell-expressed programmed cell death protein 1 (PD-1) functions as a negative regulator of the suppressive activity of these cells [99]. Therefore, even though the goal of PD-1 blockade therapy is to revitalize fatigued $CD8^+$ T cells, it's possible that this treatment could unintentionally increase Treg cells' suppressive function in the TME [99]. nTreg cells have the ability to secrete immunosuppressive cytokines such as TGF-β, IL-10, and IL-35, which can further impair anti-tumor immunity [100].

Th17 plasticity and cytokine profile in cancer

Unlike Th1 and Th2, Th17 cells are not a "fixed" subset. They can convert into other T helper types by the effect of the microenvironment, a phenomenon known as "Plasticity" [101]. Research indicates that Th1 and Th2 cells are regarded as more phenotypically stable, whereas Th17 cells demonstrate a significant level of plasticity, enabling them to differentiate into various subtypes in response to particular stimuli or pathogenic environments [102, 103].

Given the great phenotypic flexibility of Th17 cells, it is not unexpected that the available data about Th17 cells'

role in cancer is wildly contradictory and tumor-specific [68]. Th17 cells are more plastic compared to other T cells because of their capacity to adopt a variety of functional phenotypes and their intricate nature, which involves both cytokine-dependent and -independent actions [104]. A unique feature of RORγ as compared to T-bet or GATA3, is that its expression is not stabilized by positive feedback loops, making it extremely susceptible to variations in the environment [105]. These variations result in strong phenotypic plasticity at the cellular level. Notably, phenotypic shifts between Th17 cells and every other Th subtype have been documented [106]. One of the most significant subtypes of Th17 plasticity is Th17/Th1. These cells show double-positive Th1/Th17 features, co-expressing cytokine receptors (IL-12Rβ2 and IL-23R) and distinctive transcription factors (RORγt and T-bet) [67]. Studies conducted in vitro demonstrate the importance of growth factors and cytokines in plasticity [107, 108]. While adequate TGF-β promotes the maintenance of the Th17 phenotype, low or missing TGF-β with adequate IL-12 and IL-23 cytokines appears to favor conversion towards Th1 by activating STAT4 [107, 108]. The fact that Th17 plasticity is unidirectional is an important conclusion from earlier studies. It is easy for Th17 cells to become Th1-like cells, but not the other way around [102]. These Th17-derived Th1-like cells have a unique surface marker profile (CD161, CCR6, and IL-17RE) that allows them to be identified from traditional Th1 cells [62, 109]. Furthermore, they have a distinct cytokine profile, co-expressing pro-inflammatory mediators such as IL-26, chemokine (C-C motif) ligand 20 (CCL20), IFN-γ, GM-CSF, and IL-22 [12, 109]. Expression of these cytokines depends on the secretion of IL-6, TGF-β, IL-1β, IL-12 and IL-23 by APCs during differentiation or during reactivation of already-differentiated classical Th17 cells [67]. Notably, it has been revealed that Th17/Th1 differentiation can be stimulated by DCs expressing the notch ligand DLL4 through direct activation of T-bet and RORγt [110]. The discovery of Th17 cell infiltration via chemokine receptor interactions into a variety of tumor forms, such as B cell (non-hodgkin) cancer, BC, colon cancer, gastric cancer, hepatocellular cancer, melanoma, myeloma, ovarian cancer, pancreatic cancer, and so on, in recent research has revealed even another level of intricacy [7, 12, 111–113]. Furthermore, recent studies indicate that RORγt$^+$ and T-bet$^+$ cells within tumor-infiltrating lymphocytes (TILs) may be in balance in a variety of malignancies, including ovarian and BC [114]. The differentiation pathways of Th17 and Treg CD4$^+$ T cell subsets are quite similar. TGF-β alone drives Treg cell differentiation while it induces Th17 cell differentiation and inhibits Treg cell differentiation in the presence of other cytokines such as IL-6 or IL-21 [10]. As the constitutive ratio of Tregs and Th17 cells is modified in the TME, human Th17 cells exhibit substantial developmental plasticity and differentiate into Treg cells, an immunosuppressive subset infiltrating the TME [115]. Even in the presence of Th17-polarizing cytokines, Th17-derived Tregs avoid reverting back to the Th17 phenotype, suggesting that this conversion is highly persistent [116]. Ye et al.'s in vitro research provides strong support for this trans differentiation: first, they obtained a Th17 subpopulation by stimulating TILs from ovarian and colon cancers with a CD3 monoclonal antibody as well as IL-2; and then, they used flow cytometry to detect the results after amplifying this subpopulation three times and found a significant increase in the FoxP3$^+$ cell subtype with an obvious decrease in the IL-17$^+$ cells, a TCR stimulation dependent differentiation [116]. It has been shown that Th17$^+$FoxP3$^+$ double-positive T cells exist in a variety of tumor environments. These cells are highly prevalent in the colitis microenvironment linked to colon cancer, according to Kryczek et al. In terms of function, these cells encouraged the production of inflammatory cytokines in the colitis tissues while inhibiting T-cell activation [117]. Similar findings were reported in cases of esophageal cancer in humans [118]. Research on B-cell non-Hodgkin's lymphoma indicates that cancerous B cells have the ability to upregulate FoxP3 expression and encourage the growth of Treg cells, which in turn inhibits Th17 differentiation and induce a suppressive TME [111]. Beyond Th17/Th1 and Th17/Treg plasticity, studies indicate that people with asthma have Th17/Th2 hybrid cells in their blood. These cells generate a mixed cytokine profile consisting of IL-17, IL-22 (Th17), IL-4, IL-5, and IL-13 (Th2), and they co-express the transcription factors GATA3 and RORγt, which are indicative of both lineages [119]. It has also been demonstrated that Th17 cells in peyer's patches take on the Tfh phenotype [120]. Researchers have shown that Th17 cells within Peyer's patches may dynamically change to Tfh cells (expressing Bcl6, CXCR5, PD-1, and IL-21) by the use of IL-17 fate reporter mice. This process promotes the formation of IgA-secreting germinal center B cells [120]. Figure 2 provides a schematic representation of the plasticity of Th17 cells as they differentiate into other T cell phenotypes.

Th17 dual function in various human cancers

The impact of Th17 cells on cancer development is multifaceted, as they can either facilitate tumor progression or impede tumor growth, contingent on the individual characteristics of the tumor (Fig. 3). This section presents findings on the opposing roles of Th17 cells in BC, melanoma, lung cancer, CRC, and HCC.

BC

BC is a global problem due to its high mortality and prevalence, especially among women. Despite treatment

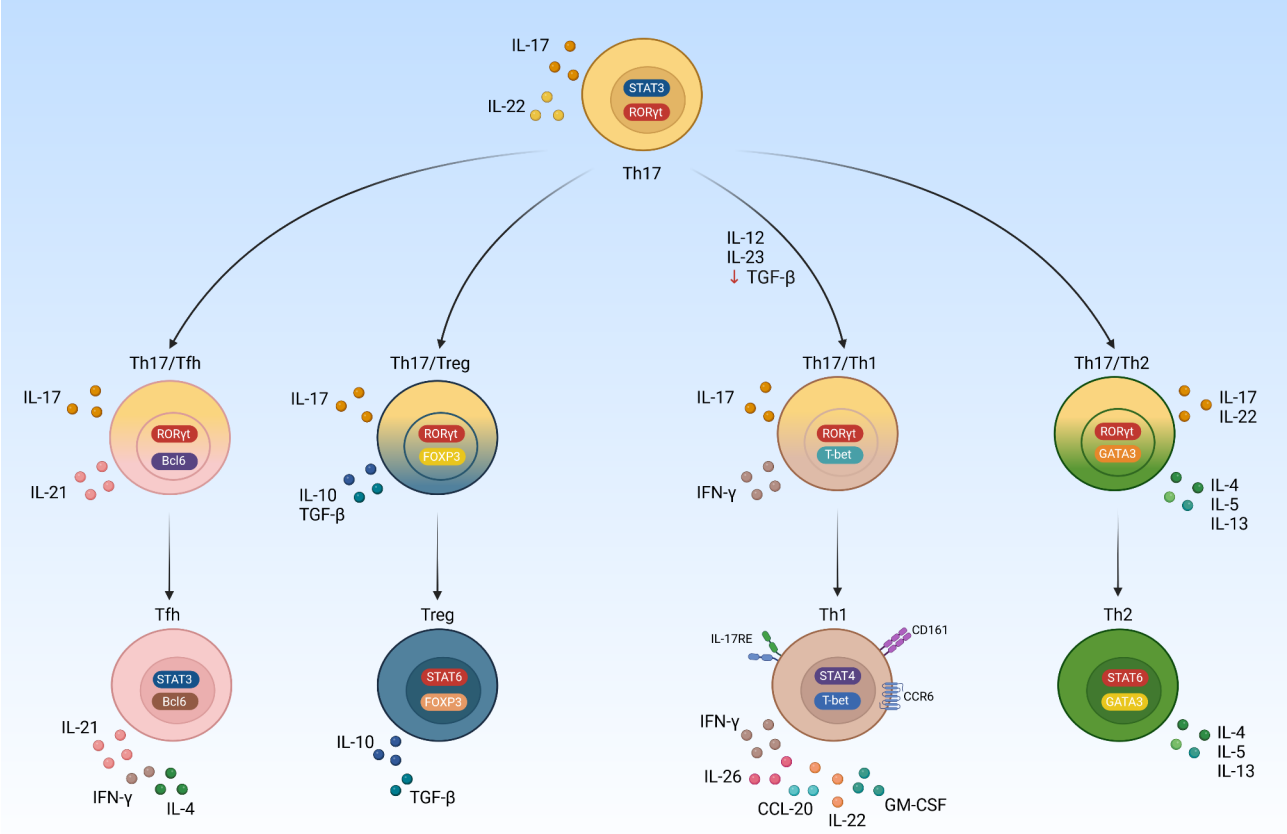

Fig. 2 Th17 plasticity and cytokine profile in cancer. Th17 cells differentiate into various subtypes under the influence of different cytokines, exhibiting both anti-tumor and pro-tumor activities within the tumor microenvironment. Each subtype secretes distinct cytokines and chemokines that play a significant role in shaping the tumor response. *Abbreviations*: IL: interleukin, Th: T helper, TGF-β: transforming growth factor beta, IFN-γ: interferon-gamma, Treg: regulatory T cell, GM-CSF: granulocyte-macrophage colony-stimulating factor, CCL-20: C-C motif ligand 20, Tfh: T follicular helper, IL-17RE: IL-17 receptor E, CCR: CC chemokine receptor

progress, no definitive cure for BC has been reported [1]. However, substantial research has been done to find effective treatments and identify BC progression mechanisms and causes [121, 122]. BC spreads due to many reasons, including Th17 cells' chemokines, cytokines, and inflammatory pathways [12]. Karpisheh et al. gathered comprehensive evidence of the dual role of Th17 in BC pathogenesis [123]. The dual roles of Th17 cells in BC, encompassing both tumor-promoting and anti-tumor functions, are examined in this section. Regarding the tumor-promoting characteristics of Th17 cells, a multitude of studies have indicated an increased presence of these cells in the tumor tissues and PBMCs of BC patients. Notably, Th17 cells exhibit heightened activity in individuals with advanced stages of the disease [124, 125]. Du et al. found that breast tumor tissue expressed IL-17. By increasing tumor microvessel accumulation, IL-17 boosted angiogenesis, metastasis, tumor cell proliferation and growth, and BC progression rate. In addition, they found that IL-17 injection into tumor-bearing animals greatly enhanced tumor progression, but in vitro exposure did not [126]. The findings of Chen and colleagues established a correlation between elevated levels of IL-17 secretory cells and a higher histological grade in BC [127]. In another study, IL-22, a major Th17 cytokine, increased angiogenesis, proliferation, and tumorogenesis [128]. According to a different study on BC patients, IL-17 significantly increased the expression of the vascular endothelial growth factors (VEGF), CXCL8, matrix metalloproteinase (MMP)-2, and MMP-9, promoting the growth of tumor cells. Tumor invasion and increased expression of IL-17 A were positively correlated with the quantity of Treg cells in invasive breast tumors [129]. Thibaudin et al. found that ectonucleotidase-expressing $CD25^{high}$ Th17 cells grew rapidly in tumor tissue and suppressed $CD8^{+}$ and $CD4^{+}$ T cells by inhibiting and activating them, respectively. They suggested that these cells hindered the immune system's anticancer responses [130]. Moreover, it was found that Th17 cells regulate CXCL1 expression throughout cancer growth. Evidence suggests that CXCL1 expression on tumor cells and its interaction with the CXCR2 receptor can activate

