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REVIEW

Th17 cells: positive or negative role in tumor?

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Abstract Th17 cells have been recently identified as a distinct Th cell lineage and found in an experimental animal model of cancer and in human cancers, but whether these cells promote tumor growth or regulate antitumor responses remains controversial. This review provides a summary of the current literature regarding interleukin (IL)-17/IL-23 and Th17 cells in cancer and discusses their potential roles in cancer development. Finally, we note several issues in this research area that must be resolved before the design of novel therapeutic approaches specifically targeting Th17 cells in cancer become feasible.

Keywords Th17 cells · IL-17 · IL-23 · RORγt · Tumor immunity

Introduction

CD4+ T cells are essential in regulating the immune response in that they coordinate the functions of other immune cell types. Following activation, naive CD4+ T cells can be induced to differentiate into various Th subsets. Approximately 20 years ago, it was shown that CD4+ T helper cells differentiate into Th1 or Th2 subsets with distinct cytokine profiles and functions [1]. Th1 cells typically produce interferon (IFN)-γ and are involved in autoimmune diseases and immunity against intracellular pathogens. Th2 cells produce interleukin (IL)-4, IL-5, and IL-13 and participate in humoral immunity against parasites and in allergic reactions [2–4]. CD4+ Th cells can also develop into T regulatory (Treg) cells as defined by expression of forkhead box P3 (FoxP3). They play an anti-inflammatory role and maintain tolerance to self-components by contact-dependent suppression or by releasing anti-inflammatory cytokines such as transforming growth factor (TGF) β, IL-10 [5–9].

More recently, a novel type of CD4+ Th cell, Th17, was identified in both mice and human [10–18]. Th17 cells are characterized by the production of IL-17A, IL-17F, IL-21, IL-22, IL-26 (in humans), and CCL20 [19–21]. There is growing evidence that in both mice and humans Th17 cells are pathogenic in inflammation and in autoimmune diseases [13, 22–27]. However, there is little information on the prevalence and regulation of Th17 cells in cancer. This review provides a summary of the development and transcriptional programming of Th17 cells and highlights our current knowledge on IL-17/IL-23 and Th17 cells in cancer immunity.

Development and plasticity of Th17 cells

The development of Th17 cells is independent of the cytokines required for Th1 or Th2 differentiation; indeed, IFN-γ and IL-4 inhibit IL-23-dependent IL-17 production (Fig. 1). Several groups have found differences in the development and regulation of Th17 cells in humans versus mice [15, 28, 29]. TGF-β and IL-6 are required to induce the development of Th17 cells in mice [30–33]. Although IL-23 is not needed for the early differentiation of mice Th17 cells, it seems to be important in the expansion, maintenance, and/or survival of the Th17 cell subset [30–33]. However, the precise conditions for human Th17 cell development are still not completely understood and remain controversial. Some groups reported that IL-1β,

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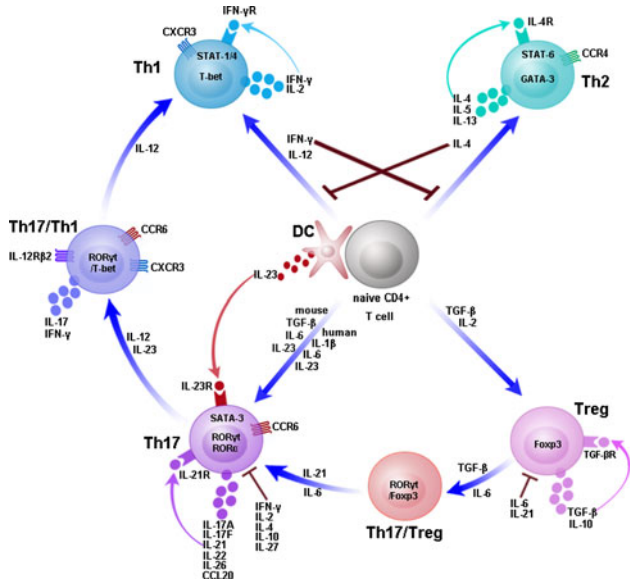

