

Review Article



IL-17-Producing Cells in Tumor Immunity: Friends or Foes?

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OPEN ACCESS

Received: Dec 29, 2019

Revised: Jan 25, 2020

Accepted: Jan 26, 2020

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Conflict of Interest

The authors declare no potential conflicts of interest.

Abbreviations

5-FU, Fluorouracil; CAR, chimeric Ag receptor; CRC, colorectal cancer; CRISPR, Clustered regularly interspaced short palindromic

ABSTRACT

IL-17 is produced by RAR-related orphan receptor gamma t (ROR γ t)-expressing cells including Th17 cells, subsets of $\gamma\delta$ T cells and innate lymphoid cells (ILCs). The biological significance of IL-17-producing cells is well-studied in contexts of inflammation, autoimmunity and host defense against infection. While most of available studies in tumor immunity mainly focused on the role of T-bet-expressing cells, including cytotoxic CD8⁺ T cells and NK cells, and their exhaustion status, the role of IL-17-producing cells remains poorly understood. While IL-17-producing T-cells were shown to be anti-tumorigenic in adoptive T-cell therapy settings, mice deficient in type 17 genes suggest a protumorigenic potential of IL-17-producing cells. This review discusses the features of IL-17-producing cells, of both lymphocytic and myeloid origins, as well as their suggested pro- and/or anti-tumorigenic functions in an organ-dependent context. Potential therapeutic approaches targeting these cells in the tumor microenvironment will also be discussed.

Keywords: Tumor microenvironment; Th17 cells; Interleukin-17; T-lymphocytes

INTRODUCTION

CD4⁺ T-cell subsets act as an essential arm of adaptive immunity-as helpers of CD8⁺ T- and B-cells, recruiters of immune cells to the inflammation site and initiators of immunological memory. CD4⁺ effector T-cells subsets can be divided into distinct lineages: Th1, Th2, Th17, Tfh, and Tregs-each with unique roles in host defense and immunity. In response against extracellular pathogens, Th17 cells function to recruit neutrophils and macrophages via the induction of chemokines such as CXCL1, CXCL2 and CXCL8 (1). Signals that drive Th17 differentiation include TGF β , IL-6, IL-1 β , or IL-21 (2,3). Although not required initially, IL-23 was also shown to be important for terminal differentiation and maintenance of Th17 cells (4). IL-17 production is a key feature of Th17, along with expression of the lineage-defining transcription factor RAR-related orphan receptor gamma t (ROR γ t) (5). Other cytokine production, such as IL-17F, IL-21, GM-CSF, and IL-22, has also been associated with Th17, and these effector cytokines allow Ag-specific Th17 cells to be pathogenic in autoimmunity (6-9).

repeats; DC, dendritic cell; EGFR, epidermal growth factor receptor; ICOS, inducible T-cell costimulatory; ILC, innate lymphoid cell; HCC, hepatocellular carcinoma; MDSC, myeloid-derived suppressor cells; MMP, matrix metalloproteinase; MPE, malignant pleural effusions; NKT17, IL-17 producing invariant NKT cells; NSCLC, non-small cell lung carcinoma; PGE2, prostaglandin E2; ROR γ t, RAR-related orphan receptor gamma; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; Tc17, IL-17 producing CD8+ T; TIL, tumor-infiltrating lymphocyte; $\gamma\delta$ T17, IL-17 secreting $\gamma\delta$ T

Author Contributions

Conceptualization: Kuen DS, Chung Y; Data acquisition: Kuen DS; Funding acquisition: Kuen DS, Kim BS, Chung Y; Supervision: Chung Y; Visualization: Kuen DS; Writing- original draft: Kuen DS; Writing-review & editing: Kim BS, Chung Y.