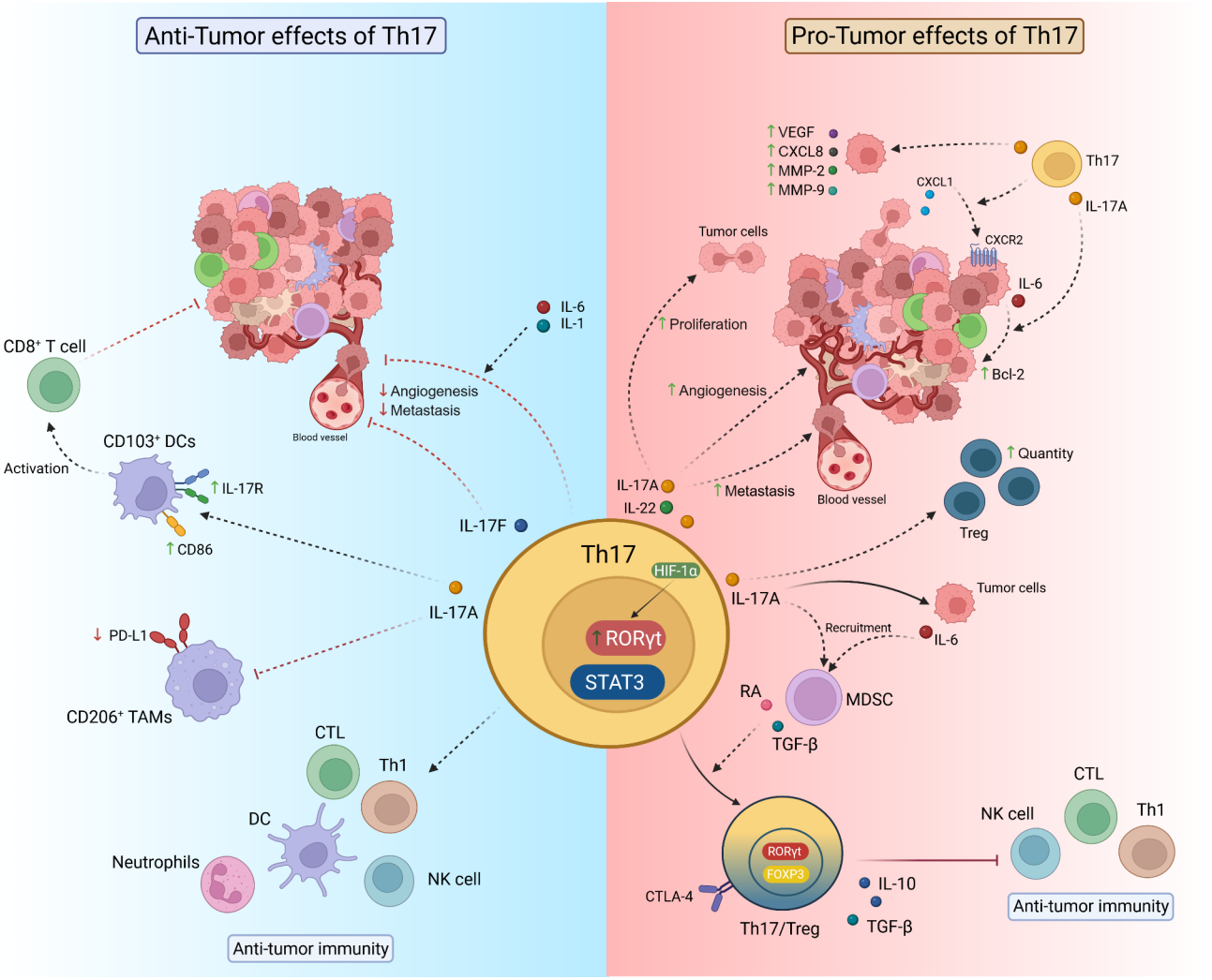

Fig. 3 Th17 dual function in various human cancers. The TH17 cell subset can promote tumor progression through the secretion of cytokines such as IL-17 A and IL-22, which facilitate tumor cell proliferation, angiogenesis, metastasis, differentiation into Treg cells, and the recruitment of myeloid-derived suppressor cells (MDSCs), thereby exerting pro-tumor effects. Conversely, this cell lineage can also inhibit metastasis, angiogenesis, and tumor-associated macrophages (TAMs) through the release of cytokines including IL-1, IL-6, IL-17 A, and IL-17 F. Additionally, it can stimulate the recruitment and activity of cytotoxic T lymphocytes (CTLs), TH1 cells, dendritic cells (DCs), natural killer (NK) cells, and neutrophils, resulting in anti-tumor effects. *Abbreviations*: IL: interleukin, DCs: dendritic cells, IL-17R: IL-17 receptor, PD-L1: programmed cell death ligand 1, TAMs: tumor associated macrophages, Th: T helper, NK cell: natural killer cell, MMP: matrix metalloproteinase, CXCL: C-X-C motif ligand, VEGF: vascular endothelial growth factor, Treg: regulatory T cell, MDSC: myeloid-derived suppressor cell, TGF-β: transforming growth factor beta, CTL: cytotoxic T lymphocyte, CTLA-4: cytotoxic T-lymphocyte associated protein 4, RA: retinoic acid

the NF-κB/ AKT pathway, leading to metastasis, angiogenesis, growth, and progression of BC [131]. Evidence shows that aggressive molecular subtypes TN, Luminal B, and HER2 have higher levels of IL-17 A than less aggressive Luminal A. Also, it was demonstrated that Th17 increased BC risk [132]. Scientists also indicated that IL-17-producing neutrophils and γδ cells boosted BC cell invasion and metastasis. Breast tumor cells stimulated neutrophil polarization and proliferation, suppressing $CD8^+$ T cells and increasing dissemination to adjacent organs [133]. IL-17 A also promoted cell growth and proliferation, according to Kim et al. [134]. Moreover, in vitro, recombinant IL-17 had minimal influence on cancer cell proliferation in mouse BC cells, while angiogenesis and tumor size increased in animals [126]. A study by Huang et al. found that Treg cells increased IL-17RB production in BC cells by secreting TGF-β1 and activating the Smad2/4/3 signaling pathway in tumor-draining LNs (TDLNs), leading to cancer cell proliferation, angiogenesis, and metastasis [135]. Additionally, IL-17E has been shown to generate anti-tumor responses in vitro and in vivo. IL-17E's anti-tumor effect was linked to increased peripheral blood eosinophils and IL-5 levels in tumor-bearing animals [136]. In contrast, Jiang et al. found

Table 1 Different Th subsets and their function in the TME

Th subsets	Transcription factors	Differentiation cytokines	Effector molecules	Main functions in the TME	Clinical relevance	Refs
Th1	STAT4, T-bet	IL-12, IFN-Y	IFN-γ, cytolytic enzymes (e.g., perforin, granzymes)	Promote anti-tumor immunity by activating cytotoxic T cells and macrophages, inhibit tumor angiogenesis	Th1 cells have been linked to a positive outlook in different types of cancer due to their ability to produce molecules that can directly eliminate cancer cells and hinder the formation of new blood vessels	[206–211]
Th2	STAT6, GATA3	IL-4	IL-4, IL-5, IL-13, TGF-β, matrix metalloproteinases	Promote tumor growth and metastasis by inducing immunosuppressive mechanisms, angiogenesis, and tissue remodeling	Th2 cells have been linked to unfavorable outcomes in numerous types of cancer due to their ability to produce molecules that support tumor progression, metastasis, and suppression of the immune system	[206, 208, 209, 211, 212]
Th9	STAT6, PU-1, IRF4, BATF	IL-4, TGF-β	IL-9, granzymes, perforin	Enhance anti-tumor immunity by recruiting and activating cytotoxic cells, inhibit tumor angiogenesis	Th9 cells have demonstrated encouraging anti-tumor properties in preclinical studies, however, their significance in clinical settings is currently under scrutiny	[208, 211, 213, 214]
Th17	STAT3, RORγt	IL-1, IL-23, IL-6, TGF-β	IL-17, IL-22, matrix metalloproteinases, angiogenic factors	Promote tumor growth and metastasis by inducing inflammation, angiogenesis, and immunosuppression Inhibit tumor progression by recruiting different mechanisms	Th17 cells can have both pro-tumor and anti-tumor effects, depending on the specific context and balance of their effector molecules	[188, 188, 211, 215, 216]
Th22	STAT3, AhR, RORγt, RUNX3	IL-6, TNF-α	IL-22, matrix metalloproteinases, angiogenic factors	Promote tumor growth and metastasis by inducing tissue remodeling, angiogenesis, and immunosuppression	Th22 cells are associated with poor prognosis in in numerous types of cancer due to their ability to produce molecules that support tumor growth, metastasis, and immunosuppression	[208, 211, 217, 218]
Treg	STAT6, FOXP3	IL-2, TGF-β	IL-10, TGF-β	Suppress anti-tumor immune responses, promote tumor growth and metastasis	Tregs have been linked to unfavorable outcomes in numerous types of cancer due to their ability to inhibit anti-tumor immune reactions and facilitate the advancement of tumors.	[208,211, 215, 219,]
Tfh	STAT3, Bcl6, ASCL2	IL-6	IL-21	Promote B cell-mediated anti-tumor immunity, but can also induce immunosuppression	The effects of Tfh cells on tumors can vary, as they have the potential to either promote or inhibit tumor growth, depending on the specific context and the balance of their effector molecules.	[208, 211]

Abbreviations: Th1: T helper 1 cells, Th2: T helper 2 cells, Th9: T helper 9 cells, Th17: T helper 17 cells, Th22: T helper 22 cells, Treg: regulatory T cells, Tfh: follicular helper T cells, IFN-γ: interferon gamma, IL-2: interleukin-2, IL-4: interleukin-4, IL-5: interleukin-5, IL-6: interleukin-6, IL-9: interleukin-9, IL-10: interleukin-10, IL-12: interleukin-12, IL-13: interleukin-13, IL-17: interleukin-17, IL-21: interleukin-21, IL-22: interleukin-22, TGF-β: transforming growth factor beta, TNF-α: tumor necrosis factor alpha, STAT4: signal transducer and activator of transcription 4, T-bet: T-box transcription factor TBX21, GATA3: GATA binding protein 3, PU.1: transcription factor PU.1, RORγt: RAR-related orphan receptor gamma, Foxp3: forkhead box P3, Bcl6: B-cell lymphoma 6 protein, AhR: aryl hydrocarbon receptor, TME: tumor microenvironment

that macrophages and $CD4^+$ T cells released IL-17E in a breast tumor model. IL-17E suppression reduced tumor cell growth, proliferation, and metastasis by decreasing macrophages and type 2 T cells in the TME. They found that inhibiting this cytokine may help cure metastatic BC [137]. Further research is required to explore the influence of IL-17E on the treatment and progression of BC, given the inconsistencies observed in these two studies [123].