Fig. 1 Development and plasticity of T helper cell subsets. Naive CD4+ T cells can differentiate into Th1, Th2, Treg, or Th17 cells under the influence of different cytokines. IL-12 enhances expression of T-bet and STAT-1/4 and promotes development of Th1 cells, which secrete IFN-γ and IL-2. IL-4 enhances expression of GATA-3 and STAT-6 and promotes development of Th2 cells, which secrete IL-4, IL-5, and IL-13. TGF-β and IL-2 promote induction of Treg cells, which secrete TGF-β and IL-10. TGF-β, IL-6, IL-23 or IL-1β promote development of Th17 cells, which secrete IL-17A, IL-17F, IL-21, IL-22, IL-26 (in humans), and CCL20. IL-23 produced by dendritic cell (DC) allows the expansion, maintenance, and/or survival of Th17 cells. IFN-γ, IL-4, IL-21, and TGF-β drive T helper cell subset development in an autocrine manner. Th17/Th1 and Th17/Treg cell intermediates display intermediate phenotypes. Th17 cells can arise from Treg cells and convert into Th1 cells

IL-6, and IL-23 were sufficient to promote Th17 cell differentiation in humans and that TGF-β is not needed [15, 29, 34]. In contrast, subsequent studies showed a requirement for TGF-β in the induction of human Th17 cells [35–37]. It has been recently shown in both mice and humans that TGF-β is not essential in Th17 cell development, in fact it has been demonstrated that TGF-β plays only an indirect role by suppressing Th1 and Th2 cell development [38, 39]. Nonetheless, it is largely agreed that, in contrast to mice, the combination of TGF-β and IL-6 alone is not sufficient to drive human Th17 cell differentiation. IL-1β and IL-23 have critical functions in the progress of human Th17 cell development while other cytokines direct the development and regulation of these cells. The discrepancy between humans and mice has been attributed to the different cell origins. So far, all studies agree that mouse Th17 cells share a common origin with Treg cells. However, Cosmi et al. have recently shown that CD161 is expressed by human Th17 cells and that Th17 cells originate from a naive CD4+ CD161+ cell present in umbilical cord blood (UCB) and thymus [40]. IL-21, a member of the IL-2 cytokine family, was not only produced by Th17 cells but also shown to be a component of an autocrine loop driving mouse and human Th17 cell development [36, 41–43]. IL-2, a growth factor for most T cells, has been shown to promote Foxp3 expression in Th17 cells and to inhibit cellular differentiation [44]. Two groups demonstrated that IL-10 negatively regulates the differentiation of Th17 cells in mice and humans [45, 46]. IL-27 suppressed Th17 differentiation by a mechanism involving signal transducers and activators of transcription (STAT) 1 [47, 48].

The discovery that the early differentiation of Treg and Th17 cells from naive CD4+ T cells shares a requirement for TGF-β indicated that there is substantial plasticity in the early and late stages of Th17 and Treg cell development [30, 49]. In the two lineages, TGF-β-induced differentiation appears to be reciprocally related, since naive CD4+ T cells promote the development of Treg by TGF-β whereas both TGF-β and IL-6 promote Th17 development. A number of groups have demonstrated that Th17 cells can arise from Treg cells in both mice and humans [50–54]. Transient coexpression of retinoid-related orphan receptor gamma-t (RORγt) and Foxp3 was found in the early response stages of naive T cells that had been stimulated with TGF-β alone or in combination with IL-6 [55–57]. Xu et al. showed that mature Treg cells themselves differentiate into Th17 cells in the presence of IL-6 [51]. IL-6 and IL-21 may be involved in the switch of Th17/Treg cells into Th17 cells. A potential role of Foxp3 in the suppression of Th17 cell development through inhibition of both retinoid-related orphan receptor alpha (RORα) and RORγt has been reported. The populations of Treg cells that co-express Foxp3 and IL-17 can retain their suppressive function [54, 58].

To date, several reports have shown that Th17 cells can shift to Th1 cells but that the reverse is not true [59–62]. Th17 cells producing both IL-17 and IFN-γ (Th17/Th1) were detected in significant numbers in the gut of patients with Crohn's disease and uveitis [16, 63, 64]. Th17/Th1 cells have also been described in murine models of graft versus host disease [65]. Th17 cells up-regulated T-bet expression and shift to the production of IFN-γ in the presence of IL-12 and/or IL-23 [16, 59, 60]. IL-12 may be involved in the switch of Th17/Th1 cell into Th1. Th1 cells express CCR5 and CXCR3, whereas Th2 cells express chemokine receptor CCR4 [66–69]. The expression of CCR6 and IL-23R reportedly defines a population of Th17 cells that selectively express IL-17 but not IFN-γ, whereas cells expressing CCR6 and CXCR3 produce IL-17 and IFN-γ (Th17/Th1) [14, 16, 70].

Transcriptional control of the Th17 cell lineage

After antigen-specific activation, differentiation of the CD4+ Th cell subset requires a series of transcription

factors, specifically T-bet for Th1 cells and STAT-6 and GATA binding protein 3 (GATA-3) for Th2 cells [71]. Foxp3 was identified as the specific transcription factor for Treg cells, controlling the expression of multiple genes that mediate important cellular functions [9, 72].