As such, the differentiation requirements, effector functions, and the regulation of IL17-producing T-cells in the context of autoimmunity, allergic diseases, and host defense against bacterial infections and other opportunistic pathogens are well studied (10). However, almost 15 years after the discovery of Th17 as a distinct lineage of CD4+ T-cell subset, the scientific community is still debating its exact role in tumor immunity. This seems to be due to a couple of reasons: first of which is the wide diversity, and the relative plasticity of the IL-17 producing cells in the tumor microenvironment (Fig. 1). Confounding the matter is the tissue-specific niche that also diversifies the regulatory mechanism induced by IL-17 signaling. Lastly, the pleiotropic nature of IL-17, along with other related cytokines (i.e. IL-1 β , IL-22, IL-23, TNF- α , IFN- γ) that are often secreted in conjunction with IL-17, can bring about drastically different net outcomes in a complex and dynamic disease such as cancer. As such, type 17 refers to the effector cellular program encompassing IL-17 and related cytokine signatures. The dominant “type 17”-driven mechanism at play seems to shift as the disease progresses. The pro-tumorigenic and anti-tumor properties of tumor-infiltrating type 17 compartments will be explored.

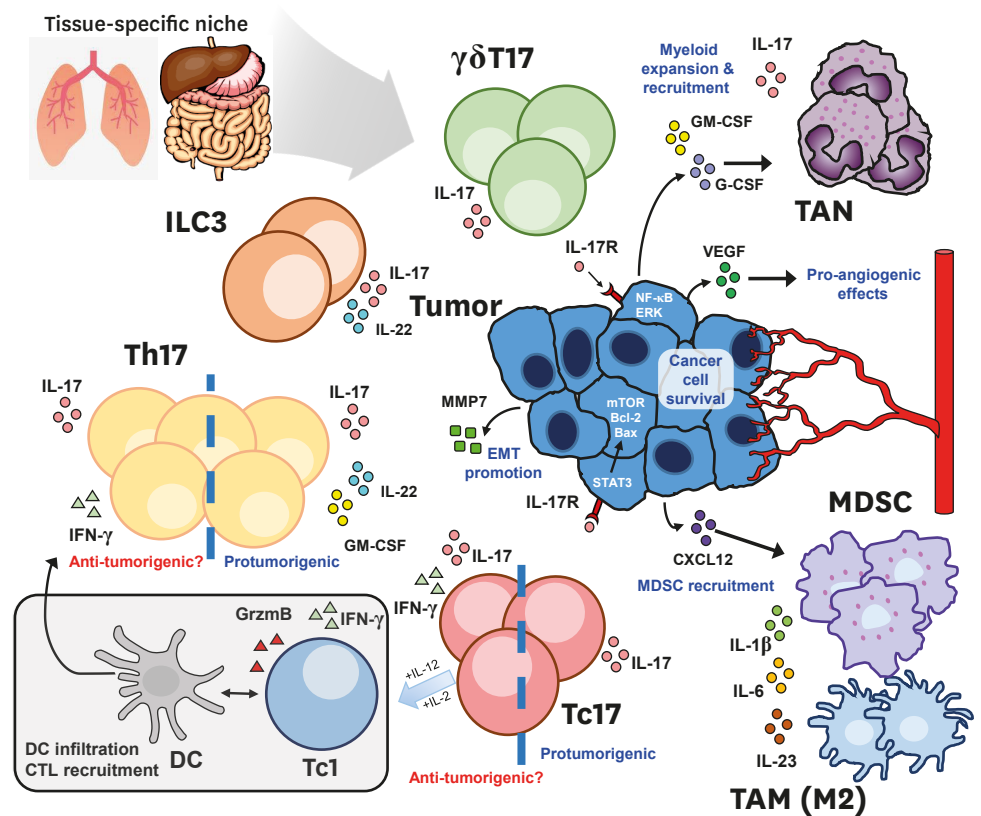


Figure 1. Type17 compartments in the tumor microenvironment. The tissue-specific niche, and the stage of cancer progression dictate the heterogeneous composition of type 17 compartment in the tumor microenvironment. Both innate and adaptive arms of the immune system are capable of producing IL-17. Studies involving both CD4+ Th17 and CD8+ Tc17 T-cells reported protumorigenic or anti-tumorigenic roles. Anti-tumorigenic Th/c17 cells co-secrete IFN- γ , and exhibit type 1-17 hybrid phenotypes that lead to enhanced dendritic cell infiltration and tumor-Ag presentation, type 1-helper function or Tc1 conversion in the case of Tc17 cells under the appropriate cytokine stimuli. However, an increasing amount of evidence illustrate the protumorigenic mechanisms (highlighted in blue) of type 17 cells within the immunosuppressive endogenous microenvironment within the growing tumor. Largely, they work by two broad mechanisms: 1) the IL-17 mediated recruitment of immunosuppressive myeloid compartment, either directly by type 17 cells or indirectly by cancer cells in a chemokine dependent manner, 2) cancer intrinsic IL-17 signaling, leading to enhanced cancer cell survival, EMT and angiogenesis promotion. EMT, epithelial-mesenchymal transition; TAM, tumor-associated macrophage.