On the other hand, Th17 cell exhibits an anti-tumor characteristic. In this regard, research indicates that Th17 cell number is positively linked to IL-6, IL-17, and IL-1β cytokine expression and negatively linked to increased metastatic lymph nodes and tumor cell angiogenesis. In BC tissues, more Th17 cells increased anti-tumor immune responses [138]. Therefore, Faucheux et al. also showed that boosting Th17 cell populations improved patient survival. In BC tissues, Th17 cell expansion induced anti-tumor immune responses, limiting BC development [139]. Numerous elements lead to the existence of contradictions in the literature. One notable paradox is the limited number of studies indicating that Th17 cells confer protection to patients with BC. The scarcity of research utilizing animal models complicates the extrapolation of these findings to human subjects. Consequently, additional research is warranted. Various studies have identified phenotypic variations of BC within individual patients, which may account for these inconsistencies. The immune responses, underlying causes of the disease, and responses to treatment

differ among the various BC phenotypes. Therefore, it is essential for future research to evaluate the frequency and functionality of Th17 cells across different BC phenotypes [123].

Melanoma

Melanoma is a tumor derived from melanocytes, specialized pigmented cells, mainly found in the skin [140, 141]. The 17 cells are common in the microenvironment of melanoma. However, the role of these cells in tumor immunopathology is paradoxical as Th17 cells have shown both antitumor and pro-tumor effects in melanoma [75]. Chen and Gao have gathered sufficient evidence of this dual role of Th17 cells in melanoma [142]. Based on recent studies, there are at least two distinct immunological phenotypes in melanoma. One type is the Th17 immune phenotype (class A), characterized by high expression of WNT5A, increased cyclin activity, and cancer-testis antigens with a poor prognosis. A more differentiated state, increased reactivity to immune cytokines, and an improved prognosis is linked to the Th1 immunological phenotype of class (B) [143]. Metastases exhibiting a Th17 phenotype were more frequently BRAF mutated when comparing class comparisons between BRAF mutant and wild-type metastatic melanoma models. Furthermore, genes connected to the IL-17 pathway showed differential expression in BRAF mutants compared to wild-type models. Therefore, in the case of malignant melanoma, Th17 cells may also exert a significant pro-tumor effect [144, 145]. Multiple lines of evidence show that Th17 cells in melanoma can have strong pro-tumor effects. Reduced apoptosis, enhanced invasiveness, and increased metastatic behavior have all been linked to BRAF mutations [146]. Studies have shown that Th17-derived IL-17 is related to melanoma tumor angiogenesis, promoting the growth and survival of tumors [147, 148]. According to Lin Wang et al. IL-17 promoted the secretion of IL-6 by directly affecting cells that express IL-17 receptors, including fibroblasts, endothelial cells, melanoma cells, and DCs. As a consequence, the melanoma growth was accelerated. Following the activation of oncogenic STAT3 by IL-6 in melanoma cells, the expression of pro-survival genes such as Bcl-2 and Bcl-xl was increased [149]. Additionally, the Th17/Tregs plasticity in the melanoma microenvironment may be another mechanism involved in the Th17 cell's pro-tumor impact in melanoma. Th17 cells can inhibit anti-tumor immunity and serve as regulatory cells. Tregs are produced through lineage conversion of Th17 cells [150, 151]. The intermediate phenotypes that co-express the transcript components FoxP3 and RORγt are the outcome of this conversion [151, 152]. Following anti-CD3 antibody stimulation, tumor-infiltrating Th17Th1cells can express FoxP3, CD25, and CTLA4, which are markers of Treg cells, and produce levels of IL-10 and TGF-β1 [153].

However, some other studies demonstrated evidence of anti-tumor effects of Th17 cells. For example, the adoptive transfer of Th17-polarized cells specific to tumors into large, well-established B16 melanoma mice was more successful than Th1 cells at mediating the eradication of advanced melanoma. IFN-γ and IL-17 production were required for this therapeutic effect to occur [154]. Adoptive transfer of Th17 cells specific to tumors also inhibits the growth of tumors, according to another study [155]. The impact of Th17 cells in eradicating melanoma was hindered by deficient IFN-γ or IL-17 A [147]. Martin-Orozco et al. discovered that Th17 cell treatment induced a striking activation of tumor-specific $CD8^+$T cells, which were essential for the anti-cancer effect [155]. Tumor-infiltrating Th17 cells induced the expression of CCL2/20 in tumor tissues, which attracted DCs, $CD4^+$ and $CD8^+$ T cells, and other inflammatory leukocytes to promote anti-tumor immunity [155, 156]. Additionally, Th17 cells can boost $CD8^+$ T cells to have an anti-tumor effect. In another study, researchers primed TRP-1 transgenic Th17 cells and Pmel-1 T cell receptor (TCR) transgenic $CD8^+$ T cells ex vivo using a RORγ agonist. They discovered that these cells could successfully regress melanoma when compared to those Th17 cells that were not treated. The anti-cancer impact was significantly increased in mice with existing melanoma when co-infused with equal quantities of TRP-1, Th17 cells, and Pmel-1 Tc17 cells. These findings support earlier results and provide additional evidence that Th17 cells can enhance $CD8^+$ T cells to have anti-tumor effects [157]. Based on the observation that Th17 cells that were $IL2^{-/-}$ and $Kb^{-/-}$ (without major histocompatibility complex type I; MHC I) lost their anti-tumor immunity, it is possible that Th17 cells stimulated the CTL response via IL-2 and peptide/MHC-I, which can be recognized by $CD8^+$ T cells and induce $CD8^+$ T cell activation. The results indicate that Th17 cells present in the tumor may have a dual role, acting as both effectors and regulators in the melanoma microenvironment. Therefore, Th17 cells may play a role in the development of melanoma. This process may be influenced by myeloid-derived suppressor cells that infiltrate the tumor and promote the conversion of Th17 cells to Tregs through the secretion of TGF-β and retinoic acid [158].

Lung cancer

NSCLC comprises the majority of lung cancers [159] and is the primary cause of death in cancer patients worldwide [160]. This unfortunate outcome is probably related to the lack of a comprehensive understanding of the NSCLC TME, which is a complex mixture of immune

cells, fibroblasts, lymphatic and blood vessels [161]. This microenvironment aids tumor cells in proliferation, invasion, and metastasis and contributes to disease progression [162]. Several studies aimed to identify the role of IL-17 and Th17 specifically in NSCLC progression [163, 164]. Many of these studies found an increased frequency of Th17 as well as enhanced production of IL-17 in patients [163, 165, 166]. IL-17 A was shown to be able to promote the stemness, migration, and invasion of NSCLCs through STAT3/ nuclear factor kappa B (NF-kB)/Notch1 signaling pathways. Furthermore, blocking these pathways indicates capability to suppress NSCLC stemness, migration, and invasion. In addition, Th17 cells in NSCLC were strongly correlated with poor prognosis [163] and poor survival of NSCLC patients [167]. The recruitment of these cells appears to be a consequence of Kras mutation in lung epithelial cells as explained by Chang et al. [168]. IL-17 produced by Th17 contributes to inflammation, tumor growth, and recruitment of tumorigenic cells [168]. Armstrong et al. compared the Th17/IL17A axis in the TMEs of K-ras-driven and Ptsd/d NSCLC models and elaborated on mechanisms underlying the dual role of Th17 in NSCLC [169]. They discovered that in K-ras-driven mice, Th17 cells were drawn to the TME, promoting tumor cell proliferation. Th17-derived IL17A attracted myeloid derived suppressor cells (MDSCs) to suppress the anti-tumor function of $CD8^+$ T cells. IL17A can directly cause tumor cells to produce more IL-6. IL-6 can work in two ways: autocrine to promote tumor cell proliferation and paracrine to enhance MDSC recruitment. MDSC invasion can also be boosted through GM-CSF, granulocyte-colony stimulating factor (G-CSF) produced by tumor cells. On the contrary, Th17/IL17A in the TME of the Ptsd/d NSCLC model inhibits tumor growth. Th17 cells are essential for the recruitment of $CD103^+$ DCs, which activate $CD8^+$ T cells for anti-tumor action. IL17A increases the expression of IL-17R and CD86 on $CD103^+$ DCs, which provides signals for $CD8^+$ T cell activation. Activated $CD8^+$ T cells release IFN-γ, which activates both $CD8^+$ T cells and DC tumoricidal activity, resulting in tumor cell death. IL17A may suppress $CD206^+$ tumor-associated macrophages (TAMs), reducing PD-1 and programmed death ligand 1 (PD-L1) interactions between lymphocytes and TAMs and allowing lymphocytes to exert anti-tumor activity.

Furthermore, Th17 cells enhanced the production of chemoattractants CCL2 and CCL20 in the microenvironments of lung tumors and facilitated the recruitment of different inflammatory leukocytes (DCs, CD4+, and CD8+T cells). Experimental evidence has demonstrated that Plasmacytoid dendritic cells (pDC) stimulated by CpG-activated and antigen presentation trigger the differentiation and growth of Th17 cells, resulting in the production of significant quantities of additional inflammatory cytokines, including IFN-γ [170]. When pDCs lack MHC II expression, the proliferation of Th17 cells in tumor tissue is diminished, and the Th17 response is impaired, resulting in a decline in the recruitment of immune cells such as cytotoxic T lymphocytes (CTL), which eventually contributes to tumor development [171].

The overall body of research indicates that Th17 cells have opposing roles in distinct genetic drivers of cancer, while some critical gaps in our understanding still need to be filled. It seems that identical immunological contexts elicit varied responses from various malignancies [169].

CRC

CRC is the most common cancer in the digestive system and is the second leading cause of cancer-related death; with a mortality rate of 8-9%, often diagnosed in advanced stages and with low overall survival rates. Chronic inflammation is linked to tumorigenesis, with local inflammation in tumor tissue being infiltrated by inflammatory immune cells, which can either progress or suppress tumor cell survival and growth [172–174]. Human CRCs are characterized by the presence of $CD4^+$ T lymphocytes and macrophages producing IL-17 A, which contribute to poor prognosis. These cells, which are abundant in CRCs and have potent immunosuppressive functions, sustain oncogenesis and tumor progression. Studies have shown that IL-17 A, IL-17 F, IL-21, and IL-22 are overexpressed in CRCs, leading to reduced disease-free survival (DFS) in patients with these conditions [79, 175–178]. Doulabi et al. found that circulating Th17 and Th22 cells in CRC patients were significantly higher than in healthy controls. Infiltrating Th1, Th17, Th22, and $CD4^+$ cells co-producing IL-17/IL-22 were also higher in tumor tissues compared to para-tumor tissues. The percentage of circulating and intra-tumoral Th17, Th22, and $CD4^+$ cells co-producing IL-17/IL-22 was higher in advanced stages [172]. Another study examined IL-17 A dynamics along the human colorectal adenoma-carcinoma spectrum and has found that the expression of IL-17 A, at both the mRNA and protein levels, was significantly increased in the adenoma stage and persisted to the CRC stage [179]. It has been found that a high RORγt/CD3 ratio correlated with lymph node metastasis and is a decisive prognostic factor for shortened postoperative survival, suggesting Th17 cells may increase the metastatic ability of tumor cells in CRC [180]. A recent investigation revealed that TWEAK, a cytokine synthesized and released by Th17 cells, interacts with Fn14 receptors present on malignant cells. This interaction facilitates the migration and invasion of colorectal cancer (CRC) cells to the liver, thereby contributing to the development of colorectal cancer liver metastasis (CRLM)

[181]. Single-cell RNA sequencing analysis revealed distinct distributions of nonmalignant cells within the primary tumors of patients diagnosed with metastatic colorectal cancer (mCRC) in contrast to those with non-metastatic colorectal cancer. Notably, this analysis indicated that Th17 cells were predominantly localized in the primary lesions associated with mCRC [181].