RORγt was the first transcription factor to be selectively expressed in Th17 cells [73]. Gene profiling analysis of Th17 cells showed that the overexpression of RORγt promotes Th17 differentiation and substantially up-regulates IL-17, whereas RORγt-deficient cells produce very little IL-17 [73, 74]. Two groups have shown that, in the human system, the overexpression of RORC2 (the human ortholog of RORγt) in naive T cells induces the expression of IL-17A, IL-17F, IL-26, and CCR6 [35, 75]. A recent report established that RORα was up-regulated in Th17 cells [76]. Although RORα deletion had minimal effects on IL-17 production, a deficiency in both RORγt and RORα completely abolished IL-17 production and completely inhibited EAE disease. This suggests that the two receptors functionally synergize to promote Th17 cell differentiation.

Recently, STAT-3, the major signal transducer for IL-6, IL-21, and IL-23, was identified as a crucial transcription factor regulating Th17 cell lineage development [20, 77–79]. Retroviral expression of a hyperactive STAT-3 enhanced Th17 cell differentiation, while STAT3 deficiency impaired Th17 cell differentiation through blunted RORγt expression [41, 77]. It was recently shown that interferon regulatory factor 4 (IRF4) is also critical in Th17 cell differentiation, not only through the conventional IL-6 and TGF-β pathway but also through the IL-21-mediated pathway [80–82]. In Irf4−/− Th cells or wild-type Th cells transfected with IRF4 siRNA, the expression of RORγt was decreased whereas Foxp3 expression increased. Most recently, aryl hydrocarbon receptor (AHR), a ligand-dependent transcription factor, was shown to participate in Th17 cell differentiation [83–85]. In addition, Ets-1, STAT-5, and the suppressor of cytokine signaling 3 (SOCS3) were found to negatively regulate Th17 cell differentiation [44, 86, 87]. However, the mechanism by which Ets-1 and SOCS3 inhibit Th17 cell differentiation remains unclear.

The paradox of Th17 cell functions in tumors

Th17 cells have been shown to play important roles in inflammation and autoimmune diseases, but relatively little is known about their specific roles in tumor immunity. Both experimental animal models and clinical studies have suggested functions for Th17 cells and Th17-related cytokines, such as IL-17 and IL-23, in tumor development (Table 1), but it is not yet clear whether Th17 cells promote or inhibit tumor progression, and the mechanism of their involvement in tumor immunity is unknown.

Evidence of IL-17/IL-23 and Th17 cells in tumors

In previous studies, IL-17 mRNA and protein were detected in a considerable proportion of ovarian, breast, and colorectal cancers, as well as in non-small cell lung cancer (NSCLC), prostate cancer, and Sezary syndrome [88–93]. IL-23 is a member of the proinflammatory heterodimeric cytokine family and consists of a p19 subunit and a p40 subunit that is shared with IL-12 [94]. IL-23 but not IL-12 was shown to be an important molecular link between tumor-promoting and proinflammatory processes. IL-23p19 mRNA was found to be significantly overexpressed in the majority of cancer samples from various organ types, including colon, ovarian, head and neck, lung, and stomach cancers as well as melanoma [95]. An increase in Th17 cells has been detected in the peripheral blood, the tumor

Table 1 List of Th17 cells and IL-17/IL-23 in cancers

Cancer type	Experimental approaches	Reference
Lymphoma	Clinical research	[93, 106]
Ovarian cancer	Clinical research	[88, 97, 105, 122]
Breast cancer	Clinical research; animal model	[89, 107]
Colorectal cancer	Clinical research; animal mode	[90, 91, 101, 108, 112, 127]
Lung cancer	Animal model	[92, 95],
Myeloma	Clinical research	[102, 103]
Renal cell carcinoma	Clinical research	[117]
Cervical carcinoma	Animal mode	[110]
Fibrosarcoma	Animal model	[114, 124]
Gastric cancer	Clinical research	[99]
Hepatocellular carcinoma	Clinical research	[100]
Acute myeloid leukemia	Clinical research	[104]
Prostate cancer	Clinical research	[109, 133]
Melanoma	Animal model	[95, 112, 130, 131]