This review first summarizes current understanding of the various type 17 compartments present in the tumor microenvironment, and the tissue-specific niche affecting the dominant type 17 mechanism at play. Additionally, the consequent protumorigenic or anti-tumor outcomes, as well as the prognostic factors for each cancer type are also discussed. Additionally, current type 17 mechanisms of resistance against conventional chemo-/radiotherapies, as well as current efforts to utilize type 17 axis in future cellular and immunotherapies will also be discussed. Although there are still many unanswered questions and missing pieces, the present review, along with others, can serve as a starting point for future discussions.

PRODUCERS OF IL-17 IN THE TUMOR MICROENVIRONMENT

Diverse cellular sources of IL-17 exist in the tumor microenvironment. Type 17 cellular compartments present in the tumor microenvironment are graphically outlined in **Fig. 1**.

Th17 cells

Tumor-infiltrating Th17 cells have been observed in both mouse (**Table 1**) and humans (**Table 2**) (11-64). Mechanistic studies add strength to the idea that chronic infection and inflammation are important environmental factors for tumorigenesis and such conditions also foster type 17 cell generation. For example, many have noted that Th17 frequency is higher in the tumor than in healthy tissues or PBMCs. Tumor cells, as well as tumor-derived fibroblasts and APCs in the tumor microenvironment have been demonstrated to produce the cytokine milieu that elicit Th17 generation and/or recruitment (58,65). Interestingly, tumor-derived TGFβ rather inhibited Th17 cell expansion, while promoting Treg generation. Others have suggested that tumor and/or tumor-associated myeloid cells can actively recruit Th17 cells via chemokine secretions (66,67).

Table 1. Summary of findings from mouse cancer model studies: function of type 17 lymphocytes

Cancer model	Sub-type	Function of type 17 cells (pro- or anti-tumorigenic?)	Ref.
Subcutaneous injection	EL4, CT26	Pro-tumorigenic	(11)
	B16 melanoma	Anti-tumorigenic	(12)
	MC38	Anti-tumorigenic	(13)
	KPC, Braf-Pten, B16-melanoma	Pro-tumorigenic	(14)
	Hepa1-6 HCC	Pro-tumorigenic	(15)
	MA782 (orthotopic)	Pro-tumorigenic	(16)
	4T1 (orthotopic)	Pro-tumorigenic	(16,17)
Intraperitoneal injection	ID8 ovarian cancer	Pro-tumorigenic	(18,19)
Intravenous injection	B16 melanoma, LLC	Anti-tumorigenic	(20)
	MC38	Anti-tumorigenic	(13)
Oncogene-activated	Constitutive MYC expression in early B-cells	Pro-tumorigenic	(21)
	K14 ^{Cre} x <i>Cdh11^f/xTrp53^{f/f}</i>	Pro-tumorigenic	(22)
	(KEP) mice spontaneous breast cancer		
	Kras ^{G12D} xCCSP ^{Cre} Lung Cancer	Pro-tumorigenic	(23)
	Kras ^{LSL-G12D} xp53 ^{f/f} xSftpc ^{Cre} Lung Cancer	Pro-tumorigenic	(24)
Pten ^{f/f} xSMAD4 ^{f/f} xCCSP ^{Cre} Lung Cancer	Anti-tumorigenic	(25)	
Carcinogen-induced	DMBA/TPA-induced skin cancer/squamous cell carcinoma	Pro-tumorigenic	(26,27)
	AOM DSS APCmin ETBF-induced colon cancer	Pro-tumorigenic	(28-30)
Inflammation-accelerated	<i>Helicobacter hepaticus</i> -infected/AOM-treated129SvEvS6. <i>Rag2^{-/-}</i>	Pro-tumorigenic	(31)