Th17 also has anti-tumor effects. Previous studies have demonstrated that the anti-tumor effect of IL-17 in various cancer types is related to enhanced recruitment and activity of lymphocytes, NK cells, and DCs into the tumor site and production of the anti-tumor cytokine IFN-γ [182–184]. IL-17 F is another potential factor involved in the development of CRC. Tong et al. have shown a protective effect of IL-17 F in the development of CRC. They found decreased tumor growth of IL-17 F-transfected HCT116 cells compared to that of mock transfectants when transplanted into nude mice. They also showed decreased VEFG and angiogenesis in IL-17 F overexpressing tumor cells [185].

In favor of the dual role of Th17 tumor-infiltrating cells, ex vivo analysis showed that tumor-infiltrating IL-17$^+$ cells mainly consist of CD4$^+$ Th17 cells with multifaceted properties. As a result of IL-17 secretion, CRC-derived Th17 triggered the release of pro-tumorigenic factors by tumor and tumor-associated stroma. However, on the other hand, they favored the recruitment of beneficial neutrophils through IL-8 secretion, and they drove highly cytotoxic CCR5+CCR6+CD8+T cells into tumor tissue through CCL5 and CCL20 release. According to these findings, the presence of intra-epithelial, but not of stromal Th17 cells, positively correlated with improved survival [186].

HCC

HCC is one of the most common cancers worldwide. It has low overall survival (OS) rates due to factors such as distant metastasis, local recurrence, treatment resistance, and lack of early diagnosis, despite advancements in molecular biology and cancer therapy [187]. Th17 cells play complex roles in inflammation and tumor immunity. They express the transcription factor, RORγ, and secret cytokines, including IL-17 A, IL-17 F, and IL-22, IL-21, which act as a pro-inflammatory mediator. IL-17 is generally believed to induce chronic inflammation and has pro-tumorigenic effects, and accumulating evidence indicated that Th17 cells promoted HCC development and were associated with poor survival [188]. Zhang et al. studied the distribution of Th17 cells in 178 HCC patients. There were increased Th17 cells in tumor tissues when compared to non-tumor regions, and intratumoral IL-17 producing cell density was an independent prognostic factor for significantly shorter overall OS and DFS [188, 189]. A study found an imbalance in Treg/Th17 cells in HCC patients' PBMCs. The increased numbers of Treg and Th17 cells were positively correlated with HCC tumor stage and size, suggesting Treg and Th17 cells may promote HCC invasion and progression, and a Treg/Th17 cell imbalance could be a key indicator for HCC progression and prognosis. Th17 cells promote tumor growth through IL-6-induced angiogenesis and inhibit it by amplifying cytotoxic lymphocyte presence [187]. Tumor-derived chemokines like monocyte chemoattractant protein-1 (MCP-1) and RANTES influence Th17 cell recruitment to tumor contexts. Th17 cells are found in tumor-infiltrating T lymphocytes in cancer patients, indicating their potential recruitment, induction, or development in the TME. This infiltration is related to poor prognosis in HCC, CRC, and pancreatic carcinoma [124, 189]. Accumulation of intra-tumoral IL-17-producing cells may promote tumor progression by fostering angiogenesis. Additionally, these IL-17-producing cells found within the tumor could potentially be used as a prognostic marker [124, 189]. The presence of IL-17 A-positive cells in tumor tissues has been associated with increased metastasis and a poorer prognosis in hepatocellular carcinoma (HCC). Subsequent studies have revealed that this correlation arises from IL-17 A's capacity to promote cell migration by activating NF-kB transcription factors and increasing the expression of MMP-2 and MMP-9 [190, 191].

Huang et al. conducted a study on thermal ablation for treating HCC in mice. The study found that thermal ablation decreased Th17 cell frequency in peripheral blood, increased Treg cell frequency, and significantly downregulated IL-17 and IL-23 levels while upregulating IL-10 and TGF-β levels, suggesting that Th17 plays a crucial role in cancer promotion [192]. Another study found that Th17 cells express higher miR-132 compared to primary CD4$^+$ cells. It positively regulates Th17 cell differentiation, enhances IL-22 production, and improves the function of Th17 on hepatic stellate cells (HSCs) for their tumor-promoting effects [193]. In hepatitis B virus (HBV)-related HCC, intra-tumoral densities of Th17 cells were augmented. These Th17 cells were thought to promote tumor progression and correlate with poor survival rates by fostering angiogenesis. In patients with HCC, high expression of intra-tumoral IL-17 and IL-17 receptor E were reported, associated with poorer survival rate and increased recurrence [194].

Anti-programmed cell death ligand 1 (PD-L1) therapy is recognized as a potential strategy for addressing hepatocellular carcinoma (HCC). Nevertheless, resistance to this treatment frequently develops in nearly all cases. Studies have indicated an elevated infiltration of pathogenic Th17 cells in HCC tissues that exhibit drug resistance. These Th17 cells produce IL-17 A, which promotes the upregulation of PD-L1 on HCC cell surfaces, thereby

contributing to the resistance against anti-PD-L1 therapy and exacerbating the clinical scenario [195].

Th17 cells can also prevent tumor cell apoptosis, decrease anti-tumor responses, increase tumor angiogenesis, and stimulate tumor metastasis and invasion. Experimental evidence suggests that IL-17 can also suppress tumors during tumorigenesis and metastasis [64]. In various human cancers, $CD3^+$ $CD4^+$ $ROR\gamma^+$ cells are present at higher frequencies in the TILs than in PBMCs, suggesting their role in anti-tumor immunity. IL-17 A is a direct target of RORγ, which is the key transcription factor controlling the development and function of $CD4^+$ Th17 and $CD8^+$ Tc17 cells. Xiao Hu et al. identified synthetic agonists that selectively activate RORγ. They enhance the effector function of type 17 cells by increasing the production of cytokines/chemokines such as IL-17 A and GM-CSF, augmenting the expression of co-stimulatory receptors like CD137, CD226, and improving survival and cytotoxic activity. They also attenuate immunosuppressive mechanisms by curtailing Treg formation, diminishing CD39 and CD73 expression, and decreasing levels of co-inhibitory receptors, including PD-1 and T cell immunoreceptor with Ig and ITIM domains (TIGIT) on tumor-reactive lymphocytes [114].

Hepatocellular carcinoma (HCC) is classified as a hypermetabolic neoplasm. The unrestrained growth of the tumor, coupled with an insufficient oxygen supply within the TME, has been shown to lead to the upregulation of HIF-1α. This factor is posited to play a crucial role in activating RORγt, functioning through the formation of a tertiary complex with RORγt and the recruitment of p300 to the promoter region of IL-17. Additionally, HIF-1α is known to inhibit the development of Tregs by interacting with FoxP3 and promoting its degradation via the proteasomal pathway [196–202].

Potential clinical implications of manipulating Th17 cells in the context of cancer therapies

Considering the conflicting findings about the Th-17 cell's pro- and anti-tumor properties, it may be necessary to tailor treatment plans to each patient's specific cancer, stage, and even associated mutations in order to determine whether Th17 activation or inhibition would be more beneficial. A clear therapeutic goal for patients with malignancies that Th17 cells worsen is to decrease the quantity of these cells in the tumor microenvironment. The mice lung cancer model demonstrated tumor reduction upon IL-17 suppression, according to a study by Chang et al. This reduction was due to a decrease in tumor cell proliferation and angiogenesis [184]. In contrast, clinical trials aimed at enhancing particularly targeted T cell populations have showed significant potential in the treatment of cancer [36]. Notably, Paulos and colleagues found that the activity of human Th17 cells was increased when they were stimulated with CD3 and ICOS agonists, as compared to when they were activated with CD28, when transferred into mice with tumors [177]. The substantial antitumor response observed after infusing Th17 cells into mice with specific types of cancer, such as melanoma, suggests that further research aimed at directing and utilizing these cells to eliminate tumor tissue in clinical settings could offer therapeutic possibilities for a wide range of malignancies [67]. In addition, for individuals with increased Th17-based inflammation in the tumor microenvironment, addressing Th17 cells or cytokines specifically may have promise [67]. Using the fully-humanized anti-IL-17 A monoclonal antibody secukinumab (AIN457) to treat ER- or triple-negative breast cancer in mice increased anti-tumor immunity (CD4+and CD8+T cells), decreased PDL-1 expression, and reduced Treg cell infiltration [172]. Interestingly, a combination treatment approach [203] anti-IL-17 A (secukinumab) and anti-PDL1 (pembrolizumab) improved antitumor immunity in support of its eradication [100]. Contrarily, researchers found that exposing breast cancer cell lines to IL-17E had an anti-tumorigenesis impact [204]. Discrepancies in results may be attributed to variations in experimental circumstances and environments [7]. Important factors to consider include the timing of breast cancer cells exposure to IL-17, the type of cells present, and the stage of the disease [50]. Furthermore, substances like phosphodiesterase-4 inhibitor (PDE-4 inhibitors) and JAK/STAT inhibitors have the ability to influence the IL-17/Th17 signaling pathway and might potentially be utilized in the treatment of lung cancer in a similar manner. Targeting this pathway could hold great promise as a treatment for lung cancer, according to the safety and effectiveness of the drugs now under development. There is new evidence that the IL-17/Th17 and PD-1 pathways are connected, which opens the prospect of a synergistic effect between anti-PD(L)1/anti-IL-17 and anti-PD(L)1/anti-IL23 targeting [205]. The available data indicates that the targeting and reprogramming of several downstream signaling pathways of IL-17 A could be a crucial complementary strategy to enhance the effectiveness of conventional cancer therapy [89]. Thus, additional investigation is required in the future to develop anti-cancer tactics that specifically focus on IL-17 signatures and their associated signaling pathways.

Conclusions

Th17 cells are acknowledged as a crucial cell type that promotes inflammation in different pathophysiologic conditions. These cells infiltrate several forms of cancers. Th17 cells can display either pro-tumor or anti-tumor properties, depending on the unique characteristics of the tumor. In this review, we have gathered evidence of

the contradictory role of Th17 cells in BC, melanoma, lung cancer, CRC and HCC. Pro-tumor effects of Th17 cells range from promoting metastasis, tumor growth and angiogenesis to recruiting MDSDs and increasing Treg to suppress anti-tumor responses. On the other hand, Th17 cells' anti-tumor effects might include recruitment of DCs and NK cells, activating $CD8^+$ T cells and subsequent tumor cell death, suppressing $CD206^+$ TAMs and reducing PD-1/PD-L1 interactions and production of anti-tumor cytokines. This opposing behavior of Th17 cells might be related to different immune responses, genetic or phenotypic variances within each cancer or small number of studies on this matter. Given the crucial significance of the T17 population in the advancement of various illnesses, it is important to understand the mechanisms underlying T17 cells' functions in different types of malignancies. This area of research holds great potential for cancer therapy development.

Abbreviations

Th	T helper
IL	Interleukin
IFN-γ	Interferon-gamma
TME	Tumor microenvironment
GM-CSF	Granulocyte-macrophage colony-stimulating factor
TGF-β	Transforming growth factor beta
IBD	Inflammatory bowel disease
Tregs	Regulatory T cells
DCs	Dendritic cells
NK	Natural killer
APCs	Antigen-presenting cells
BC	Breast cancer
CRC	Colorectal cancer
NSCLC	Non-small cell lung cancer
TAM	Tumor-associated macrophages
HCC	Hepatocellular carcinoma
TNF-α	Tumor necrosis factor-alpha
Tfh	T follicular helper
nTreg	Naturally occurring Tregs
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
PD-1	Programmed cell death protein 1
PBMCs	Peripheral blood mononuclear cells
TDLNs	Tumor-draining LNs
TCR	T cell receptor
MDSCs	Myeloid derived suppressor cells
G-CSF	Granulocyte-colony stimulating factor
PD-L1	Programmed death ligand 1
HIF	Hypoxia-inducible factor
TIGIT	T cell immunoreceptor with Ig and ITIM domains

Author contributions

K.R., Investigation, writing – original draft M. T., Investigation, writing– original draft N. A., Investigation, writing– original draft A. R., Writing – review and editing H. Y., Writing – review and editing A. A., and Z. A., Validation and visualization A. G., F.G., and S.T., Conceptualization, project administration, software, and supervision.