microenvironment and tumor-draining lymph nodes of several different human and mouse tumor types [96]. One study found a high percentage of CD4+ Th17 cells at sites of ovarian cancer but a low percentage of Th17 cells in peripheral blood mononuclear cells from healthy donors and cancer patients [97]. A recent study showed that the number of Th17 cells increased in the tumor-infiltrating lymphocytes (TILs) from melanoma and breast and colon cancers [98]. Patients with gastric cancer had a higher proportion of Th17 cells in peripheral blood and in tumor-draining lymph nodes both of which were associated with clinical stage [99]. Th17 cells were also suggested as a prognostic marker in hepatocellular carcinoma (HCC) [100]. Another study proved that the Th17 response directly contributes to enterotoxigenic *Bacteroides fragilis* (ETBF)-induced colon carcinogenesis [101]. In contrast to data on solid tumors, little is known about Th17 cells in hematological malignancies. Recently, serum IL-17 levels were shown to be elevated in patients with multiple myeloma, especially in stages II and III of the disease. Thus, current data confirm a role for IL-17 in the promotion of angiogenesis and in the progression of multiple myeloma [102]. In myeloma patients, Th17 cells are enriched in the bone marrow compared with the marrow in preneoplastic monoclonal gammopathy of undetermined significance (MGUS) [103]. Th17 cell frequencies and IL-17 concentrations were significantly higher in peripheral blood samples from untreated patients with acute myeloid leukemia (AML) than in those from healthy volunteers and were reduced in the former after chemotherapy [104].

However, some studies have found that the number of Th17 cells is decreased in several types of tumor. The levels of tumor-infiltrating Th17 cells and IL-17 in ascites were reduced in a group of ovarian cancer patients with more advanced disease and seemed to positively predict outcome [105]. A low number of Th17 cell is present in the tumor microenvironment of non-Hodgkin's lymphoma because malignant B cells may up-regulate Treg cells and inhibit Th17 cells [106]. Th17 cells are present in much lower numbers in HER2-positive breast cancer patients than in either healthy controls, or HER2-negative patients [107]. Tumor growth and lung metastasis were enhanced in IL-17-deficient mice while in vitro TGF-β and IL-6 polarized Th17 cells induced tumor regression [108]. One study in prostate cancer demonstrated that Th17 cells infiltrating the tumor correlated inversely with the Gleason score [109]. This implied that Th17 cells mediate an anti-tumor effect in the development of prostate cancer. One group found that IL-17 promoted the tumorigenicity of human cervical tumors in nude mice but inhibited the growth of hematopoietic tumors, mastocytoma P815, and plasmocytoma in immunocompetent mice [110, 111]. Although endogenous IL-23 expression has been reported to promote tumor incidence and growth, the most recent studies have shown that IL-23 induces antitumor immune responses. In IL-23-transduced tumor-cells, IL-23 was shown to be very effective in inhibiting tumor growth and lung metastases by eliciting a strong CTL memory response [112]. It has also been reported that antitumor immunity was promoted in dendritic cells transduced with IL-23 [113]. Following in vivo electroporation of IL-23 plasmid DNA into the pretibial muscles of C57BL/6 mice, the growth of pre-existing MCA205 fibrosarcoma was suppressed and the survival of the treated mice prolonged [114].

The pro and contra functions of Th17 cells in tumors

It is well established that IL-17 acts as an angiogenic factor that stimulates the migration and cord formation of vascular endothelial cells in vitro and elicits vessel formation in vivo [115, 116]. Additionally, IL-17 may promote tumor growth and metastasis through de novo carcinogenesis and tumor neovascularization via STAT-3 signaling and other mechanisms. T cell-secreted IL-17 dramatically increased tumor-cell release of IL-8, which has both chemoattractant and angiogenic activities [117]. IL-23 may up-regulate IL-17 and matrix metalloprotease 9 (MMP-9) to stimulate angiogenesis and reduce the number of CD8+ T cells in the tumor microenvironment. The mechanism of upregulation Th17 cells in tumor is not clear. Tumor-associated monocytes and some cytokines such as IL-2, IL-6 and TNF-α in the tumor microenvironment probably regulate Th17 cells. Charles et al. found that TNF-α enhanced tumor growth via the inflammatory cytokine IL-17 in a mouse model of ovarian cancer and in patients with advanced cancer [118]. A paper by Su et al. demonstrated that tumor cells and tumor-derived fibroblasts secrete monocyte chemotactic protein 1(MCP-1) and RANTES that mediate the recruitment of Th17 cells [98]. Furthermore, the group also showed that inflammatory Toll-like receptor (TLR) and nucleotide oligomerization binding domain (Nod) 2 signaling promote the generation and expansion of Th17 cells. More recently, Kuang et al. showed that tumor-activated monocytes promote expansion of Th17 cells through secreting a set of key proinflammatory cytokines in the peritumoral stroma of HCC tissues [119]. It is clear that Treg cells efficiently suppressed the function of antitumor CD8+ T cells [120, 121]. A recent study reported that IL-2 regulates the balance between tumor Treg and Th17 cells by stimulating the differentiation of the former and inhibiting that of the latter in the tumor microenvironment [96]. However, in vitro cultures of epithelial ovarian cancer (EOC) tumor samples in the presence of IL-2 contained high frequencies of Th17 cells among the tumor-infiltrating lymphocytes and tumor-associated lymphocytes [122].