AOM, azoxymethane; DMBA, 7,12-dimethylbenz[a]anthracene; DSS, dextran-sulfate sodium; ETBF, Enterotoxigenic Bacteroides fragilis; HCC, hepatocellular carcinoma; LLC, Lewis lung carcinoma; TPA, 12-O-tetradecanoylphorbol-13-acetate.

Table 2. Summary of type 17 T-cell types by human cancers and its associated prognosis

Cancer Type	Endogenous, tumor-infiltrating type 17 T-cells found	Overall survival	Ref.
Acute leukemia	Th17	Improved	(32)
Acute myeloid leukemia	Tc17	Poor	(33)
Breast	Th17	Poor*	(34,35)
Colorectal cancer	gdT17, Th17	Poor	(28-38)
Cervical carcinoma	Th17	Improved [†]	(39)
Cervical squamous cell carcinoma	CD3 ⁺ IL17 ⁺	Improved [‡]	(40)
Esophageal squamous cell carcinoma	IL17 ⁺ cells	Improved	(41,42)
Gastric carcinoma	Th17	Poor	(43,44)
Hepatocellular carcinoma	Tc17, Th17	Poor	(45-47)
Lung cancer	Th17	Improved	(48)
Lung carcinoma	Th17, gdT17	Improved	(49,50)
Melanoma	Th17, Tc17	Poor	(51)
Myeloma	Th17	Poor	(52,53)
Nasopharyngeal	Th17, Tc17	Improved?	(54)
Nasopharyngeal carcinoma	IL17 ⁺ cells	No correlation	(54,55)
Non-small cell lung	Th17	Poor	(56,57)
Ovarian	Th17	Improved	(58,59)
Pancreatic	Th17	Poor	(60)
Prostate	Th17, NKT17	Improved [§]	(61,62)
Renal cell carcinoma	Th17	Improved	(63)
Small cell lung	Th17 (peripheral)	Improved	(64)

*Improved survival was observed in non-inflamed triple negative breast cancer. [†]In cervical carcinoma, IL-17 level as a whole was associated with poor outcome, due to the pro-tumorigenic contributions of IL-17 producing neutrophils. [‡]Prognosis for IL-17+ cells in general was poor for cervical squamous cell carcinoma. [§]The prognosis for IL-17 producing cells in hormone-resistant prostate cancer.

Many have noted the positive correlation between the generation of Th17 cells in the growing tumor and cancer angiogenesis. The suggested direct link is thought to be IL-17 mediated stimulation of VEGF production from cancer cells (36,68). Similarly, microvascular density changes in mice with engrafted breast cancer cells treated with recombinant IL-17 demonstrated angiogenesis-promoting effects *in vivo*. Others have investigated whether IL-17 cytokine can affect early stages of tumorigenesis (28). IL-17 blockade significantly attenuated tumor formation in a Th17-driven colon tumorigenesis mouse model. In this model both Th17-cell and innate type 17-derived IL-17 production was suggested to induce bacteria-induced colon carcinogenesis.