Funding

This research received no grant from any funding agency, commercial or not-for-profit sectors.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

AI utilization

The authors declare that they have not used Artificial Intelligence in this study.

Competing interests

The authors declare no competing interests.

Received: 13 August 2024 / Accepted: 8 October 2024
Published online: 27 October 2024

References

1. Elahi R, Khosh E, Tahmasebi S, Esmaeilzadeh A. Immune cell hacking: challenges and clinical approaches to create smarter generations of chimeric antigen receptor T cells. Front Immunol. 2018;9:1717.
2. Tahmasebi S, Elahi R, Esmaeilzadeh A. Solid tumors challenges and new insights of CAR T cell engineering. Stem cell Reviews Rep. 2019;15:619–36.
3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
4. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331(6024):1565–70.
5. Izadi M, Tahmasebi S, Pustokhina I, Yumashev AV, Lakzaei T, Alvanegh AG, et al. Changes in Th17 cells frequency and function after ozone therapy used to treat multiple sclerosis patients. Multiple Scler Relat Disorders. 2020;46:102466.
6. Sadeghi A, Tahmasebi S, Mahmood A, Kuznetsova M, Valizadeh H, Taghizadieh A, et al. Th17 and Treg cells function in SARS-CoV2 patients compared with healthy controls. J Cell Physiol. 2021;236(4):2829–39.
7. Chang SH. T helper 17 (Th17) cells and interleukin-17 (IL-17) in cancer. Arch Pharm Res. 2019;42(7):549–59.
8. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4 + effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol. 2005;6(11):1123–32.
9. Luckheeram RV, Zhou R, Verma AD, Xia B. CD4⁺T cells: differentiation and functions. Clin Dev Immunol. 2012;2012:925135.
10. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. Annu Rev Immunol. 2009;27:485–517.
11. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med. 2005;201(2):233–40.
12. Guéry L, Hugues S. Th17 cell plasticity and functions in Cancer Immunity. Biomed Res Int. 2015;2015:314620.
13. Yasuda K, Takeuchi Y, Hirota K. The pathogenicity of Th17 cells in autoimmune diseases. Semin Immunopathol. 2019;41(3):283–97.
14. Wu B, Wan Y. Molecular control of pathogenic Th17 cells in autoimmune diseases. Int Immunopharmacol. 2020;80:106187.
15. Ye J, Livergood RS, Peng G. The role and regulation of human Th17 cells in tumor immunity. Am J Pathol. 2013;182(1):10–20.
16. Künzli M, Masopust D. CD4 + T cell memory. Nat Immunol. 2023;24(6):903–14.
17. Tahmasebi S, Alimohammadi M, Khorasani S, Rezaei N. Pro-tumorigenic and Anti-tumorigenic Roles of Pro-inflammatory Cytokines in Cancer. Handbook of Cancer and Immunology: Springer; 2022. pp. 1–25.
18. Andreu-Sanz D, Kobold S. Role and potential of different T helper cell subsets in adoptive cell therapy. Cancers (Basel). 2023;15(6).
19. Hirahara K, Vahedi G, Ghoreschi K, Yang XP, Nakayamada S, Kanno Y, et al. Helper T-cell differentiation and plasticity: insights from epigenetics. Immunology. 2011;134(3):235–45.
20. Dobrzanski MJ. Expanding roles for CD4 T cells and their subpopulations in tumor immunity and therapy. Front Oncol. 2013;3:63.
21. Saravia J, Chapman NM, Chi H. Helper T cell differentiation. Cell Mol Immunol. 2019;16(7):634–43.
22. Jorgovanovic D, Song M, Wang L, Zhang Y. Roles of IFN-γ in tumor progression and regression: a review. Biomark Res. 2020;8:49.

23. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med. 2003;348(3):203–13.
24. Huang Y, Ma C, Zhang Q, Ye J, Wang F, Zhang Y, et al. CD4 + and CD8 + T cells have opposing roles in breast cancer progression and outcome. Oncotarget. 2015;6(19):17462–78.
25. Karachaliou N, Gonzalez-Cao M, Crespo G, Drozdowskyj A, Aldeguer E, Gimenez-Capitan A, et al. Interferon gamma, an important marker of response to immune checkpoint blockade in non-small cell lung cancer and melanoma patients. Ther Adv Med Oncol. 2018;10:1758834017749748.
26. Hoepner S, Loh JM, Riccadonna C, Derouazi M, Maroun CY, Dietrich PY, et al. Synergy between CD8 T cells and Th1 or Th2 polarised CD4 T cells for adoptive immunotherapy of brain tumours. PLoS ONE. 2013;8(5):e63933.
27. Slattery ML, Lundgreen A, Bondurant KL, Wolff RK. Interferon-signaling pathway: associations with colon and rectal cancer risk and subsequent survival. Carcinogenesis. 2011;32(11):1660–7.
28. Xu X, Wang R, Su Q, Huang H, Zhou P, Luan J, et al. Expression of Th1- Th2- and Th17-associated cytokines in laryngeal carcinoma. Oncol Lett. 2016;12(3):1941–8.
29. Ruterbusch M, Pruner KB, Shehata L, Pepper M. In Vivo CD4(+) T Cell Differentiation and Function: Revisiting the Th1/Th2 Paradigm. Annu Rev Immunol. 2020;38:705 – 25.
30. Paul WE, Zhu J. How are T(H)2-type immune responses initiated and amplified? Nat Rev Immunol. 2010;10(4):225–35.
31. Zhu J. T helper 2 (Th2) cell differentiation, type 2 innate lymphoid cell (ILC2) development and regulation of interleukin-4 (IL-4) and IL-13 production. Cytokine. 2015;75(1):14–24.
32. Ellyard JI, Simson L, Parish CR. Th2-mediated anti-tumour immunity: friend or foe? Tissue Antigens. 2007;70(1):1–11.
33. De Monte L, Reni M, Tassi E, Clavenna D, Papa I, Recalde H, et al. Intratumor T helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer. J Exp Med. 2011;208(3):469–78.
34. Ubukata H, Motohashi G, Tabuchi T, Nagata H, Konishi S, Tabuchi T. Evaluations of interferon-γ/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients. J Surg Oncol. 2010;102(7):742–7.
35. Kusuda T, Shigemasa K, Arihiro K, Fujii T, Nagai N, Ohama K. Relative expression levels of Th1 and Th2 cytokine mRNA are independent prognostic factors in patients with ovarian cancer. Oncol Rep. 2005;13(6):1153–8.
36. Nevala WK, Vachon CM, Leontovich AA, Scott CG, Thompson MA, Markovic SN. Evidence of systemic Th2-driven chronic inflammation in patients with metastatic melanoma. Clin Cancer Res. 2009;15(6):1931–9.
37. Sheu BC, Lin RH, Lien HC, Ho HN, Hsu SM, Huang SC. Predominant Th2/Tc2 polarity of tumor-infiltrating lymphocytes in human cervical cancer. J Immunol. 2001;167(5):2972–8.
38. Burkholder B, Huang RY, Burgess R, Luo S, Jones VS, Zhang W, et al. Tumor-induced perturbations of cytokines and immune cell networks. Biochim Biophys Acta. 2014;1845(2):182–201.
39. DeNardo DG, Barreto JB, Andreu P, Vasquez L, Tawfik D, Kolhatkar N, et al. CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. Cancer Cell. 2009;16(2):91–102.
40. Schreck S, Friebel D, Buettner M, Distel L, Grabenbauer G, Young LS, et al. Prognostic impact of tumour-infiltrating Th2 and regulatory T cells in classical Hodgkin lymphoma. Hematol Oncol. 2009;27(1):31–9.
41. Palma M, Gentilcore G, Heimersson K, Mozaffari F, Näsman-Glaser B, Young E, et al. T cells in chronic lymphocytic leukemia display dysregulated expression of immune checkpoints and activation markers. Haematologica. 2017;102(3):562–72.
42. Yoon NK, Maresh EL, Shen D, Elshimali Y, Apple S, Horvath S, et al. Higher levels of GATA3 predict better survival in women with breast cancer. Hum Pathol. 2010;41(12):1794–801.
43. Tepper RI, Coffman RL, Leder P. An eosinophil-dependent mechanism for the antitumor effect of interleukin-4. Science. 1992;257(5069):548–51.
44. Gooch JL, Christy B, Yee D. STAT6 mediates interleukin-4 growth inhibition in human breast cancer cells. Neoplasia. 2002;4(4):324–31.
45. Schmitt E, Klein M, Bopp T. Th9 cells, new players in adaptive immunity. Trends Immunol. 2014;35(2):61–8.
46. Li Y, Yu Q, Zhang Z, Wang J, Li S, Zhang J, et al. TH9 cell differentiation, transcriptional control and function in inflammation, autoimmune diseases and cancer. Oncotarget. 2016;7(43):71001–12.
47. Kaplan MH, Hufford MM, Olson MR. The development and in vivo function of T helper 9 cells. Nat Rev Immunol. 2015;15(5):295–307.
48. Neurath MF, Kaplan MH. Th9 cells in immunity and immunopathological diseases. Semin Immunopathol. 2017;39(1):1–4.
49. Chen N, Lu K, Li P, Lv X, Wang X. Overexpression of IL-9 induced by STAT6 activation promotes the pathogenesis of chronic lymphocytic leukemia. Int J Clin Exp Pathol. 2014;7(5):2319–23.
50. Kumar S, Dhamija B, Marathe S, Ghosh S, Dwivedi A, Karulkar A, et al. The Th9 Axis reduces the oxidative stress and promotes the Survival of Malignant T Cells in cutaneous T-Cell lymphoma patients. Mol Cancer Res. 2020;18(4):657–68.
51. Feng LL, Gao JM, Li PP, Wang X. IL-9 contributes to immunosuppression mediated by regulatory T cells and mast cells in B-cell non-hodgkin's lymphoma. J Clin Immunol. 2011;31(6):1084–94.
52. Merz H, Houssiau FA, Orscheschek K, Renauld JC, Fliedner A, Herin M, et al. Interleukin-9 expression in human malignant lymphomas: unique association with Hodgkin's disease and large cell anaplastic lymphoma. Blood. 1991;78(5):1311–7.
53. Nagato T, Kobayashi H, Kishibe K, Takahara M, Ogino T, Ishii H, et al. Expression of interleukin-9 in nasal natural killer/T-cell lymphoma cell lines and patients. Clin Cancer Res. 2005;11(23):8250–7.
54. Rivera Vargas T, Humblin E, Végran F, Ghiringhelli F, Apetoh L. T(H)9 cells in anti-tumor immunity. Semin Immunopathol. 2017;39(1):39–46.
55. Lu Y, Wang Q, Xue G, Bi E, Ma X, Wang A, et al. Th9 cells represent a unique subset of CD4(+) T cells endowed with the ability to Eradicate Advanced tumors. Cancer Cell. 2018;33(6):1048–e607.
56. Lu Y, Hong S, Li H, Park J, Hong B, Wang L, et al. Th9 cells promote antitumor immune responses in vivo. J Clin Invest. 2012;122(11):4160–71.
57. Purwar R, Schlapbach C, Xiao S, Kang HS, Elyaman W, Jiang X, et al. Robust tumor immunity to melanoma mediated by interleukin-9-producing T cells. Nat Med. 2012;18(8):1248–53.
58. Végran F, Berger H, Boidot R, Mignot G, Bruchard M, Dosset M, et al. The transcription factor IRF1 dictates the IL-21-dependent anticancer functions of TH9 cells. Nat Immunol. 2014;15(8):758–66.
59. You FP, Zhang J, Cui T, Zhu R, Lv CQ, Tang HT, et al. Th9 cells promote antitumor immunity via IL-9 and IL-21 and demonstrate atypical cytokine expression in breast cancer. Int Immunopharmacol. 2017;52:163–7.
60. Tan H, Wang S, Zhao L. A tumour-promoting role of Th9 cells in hepatocellular carcinoma through CCL20 and STAT3 pathways. Clin Exp Pharmacol Physiol. 2017;44(2):213–21.
61. Ye ZJ, Zhou Q, Yin W, Yuan ML, Yang WB, Xiong XZ, et al. Differentiation and immune regulation of IL-9-producing CD4 + T cells in malignant pleural effusion. Am J Respir Crit Care Med. 2012;186(11):1168–79.
62. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17 + T helper cells. Cell. 2006;126(6):1121–33.
63. Arias C, Sepúlveda P, Castillo RL, Salazar LA. Relationship between hypoxic and Immune pathways activation in the progression of Neuroinflammation: role of HIF-1α and Th17 cells. Int J Mol Sci. 2023;24(4).
64. Akanji MA, Rotimi D, Adeyemi OS. Hypoxia-inducible factors as an alternative source of treatment strategy for Cancer. Oxid Med Cell Longev. 2019;2019:8547846.
65. Harnanik T, Soeroso J, Suryokusumo MG, Juliandhy T. Effects of hyperbaric oxygen on T helper 17/regulatory T polarization in Antigen and Collagen-induced arthritis: hypoxia-inducible Factor-1α as a target. Oman Med J. 2020;35(1):e90.
66. Ren W, Yin J, Duan J, Liu G, Tan B, Yang G, et al. mTORC1 signaling and IL-17 expression: defining pathways and possible therapeutic targets. Eur J Immunol. 2016;46(2):291–9.
67. Cerboni S, Gehrmann U, Preite S, Mitra S. Cytokine-regulated Th17 plasticity in human health and diseases. Immunology. 2021;163(1):3–18.
68. Yang XO, Nurieva R, Martinez GJ, Kang HS, Chung Y, Pappu BP, et al. Molecular antagonism and plasticity of regulatory and inflammatory T cell programs. Immunity. 2008;29(1):44–56.
69. Knochelmann HM, Dwyer CJ, Bailey SR, Amaya SM, Elston DM, Mazza-McCrann JM, et al. When worlds collide: Th17 and Treg cells in cancer and autoimmunity. Cell Mol Immunol. 2018;15(5):458–69.
70. Maruyama T, Kono K, Mizukami Y, Kawaguchi Y, Mimura K, Watanabe M, et al. Distribution of Th17 cells and FoxP3(+) regulatory T cells in tumor-infiltrating lymphocytes, tumor-draining lymph nodes and peripheral blood lymphocytes in patients with gastric cancer. Cancer Sci. 2010;101(9):1947–54.