Most recently, Vicari et al. have revealed that paclitaxel combined with PF-3512676 (formerly CpG 7909) could increase IL-17 and decrease IL-10 associated with decreased Treg in mouse tumor models [123].

The mechanism of Th17 cells' antitumor activity remains largely unknown. One publication has reported antitumor activity of IL-17 by means of a T cell-dependent mechanism [111]. Transfection of IL-17 into human tumor cell lines was shown to augment the expression of MHC class I and II antigens, thereby inducing tumor-specific antitumor immunity [124]. Two studies by Benatar et al. demonstrated that IL-17E, a novel family of cytokines that possess significant homology to IL-17, has antitumor activity in multiple tumor models, and eosinophils and B cells are involved in the antitumor mechanism of action of IL-17E [125, 126]. Further studies should be performed to examine the potential role of IL-17E in the context of IL-17 and/or Th17 antitumor activities. The expression of IL-23 in tumors produces T cell-dependent antitumor effects and induces systemic immunity [127]. Th17 cells may contribute to protective human tumor immunity by inducing Th1-type chemokines and stimulating CXCL9 and CXCL10 production to recruit effector cells to the tumor microenvironment. Leveque et al. [122] suggested that human EOC-associated Th17 cells cosecreted both IFN-γ and TNF-α. A recent study has also demonstrated that almost half of IL-17-producing CD4+ T cells isolated from HCC tissues simultaneously produced IFN-γ [119]. An interesting work of the Gaudernack group has demonstrated that IL-17-secreting T cell clones obtained from long-term survivor patients after immunotherapy also secreted IFN-γ, IL-4, IL-5, and IL-13 [128]. More recently, it was shown that Th17 cells and IL-17 participate in antitumor immunity by facilitating dendritic cell recruitment into tumor tissues and promoting the activation of tumor-specific CD8+ T cells [129]. In addition, Th17 cells eradicated established melanoma in a model of adoptive transfer of T cell receptor transgenic CD4+ T cells specific for the shared self-tumor antigen tyrosinase-related protein 1 (TRP1) [130]. Th17 frequencies increased during treatment with trastuzumab in patients with breast cancer [107]. Th17 cells were significantly increased in patients with metastatic melanoma treated with the anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) antibody tremelimumab [131]. Alvarez et al. demonstrated that fusion of dendritic cells and tumor cells (FC) transduced with adenovirus encoding CD40L (Adv-CD40L) increased Th17-type immune response and enhances the antitumor effect of FC vaccines in a murine lymphoma model [132]. Derhovanessian et al. has observed a highly significant correlation between a higher frequency of IL-17-producing T cells prevaccination and a shorter time to metastatic progression after immunotherapy [133]. These data imply the important involvement of Th17 cells in the response to cancer immunotherapy.

Conclusion

Th17 cells, a recently identified distinct lineage, seem to have critical functions in inflammation and autoimmune diseases. In contrast to the differentiation of Th1 and Th2 cells, Th17 cell differentiation requires TGF-β and IL-6. IL-23 may be important for the expansion and survival of Th17 cells, while RORγt, RORα, and STAT3 are crucial transcription factors regulating Th17 cell development. In addition, Th17 cells are reciprocally related to Foxp3+ Treg cells and can undergo a lineage shift to Th1 cells in both mice and humans. The magnitude of the data regarding Th17 cells in experimental animal models of cancer as well as in human cancers suggests that this T cell subset is involved in cancer immunity. However, the role of Th17 cells is no doubt highly complex, and it remains controversial whether these cells promote tumor growth or regulate antitumor responses. An understanding of the exact mechanism that regulates Th17 cells in vivo may help to resolve many issues in cancer development. This includes an understanding of the molecular regulation of plasticity between committed Th17 cells, Treg cells, and Th1 cells in vivo, especially in the tumor microenvironment. Finally, whether Th17 cells play the same roles in the different types and stages of cancers remains to be determined. A comprehensive approach to unraveling the role of Th17 cells in tumor development and/or immunity could help in the design of novel therapeutic approaches specifically targeting Th17 cells in cancer.

Conflict of interest statement The authors declare that they have no conflict of interest.

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