Tc17 cells

Several groups have reported the presence of IL-17 producing CD8⁺ T (Tc17) cells in cancer patients. In human hepatocellular carcinomas, these cells were reported to accumulate in the invading tumor edges, where they co-localized with tumor-associated monocytes (15). These CD68⁺ monocytes secreted a key set of cytokines, notably IL-1 β , IL-6, and IL-23, that allowed a superior induction and proliferation of Tc17 cells *ex vivo*. Tc17 cells found in the tumor expressed other signature type 17 molecules, such as ROR γ t, IL-22, and CCR6, while downregulating the conventional CTL program, such as granzyme B and perforin. Higher frequency of Tc17 cells have also been reported in nasopharyngeal carcinoma and gastric cancer patients (69,70). The biological function of these endogenous, tumor-infiltrating Tc17 population has not been elucidated. Few reports suggest a negative correlation between IL-17 producing T-cell frequency (including Tc17) and overall survival of cancer patients, suggesting protumorigenic properties (71). Mechanistic studies conducted *ex vivo* have suggested that tumor-infiltrating Tc17 cells induce the production of CXCL12 by tumor cells which in turn promote CXCR4-dependent migration of myeloid-derived suppressor cells (MDSCs) to the tumor microenvironment (70).

Due to the direct killing potential of CD8⁺ T-cells, many have attempted to take advantage of the plasticity of Tc17 cells as a cellular therapy alternative (72,73). Adoptive transfer of tumor-specific, *in vitro* differentiated Tc17 cells have shown considerable antitumor properties in certain mouse models of cancer, due to the enhanced survival capability of Tc17 cells and higher expression of stemness markers than Tc1 cells (74-77).

Innate cells of lymphoid origin: IL-17 secreting $\gamma\delta$ T ($\gamma\delta$ T17) cells, NKT, type 3 innate lymphoid cells (ILC3)

In mouse models of spontaneous breast cancer metastasis, $\gamma\delta$ T17 cells were shown to drive tumor-associated neutrophils (TAN) expansion, accumulation, phenotype in a G-CSF-dependent manner in mammary tumors (22). These TANs exert immunosuppressive functions by hindering effector CTL function, thereby facilitating cancer metastasis. Depletion of either $\gamma\delta$ T cells or neutrophils resulted in significant reduction of pulmonary and lymph node metastasis, thereby demonstrating the pro-metastatic role of $\gamma\delta$ T/IL-17/neutrophil axis in this breast cancer model (22). A mouse peritoneal/ovarian cancer model has demonstrated $\gamma\delta$ T17 accumulation in the peritoneal cavity in response to tumor challenge (18). $\gamma\delta$ T cells have been suggested to recruit macrophage subsets expressing high levels of IL-17 receptor, which have abilities to directly promote ovarian cancer cell proliferation *in vitro*. Collectively, $\gamma\delta$ T cell crosstalk with the tumor-associated myeloid compartment seems to occur via IL-17 in mouse cancer models (19). Such mechanisms of cellular crosstalk have also been demonstrated in human colorectal cancers (CRCs). Microbial products secreted by tumorous epithelial barriers induce preferential $\gamma\delta$ T17 polarization. $\gamma\delta$ T17-derived GM-CSF recruit immunosuppressive neutrophils and polymorphonuclear myeloid-derived suppressor cells into the tumor (78). $\gamma\delta$ T17 infiltration positively correlated with clinical stage and other clinicopathological features of CRCs in cohorts, demonstrating the impact of $\gamma\delta$ T17 in potential prognosis prediction. Additionally, a high proportion of tumor-infiltrating $\gamma\delta$ T-cells were found to be functionally exhausted and created an 'anergic' immunosuppressive environment in which neighboring CD4⁺ or CD8⁺ T-cells were also affected in human pancreatic ductal adenocarcinomas (79).