71. Fu LQ, Yang X, Cai MH, Yao JY, Jin WW, Mou YP, et al. Role of Treg/Th17 Imbalance, Microbiota and miRNAs in Pancreatic Cancer: Therapeutic options. Crit Rev Immunol. 2020;40(1):75–92.
72. Koyama K, Kagamu H, Miura S, Hiura T, Miyabayashi T, Itoh R, et al. Reciprocal CD4 + T-cell balance of effector CD62Llow CD4 + and CD62LhighCD25 + CD4 + regulatory T cells in small cell lung cancer reflects disease stage. Clin Cancer Res. 2008;14(21):6770–9.
73. Zhou J, Li X, Wu X, Zhang T, Zhu Q, Wang X, et al. Exosomes released from Tumor-Associated macrophages transfer miRNAs that induce a Treg/Th17 Cell Imbalance in Epithelial Ovarian Cancer. Cancer Immunol Res. 2018;6(12):1578–92.
74. Qianmei Y, Zehong S, Guang W, Hui L, Lian G. Recent advances in the role of Th17/Treg cells in tumor immunity and tumor therapy. Immunol Res. 2021;69(5):398–414.
75. Bailey SR, Nelson MH, Himes RA, Li Z, Mehrotra S, Paulos CM. Th17 cells in cancer: the ultimate identity crisis. Front Immunol. 2014;5:276.
76. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. Nat Immunol. 2009;10(8):864–71.
77. Plank MW, Kaiko GE, Maltby S, Weaver J, Tay HL, Shen W, et al. Th22 cells form a distinct th lineage from Th17 cells in Vitro with Unique Transcriptional properties and Tbet-Dependent Th1 plasticity. J Immunol. 2017;198(5):2182–90.
78. Jiang R, Tan Z, Deng L, Chen Y, Xia Y, Gao Y, et al. Interleukin-22 promotes human hepatocellular carcinoma by activation of STAT3. Hepatology. 2011;54(3):900–9.
79. Jiang R, Wang H, Deng L, Hou J, Shi R, Yao M, et al. IL-22 is related to development of human colon cancer by activation of STAT3. BMC Cancer. 2013;13:59.
80. Yao Y, Yang G, Lu G, Ye J, Cui L, Zeng Z, et al. Th22 Cells/IL-22 serves as a Protumor Regulator to drive poor prognosis through the JAK-STAT3/MAPK/AKT signaling pathway in Non-small-cell Lung Cancer. J Immunol Res. 2022;2022:8071234.
81. Zhuang Y, Peng LS, Zhao YL, Shi Y, Mao XH, Guo G, et al. Increased intratumoral IL-22-producing CD4(+) T cells and Th22 cells correlate with gastric cancer progression and predict poor patient survival. Cancer Immunol Immunother. 2012;61(11):1965–75.
82. Wang T, Zhang Z, Xing H, Wang L, Zhang G, Yu N, et al. Elevated Th22 cells and related cytokines in patients with epithelial ovarian cancer. Med (Baltim). 2017;96(43):e8359.
83. Briukhovetska D, Suarez-Gosalvez J, Voigt C, Markota A, Giannou AD, Schübel M, et al. T cell-derived interleukin-22 drives the expression of CD155 by cancer cells to suppress NK cell function and promote metastasis. Immunity. 2023;56(1):143–e6111.
84. Rui J, Chunming Z, Binbin G, Na S, Shengxi W, Wei S. IL-22 promotes the progression of breast cancer through regulating HOXB-AS5. Oncotarget. 2017;8(61):103601–12.
85. Hernandez P, Gronke K, Diefenbach A. A catch-22: Interleukin-22 and cancer. Eur J Immunol. 2018;48(1):15–31.
86. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. Nature. 2007;445(7128):648–51.
87. Gurney AL. IL-22, a Th1 cytokine that targets the pancreas and select other peripheral tissues. Int Immunopharmacol. 2004;4(5):669–77.
88. Zhu JT. Helper cell differentiation, heterogeneity, and plasticity. Cold Spring Harb Perspect Biol. 2018;10(10).
89. Ahearne MJ, Willimott S, Piñon L, Kennedy DB, Miall F, Dyer MJ, et al. Enhancement of CD154/IL4 proliferation by the T follicular helper (tfh) cytokine, IL21 and increased numbers of circulating cells resembling tfh cells in chronic lymphocytic leukaemia. Br J Haematol. 2013;162(3):360–70.
90. Gu-Trantien C, Loi S, Garaud S, Equeter C, Libin M, de Wind A, et al. CD4$^+$ follicular helper T cell infiltration predicts breast cancer survival. J Clin Invest. 2013;123(7):2873–92.
91. Ma QY, Huang DY, Zhang HJ, Chen J, Miller W, Chen XF. Function of follicular helper T cell is impaired and correlates with survival time in non-small cell lung cancer. Int Immunopharmacol. 2016;41:1–7.
92. Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, Obenauf AC, et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity. 2013;39(4):782–95.
93. Crotty ST, Follicular Helper. Cell Biology: a decade of Discovery and diseases. Immunity. 2019;50(5):1132–48.
94. Yurchenko E, Tritt M, Hay V, Shevach EM, Belkaid Y, Piccirillo CA. CCR5-dependent homing of naturally occurring CD4 + regulatory T cells to sites of Leishmania major infection favors pathogen persistence. J Exp Med. 2006;203(11):2451–60.
95. Rudensky AY. Regulatory T cells and Foxp3. Immunol Rev. 2011;241(1):260–8.
96. Togashi Y, Shitara K, Nishikawa H. Regulatory T cells in cancer immunosuppression - implications for anticancer therapy. Nat Reviews Clin Oncol. 2019;16(6):356–71.
97. Núñez NG, Tosello Boari J, Ramos RN, Richer W, Cagnard N, Anderfuhren CD, et al. Tumor invasion in draining lymph nodes is associated with Treg accumulation in breast cancer patients. Nat Commun. 2020;11(1):3272.
98. Qureshi OS, Zheng Y, Nakamura K, Attridge K, Manzotti C, Schmidt EM, et al. Trans-endocytosis of CD80 and CD86: a molecular basis for the cell-extrinsic function of CTLA-4. Science. 2011;332(6029):600–3.
99. Kumagai S, Togashi Y, Kamada T, Sugiyama E, Nishinakamura H, Takeuchi Y, et al. The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies. Nat Immunol. 2020;21(11):1346–58.
100. Chaudhry A, Samstein RM, Treuting P, Liang Y, Pils MC, Heinrich JM, et al. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. Immunity. 2011;34(4):566–78.
101. Verstappen GM, Corneth OBJ, Bootsma H, Kroese FGM. Th17 cells in primary Sjögren's syndrome: pathogenicity and plasticity. J Autoimmun. 2018;87:16–25.
102. Muranski P, Restifo NP. Essentials of Th17 cell commitment and plasticity. Blood. 2013;121(13):2402–14.
103. Pan Y, Yang W, Tang B, Wang X, Zhang Q, Li W et al. The protective and pathogenic role of Th17 cell plasticity and function in the tumor microenvironment. Front Immunol. 2023;14.
104. Bhaumik S, Basu R. Cellular and Molecular dynamics of Th17 differentiation and its developmental plasticity in the Intestinal Immune Response. Front Immunol. 2017;8:254.
105. Ciofani M, Madar A, Galan C, Sellars M, Mace K, Pauli F, et al. A validated regulatory network for Th17 cell specification. Cell. 2012;151(2):289–303.
106. Stadhouders R, Lubberts E, Hendriks RW. A cellular and molecular view of T helper 17 cell plasticity in autoimmunity. J Autoimmun. 2018;87:1–15.
107. Nistala K, Adams S, Cambrook H, Ursu S, Olivito B, de Jager W, et al. Th17 plasticity in human autoimmune arthritis is driven by the inflammatory environment. Proc Natl Acad Sci U S A. 2010;107(33):14751–6.
108. Lee YK, Turner H, Maynard CL, Oliver JR, Chen D, Elson CO, et al. Late developmental plasticity in the T helper 17 lineage. Immunity. 2009;30(1):92–107.
109. Noster R, Riedel R, Mashreghi MF, Radbruch H, Harms L, Haftmann C, et al. IL-17 and GM-CSF expression are antagonistically regulated by human T helper cells. Sci Transl Med. 2014;6(241):241ra80.
110. Meng L, Bai Z, He S, Mochizuki K, Liu Y, Purushe J, et al. The notch ligand DLL4 defines a capability of human dendritic cells in regulating Th1 and Th17 differentiation. J Immunol. 2016;196(3):1070–80.
111. Yang ZZ, Novak AJ, Ziesmer SC, Witzig TE, Ansell SM. Malignant B cells skew the balance of regulatory T cells and TH17 cells in B-cell non-hodgkin's lymphoma. Cancer Res. 2009;69(13):5522–30.
112. Zou W, Restifo NP. T(H)17 cells in tumour immunity and immunotherapy. Nat Rev Immunol. 2010;10(4):248–56.
113. Niu Y, Zhou Q. Th17 cells and their related cytokines: vital players in progression of malignant pleural effusion. Cell Mol Life Sci. 2022;79(4):194.
114. Hu X, Liu X, Moisan J, Wang Y, Lesch CA, Spooner C, et al. Synthetic RORgamma agonists regulate multiple pathways to enhance antitumor immunity. Oncoimmunology. 2016;5(12):e1254854.
115. Tanaka A, Sakaguchi S. Regulatory T cells in cancer immunotherapy. Cell Res. 2017;27(1):109–18.
116. Ye J, Su X, Hsueh EC, Zhang Y, Koenig JM, Hoft DF, et al. Human tumor-infiltrating Th17 cells have the capacity to differentiate into IFN-γ + and FOXP3 + T cells with potent suppressive function. Eur J Immunol. 2011;41(4):936–51.
117. Kryczek I, Wu K, Zhao E, Wei S, Vatan L, Szeliga W, et al. IL-17 + regulatory T cells in the microenvironments of chronic inflammation and cancer. J Immunol. 2011;186(7):4388–95.
118. Huang C, Fu ZX. Localization of IL-17 + Foxp3 + T cells in esophageal cancer. Immunol Invest. 2011;40(4):400–12.
119. Wang YH, Voo KS, Liu B, Chen CY, Uygungil B, Spoede W, et al. A novel subset of CD4(+) T(H)2 memory/effector cells that produce inflammatory IL-17 cytokine and promote the exacerbation of chronic allergic asthma. J Exp Med. 2010;207(11):2479–91.
120. Hirota K, Turner J-E, Villa M, Duarte JH, Demengeot J, Steinmetz OM, et al. Plasticity of TH17 cells in Peyer's patches is responsible for the induction of T cell–dependent IgA responses. Nat Immunol. 2013;14(4):372–9.

121. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. CA Cancer J Clin. 2014;64(1):52–62.
122. Yu L-Y, Tang J, Zhang C-M, Zeng W-J, Yan H, Li M-P et al. New immunotherapy strategies in breast Cancer. Int J Environ Res Public Health. 2017;14(1).
123. Karpisheh V, Ahmadi M, Abbaszadeh-Goudarzi K, Mohammadpour Saray M, Barshidi A, Mohammadi H, et al. The role of Th17 cells in the pathogenesis and treatment of breast cancer. Cancer Cell Int. 2022;22(1):108.
124. Asadzadeh Z, Mohammadi H, Safarzadeh E, Hemmatzadeh M, Mahdian-Shakib A, Jadidi-Niaragh F, et al. The paradox of Th17 cell functions in tumor immunity. Cell Immunol. 2017;322:15–25.
125. Joshi N, Hajizadeh F, Ansari Dezfouli E, Zekiy AO, Nabi Afjadi M, Mousavi SM, et al. Silencing STAT3 enhances sensitivity of cancer cells to doxorubicin and inhibits tumor progression. Life Sci. 2021;275:119369.
126. Du J-W, Xu K-Y, Fang L-Y, Qi X-L. Interleukin-17, produced by lymphocytes, promotes tumor growth and angiogenesis in a mouse model of breast cancer. Mol Med Rep. 2012;6(5):1099–102.
127. Chen W-C, Lai Y-H, Chen H-Y, Guo H-R, Su I-J, Chen HHW. Interleukin-17-producing cell infiltration in the breast cancer tumour microenvironment is a poor prognostic factor. Histopathology. 2013;63(2):225–33.
128. Kim K, Kim G, Kim J-Y, Yun HJ, Lim S-C, Choi HS. Interleukin-22 promotes epithelial cell transformation and breast tumorigenesis via MAP3K8 activation. Carcinogenesis. 2014;35(6):1352–61.
129. Benevides L, Cardoso CRB, Tiezzi DG, Marana HRC, Andrade JM, Silva JS. Enrichment of regulatory T cells in invasive breast tumor correlates with the upregulation of IL-17A expression and invasiveness of the tumor. Eur J Immunol. 2013;43(6):1518–28.
130. Thibaudin M, Chaix M, Boidot R, Végran F, Derangère V, Limagne E, et al. Human ectonucleotidase-expressing CD25(high) Th17 cells accumulate in breast cancer tumors and exert immunosuppressive functions. Oncoimmunology. 2016;5(1):e1055444.
131. Ma K, Yang L, Shen R, Kong B, Chen W, Liang J, et al. Th17 cells regulate the production of CXCL1 in breast cancer. Int Immunopharmacol. 2018;56:320–9.
132. Avalos-Navarro G, Muñoz-Valle JF, Daneri-Navarro A, Quintero-Ramos A, Franco-Topete RA, Morán-Mendoza AJ, et al. Circulating soluble levels of MIF in women with breast cancer in the molecular subtypes: relationship with Th17 cytokine profile. Clin Exp Med. 2019;19(3):385–91.
133. Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau C-S, et al. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. Nature. 2015;522(7556):345–8.
134. Kim G, Khanal P, Lim S-C, Yun HJ, Ahn S-G, Ki SH, et al. Interleukin-17 induces AP-1 activity and cellular transformation via upregulation of tumor progression locus 2 activity. Carcinogenesis. 2013;34(2):341–50.
135. Huang S-C, Wei P-C, Hwang-Verslues WW, Kuo W-H, Jeng Y-M, Hu C-M, et al. TGF-β1 secreted by Tregs in lymph nodes promotes breast cancer malignancy via up-regulation of IL-17RB. EMBO Mol Med. 2017;9(12):1660–80.
136. Benatar T, Cao MY, Lee Y, Lightfoot J, Feng N, Gu X, et al. IL-17E, a proinflammatory cytokine, has antitumor efficacy against several tumor types in vivo. Cancer Immunol Immunotherapy: CII. 2010;59(6):805–17.
137. Jiang Z, Chen J, Du X, Cheng H, Wang X, Dong C. IL-25 blockade inhibits metastasis in breast cancer. Protein Cell. 2017;8(3):191–201.
138. Yang L, Qi Y, Hu J, Tang L, Zhao S, Shan B. Expression of Th17 cells in breast cancer tissue and its association with clinical parameters. Cell Biochem Biophys. 2012;62(1):153–9.
139. Faucheux L, Grandclaudon M, Perrot-Dockès M, Sirven P, Berger F, Hamy AS et al. A multivariate Th17 metagene for prognostic stratification in T cell non-inflamed triple negative breast cancer. Oncoimmunology. 2019.
140. Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature. 2007;445(7130):851–7.
141. Miller AJ, Mihm MC. Jr. Melanoma. N Engl J Med. 2006;355(1):51–65.
142. Chen C, Gao F-H. Th17 cells paradoxical roles in Melanoma and potential application in Immunotherapy. Front Immunol. 2019;10:187.
143. Spivey TL, De Giorgi V, Zhao Y, Bedognetti D, Pos Z, Liu Q, et al. The stable traits of melanoma genetics: an alternate approach to target discovery. BMC Genomics. 2012;13:156.
144. Tomei S, Bedognetti D, De Giorgi V, Sommariva M, Civini S, Reinboth J, et al. The immune-related role of BRAF in melanoma. Mol Oncol. 2015;9(1):93–104.
145. Tomei S, Bedognetti D, De Giorgi V, Sommariva M, Civini S, Reinboth J, et al. The immune-related role of BRAF in melanoma. J Translational Med. 2015;13(1):K19.
146. Holderfield M, Deuker MM, McCormick F, McMahon M. Targeting RAF kinases for cancer therapy: BRAF-mutated melanoma and beyond. Nat Rev Cancer. 2014;14(7):455–67.
147. Muranski P, Borman ZA, Kerkar SP, Klebanoff CA, Ji Y, Sanchez-Perez L, et al. Th17 cells are long lived and retain a stem cell-like molecular signature. Immunity. 2011;35(6):972–85.
148. Hayata K, Iwahashi M, Ojima T, Katsuda M, Iida T, Nakamori M, et al. Inhibition of IL-17A in tumor microenvironment augments cytotoxicity of tumor-infiltrating lymphocytes in tumor-bearing mice. PLoS ONE. 2013;8(1):e53131.
149. Wang L, Yi T, Kortylewski M, Pardoll DM, Zeng D, Yu H. IL-17 can promote tumor growth through an IL-6-Stat3 signaling pathway. J Exp Med. 2009;206(7):1457–64.
150. Koenen HJPM, Smeets RL, Vink PM, van Rijssen E, Boots AMH, Joosten I. Human CD25highFoxp3pos regulatory T cells differentiate into IL-17-producing cells. Blood. 2008;112(6):2340–52.
151. Valmori D, Raffin C, Raimbaud I, Ayyoub M. Human RORγt+TH17 cells preferentially differentiate from naive FOXP3+Treg in the presence of lineage-specific polarizing factors. Proc Natl Acad Sci USA. 2010;107(45):19402–7.
152. Ye J, Livergood R, Peng G. The role and regulation of human Th17 cells in Tumor Immunity. Am J Pathol. 2012;182.
153. Su X, Ye J, Hsueh EC, Zhang Y, Hoft DF, Peng G. Tumor microenvironments direct the recruitment and expansion of human Th17 cells. Journal of immunology (Baltimore, Md: 1950). 2010;184(3):1630-41.
154. Muranski P, Boni A, Antony PA, Cassard L, Irvine KR, Kaiser A, et al. Tumor-specific Th17-polarized cells eradicate large established melanoma. Blood. 2008;112(2):362–73.
155. Martin-Orozco N, Muranski P, Chung Y, Yang XO, Yamazaki T, Lu S, et al. T helper 17 cells promote cytotoxic T cell activation in tumor immunity. Immunity. 2009;31(5):787–98.
156. Ankathatti Munegowda M, Deng Y, Mulligan SJ, Xiang J. Th17 and Th17-stimulated $CD8^+$ T cells play a distinct role in Th17-induced preventive and therapeutic antitumor immunity. Cancer Immunol Immunotherapy: CII. 2011;60(10):1473–84.
157. Hu X, Majchrzak K, Liu X, Wyatt MM, Spooner CJ, Moisan J, et al. In Vitro Priming of Adoptively Transferred T Cells with a RORγ agonist confers durable memory and stemness in vivo. Cancer Res. 2018;78(14):3888–98.
158. Hoechst B, Gamrekelashvili J, Manns MP, Greten TF, Korangy F. Plasticity of human Th17 cells and iTregs is orchestrated by different subsets of myeloid cells. Blood. 2011;117(24):6532–41.
159. Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. Int J Cancer. 2005;117(2):294–9.
160. Torre LA, Siegel RL, Jemal A. Lung Cancer statistics. Adv Exp Med Biol. 2016;893:1–19.
161. Tlsty TD, Coussens LM. Tumor stroma and regulation of cancer development. Annu Rev Pathol. 2006;1:119–50.
162. Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhouser ML, Wener MH, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol. 2009;27(21):3437–44.
163. Wang R, Yang L, Zhang C, Wang R, Zhang Z, He Q, et al. Th17 cell-derived IL-17A promoted tumor progression via STAT3/NF-κB/Notch1 signaling in non-small cell lung cancer. Oncoimmunology. 2018;7(11):e1461303.
164. Duan M-C, Han W, Jin P-W, Wei Y-P, Wei Q, Zhang L-M, et al. Disturbed Th17/Treg Balance in patients with non-small cell Lung Cancer. Inflammation. 2015;38(6):2156–65.
165. Chen G, Zhang P-G, Li J-S, Duan J-J, Su W, Guo S-P, et al. Th17 cell frequency and IL-17A production in peripheral blood of patients with non-small-cell lung cancer. J Int Med Res. 2020;48(6):300060520925948.
166. Liao C, Yu Z-B, Meng G, Wang L, Liu Q-Y, Chen L-T, et al. Association between Th17-related cytokines and risk of non-small cell lung cancer among patients with or without chronic obstructive pulmonary disease. Cancer. 2015;121(Suppl 17):3122–9.
167. Salazar Y, Zheng X, Brunn D, Raifer H, Picard F, Zhang Y et al. Microenvironmental Th9 and Th17 lymphocytes induce metastatic spreading in lung cancer. United States2020.
168. Chang SH. Tumorigenic Th17 cells in oncogenic Kras-driven and inflammation-accelerated lung cancer. Oncoimmunology. 2015;4(1):e955704.
169. Armstrong D, Chang C-Y, Lazarus DR, Corry D, Kheradmand F. Lung Cancer Heterogeneity in Modulation of Th17/IL17A responses. Front Oncol. 2019;9:1384.
170. Xu L, Wang C, Zhou Y, Ren T, Wen Z. CpG oligonucleotides induce the differentiation of CD4(+)Th17 cells by triggering plasmacytoid dendritic cells in adoptively cell transfer immunotherapy. Immunol Lett. 2012;142(1–2):55–63.

171. Guéry L, Dubrot J, Lippens C, Brighouse D, Malinge P, Irla M, et al. Ag-presenting CpG-activated pDCs prime Th17 cells that induce tumor regression. Cancer Res. 2014;74(22):6430–40.
172. Doulabi H, Rastin M, Shabahangh H, Maddah G, Abdollahi A, Nosratabadi R, et al. Analysis of Th22, Th17 and CD4(+)cells co-producing IL-17/IL-22 at different stages of human colon cancer. Biomed Pharmacother. 2018;103:1101–6.
173. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol. 2013;14(10):1014–22.
174. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
175. De Simone V, Pallone F, Monteleone G, Stolfi C. Role of T(H)17 cytokines in the control of colorectal cancer. Oncoimmunology. 2013;2(12):e26617.
176. Liu J, Duan Y, Cheng X, Chen X, Xie W, Long H, et al. IL-17 is associated with poor prognosis and promotes angiogenesis via stimulating VEGF production of cancer cells in colorectal carcinoma. Biochem Biophys Res Commun. 2011;407(2):348–54.
177. Blatner NR, Mulcahy MF, Dennis KL, Scholtens D, Bentrem DJ, Phillips JD, et al. Expression of RORgammat marks a pathogenic regulatory T cell subset in human colon cancer. Sci Transl Med. 2012;4(164):164ra59.
178. Stolfi C, Rizzo A, Franze E, Rotondi A, Fantini MC, Sarra M, et al. Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. J Exp Med. 2011;208(11):2279–90.
179. Cui G, Yuan A, Goll R, Florholmen J. IL-17A in the tumor microenvironment of the human colorectal adenoma-carcinoma sequence. Scand J Gastroenterol. 2012;47(11):1304–12.
180. Yoshida N, Kinugasa T, Miyoshi H, Sato K, Yuge K, Ohchi T, et al. A high RORgammaT/CD3 ratio is a strong prognostic factor for postoperative survival in Advanced Colorectal Cancer: analysis of helper T cell lymphocytes (Th1, Th2, Th17 and Regulatory T Cells). Ann Surg Oncol. 2016;23(3):919–27.
181. Liu X, Wang X, Yang Q, Luo L, Liu Z, Ren X, et al. Th17 cells secrete TWEAK to trigger epithelial-mesenchymal transition and promote colorectal Cancer Liver Metastasis. Cancer Res. 2024;84(8):1352–71.
182. O'Sullivan T, Saddawi-Konefka R, Gross E, Tran M, Mayfield SP, Ikeda H, et al. Interleukin-17D mediates tumor rejection through recruitment of natural killer cells. Cell Rep. 2014;7(4):989–98.
183. Lu L, Pan K, Zheng HX, Li JJ, Qiu HJ, Zhao JJ, et al. IL-17A promotes immune cell recruitment in human esophageal cancers and the infiltrating dendritic cells represent a positive prognostic marker for patient survival. J Immunother. 2013;36(8):451–8.
184. Cui G. T(H)9, T(H)17, and T(H)22 cell subsets and their main Cytokine products in the pathogenesis of Colorectal Cancer. Front Oncol. 2019;9:1002.
185. Tong Z, Yang XO, Yan H, Liu W, Niu X, Shi Y, et al. A protective role by interleukin-17F in colon tumorigenesis. PLoS ONE. 2012;7(4):e34959.
186. Amicarella F, Muraro MG, Hirt C, Cremonesi E, Padovan E, Mele V, et al. Dual role of tumour-infiltrating T helper 17 cells in human colorectal cancer. Gut. 2017;66(4):692–704.
187. Lan YT, Fan XP, Fan YC, Zhao J, Wang K. Change in the Treg/Th17 cell imbalance in hepatocellular carcinoma patients and its clinical value. Med (Baltim). 2017;96(32):e7704.
188. Bian J, Lin J, Long J, Yang X, Yang X, Lu X, et al. T lymphocytes in hepatocellular carcinoma immune microenvironment: insights into human immunology and immunotherapy. Am J Cancer Res. 2020;10(12):4585–606.
189. Zhang JP, Yan J, Xu J, Pang XH, Chen MS, Li L, et al. Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients. J Hepatol. 2009;50(5):980–9.
190. Li J, Lau GK, Chen L, Dong SS, Lan HY, Huang XR, et al. Interleukin 17A promotes hepatocellular carcinoma metastasis via NF-kB induced matrix metalloproteinases 2 and 9 expression. PLoS ONE. 2011;6(7):e21816.
191. Pan Y, Yang W, Tang B, Wang X, Zhang Q, Li W, et al. The protective and pathogenic role of Th17 cell plasticity and function in the tumor microenvironment. Front Immunol. 2023;14:1192303.
192. Huang S, Qu N, Men Y, Liu Z. Effects of thermal ablation on Treg/Th17 in hepatocellular carcinoma of mice. Eur J Inflamm. 2019;17:2058739219832489.
193. Feng R, Cui Z, Liu Z, Zhang Y. Upregulated microRNA-132 in T helper 17 cells activates hepatic stellate cells to promote hepatocellular carcinoma cell migration in vitro. Scand J Immunol. 2021;93(5):e13007.
194. Zhang H, Jiang Z, Zhang L. Dual effect of T helper cell 17 (Th17) and regulatory T cell (Treg) in liver pathological process: from occurrence to end stage of disease. Int Immunopharmacol. 2019;69:50–9.
195. Song M, Wang L, Jiang S, Liang J, Li W, Rao W, et al. Pathogenic Th17 cell-mediated liver fibrosis contributes to resistance to PD-L1 antibody immunotherapy in hepatocellular carcinoma. Int Immunopharmacol. 2024;129:111601.
196. Guo Y, Xiao Z, Yang L, Gao Y, Zhu Q, Hu L, et al. Hypoxia–inducible factors in hepatocellular carcinoma (review). Oncol Rep. 2020;43(1):3–15.
197. Chen C, Lou T. Hypoxia inducible factors in hepatocellular carcinoma. Oncotarget. 2017;8(28):46691–703.
198. Sin SQ, Mohan CD, Goh RMW, You M, Nayak SC, Chen L, et al. Hypoxia signaling in hepatocellular carcinoma: challenges and therapeutic opportunities. Cancer Metastasis Rev. 2023;42(3):741–64.
199. Xia Y, Brown ZJ, Huang H, Tsung A. Metabolic reprogramming of immune cells: shaping the tumor microenvironment in hepatocellular carcinoma. Cancer Med. 2021;10(18):6374–83.
200. Semenza GL. Hypoxia-inducible factor 1 (HIF-1) pathway. Sci STKE. 2007;2007(407):cm8.
201. Dang EV, Barbi J, Yang HY, Jinasena D, Yu H, Zheng Y, et al. Control of T(H)17/T(reg) balance by hypoxia-inducible factor 1. Cell. 2011;146(5):772–84.
202. Manoochehri Khoshinani H, Afshar S, Najafi R, Hypoxia. A double-edged Sword in Cancer Therapy. Cancer Invest. 2016;34(10):536–45.
203. Mehner C, Hockla A, Miller E, Ran S, Radisky DC, Radisky ES. Tumor cell-produced matrix metalloproteinase 9 (MMP-9) drives malignant progression and metastasis of basal-like triple negative breast cancer. Oncotarget. 2014;5(9):2736–49.
204. Esfahani K, Miller WH. Jr. Reversal of autoimmune toxicity and loss of Tumor Response by Interleukin-17 blockade. N Engl J Med. 2017;376(20):1989–91.
205. Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, et al. Phenotypic and functional features of human Th17 cells. J Exp Med. 2007;204(8):1849–61.
206. Shang Q, Yu X, Sun Q, Li H, Sun C, Liu L. Polysaccharides regulate Th1/Th2 balance: a new strategy for tumor immunotherapy. Volume 170. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie; 2024. p. 115976.
207. Zou X, Huo F, Sun L, Huang J. Peripheral helper T cells in human diseases. J Autoimmun. 2024;145:103218.
208. Zheng Z, Wieder T, Mauerer B, Schäfer L, Kesselring R, Braumüller H. T cells in Colorectal Cancer: unravelling the function of different T cell subsets in the Tumor Microenvironment. Int J Mol Sci. 2023;24(14).
209. Jou E. Type 1 and type 2 cytokine-mediated immune orchestration in the tumour microenvironment and their therapeutic potential. Explor Target antitumor Therapy. 2023;4(3):474–97.
210. Khokhar M, Purohit P. The emerging role of T helper 9 (Th9) cells in immunopathophysiology: a comprehensive review of their effects and responsiveness in various disease states. Int Rev Immunol. 2024:1–20.
211. Roostaee A, Yaghobi R, Afshari A, Jafarinia M. Regulatory role of T helper 9/interleukin-9: transplantation view. Heliyon. 2024;10(4):e26359.
212. Cui H, Wang N, Li H, Bian Y, Wen W, Kong X, et al. The dynamic shifts of IL-10-producing Th17 and IL-17-producing Treg in health and disease: a crosstalk between ancient Yin-Yang theory and modern immunology. Cell Communication Signaling: CCS. 2024;22(1):99.
213. Xing J, Man C, Liu Y, Zhang Z, Peng H. Factors impacting the benefits and pathogenicity of Th17 cells in the tumor microenvironment. Front Immunol. 2023;14:1224269.
214. Wang ZN, Xu T, Liu KS. Research progress on Th22 cells and related cytokines in tumors: current status and future perspectives. Am J cancer Res. 2023;13(8):3315–23.
215. Sun L, Su Y, Jiao A, Wang X, Zhang B. T cells in health and disease. Signal Transduct Target Therapy. 2023;8(1):235.
216. Wang Y, Li J, Nakahata S, Iha H. Complex Role of Regulatory T Cells (Tregs) in the Tumor Microenvironment: their Molecular mechanisms and Bidirectional effects on Cancer Progression. Int J Mol Sci. 2024;25(13).
217. Wang W, Ding M, Wang Q, Song Y, Huo K, Chen X, et al. Advances in Foxp3 + regulatory T cells (Foxp3 + Treg) and key factors in digestive malignancies. Front Immunol. 2024;15:1404974.
218. Wang JN, Zheng G, Wu W, Huang H. Follicular helper T cells: emerging roles in lymphomagenesis. J Leukoc Biol. 2024;116(1):54–63.
219. Cui C, Craft J, Joshi NS. T follicular helper cells in cancer, tertiary lymphoid structures, and beyond. Semin Immunol. 2023;69:101797.

Publisher's note