IL-17 producing invariant NKT cells (NKT17), marked by CD24⁻CD44⁺NK1.1⁺, have been described to be endogenously enriched within certain tissues such as the lungs, intestines, and skin (80,81). Cancers arising in such tissue niches are expected to contain a higher frequency of NKT17. However, the precise role of NKT17 in tumorigenesis and tumor immunity so far remains elusive. ILC3s represent another innate lymphocyte compartment capable of producing IL-17 in the tumor microenvironment (82,83). Higher percentage of ILC3 was associated with IL-23 expression in non-small-cell lung carcinoma (NSCLC) cells. Pulmonary squamous cell carcinomas secreted functional levels of IL-23 that enabled ILC1 conversion into ILC3 *ex vivo* (84). IL-22 producing CCR6⁺ ILC3s have been suggested to increase the tumorigenic potential of colon cancer in mouse models (29,31). Ab-mediated depletion of natural cytotoxicity triggering receptor positive ILC3s led to decrease in metastasis in a mouse model of breast cancer (17). ILC3s recruited to the tumor microenvironment interact with stromal cells to create favorable conditions for cancer metastasis.

Innate sources of myeloid origin: macrophages, mast cells, neutrophils

Myeloid cells, most notably CD68⁺ macrophages (85,86), neutrophils (40), and mast cells (87,88) have also been shown to secrete IL-17. In fact, IL-17 secreted from myeloid cells (granulocytes and mast cells) was shown to constitute a larger portion of IL-17 secretion than those derived from T-cells in certain cancers (40,88,89). Neutrophils were primarily

granulocytic in nature in squamous cervical cancers, and associated with poor survival. In addition, IL-17-expressing cells were independently associated with poor survival in early stage of the disease (40). IL-17 producing mast cells in esophageal squamous cell carcinoma were found to be densely located in the muscularis propria, and were suggested to function in the recruitment of effector CTLs and M1 macrophages to the site of tumor, thus acting as a favorable prognostic factor (41). However, in other cancer types opposite results were reported for IL-17⁺ mast cells (88).

Type 17 ‘package’ delivery: co-secretion of other effector cytokines

Confounding the matter, co-secretion of other effector cytokines, such as IL-21, IL-22, and GM-CSF, by type 17 cells in the tumor microenvironment adds another dimension of complexity. IL-21 has pleiotropic effects on both innate and adaptive immunity. IL-21 secretion has shown to enhance the cytotoxicity of CD8⁺ T-cells, and regulate NK cell maturation, while it can also hinder Ag presentation of dendritic cells and act as a pro-apoptotic signal. (90). As such, IL-21 has been tested in several phase II clinical trials for its potent anti-tumor effects either alone (91,92), or as a component of adoptive cellular therapy (93). However, little is known regarding the biological function of endogenous IL-21 derived from type 17 cells in the tumor.

IL-22 is known to be secreted by a special subset of Th17 cells residing in epidermis (94,95). In the context of cancer, IL-22 was suggested to favor tumor growth in several cancer models including nonmelanoma skin, colon and lung cancers (96,97). IL-22 receptor expression is limited to epithelial cells and IL-22 signaling can contribute to pro-survival signaling, angiogenesis and metastasis, part of which may be associated with its activation of STAT3 signaling pathway in cancer cells (29,98,99). As such, blockade of IL-22 significantly lowered tumor formation in a mouse model of colon cancer (31), and IL-22 expressing tumor-infiltrating cells correlated with more advanced tumor severity and reduced survival in human cancers (31,100). High levels of IL-22 have been detected in primary tumors, malignant pleural effusions (MPEs) and in sera of NSCLC patients (101).

IL-17 signaling can induce GM-CSF production in oncogene-driven cancer cells (102). CRC patients show higher blood GM-CSF levels than healthy control. Moreover, high GM-CSF expression in the tumor tissue correlated with local and distant metastasis, and poorer prognosis in various cancer types (102-104). GM-CSF can directly affect cancer cells and educate them to be more resistant to apoptosis and more prone to metastasis (105)

Despite the diverse cellular sources of IL-17, the protumorigenic type 17 axis can be organized into two types of mechanisms. First, IL-17 both expands and mobilizes immunosuppressive granulocytes, which can hinder effector cytotoxic T-cells or make the tumor microenvironment more ‘angiogenesis-friendly’. Secondly, other cytokines relevant in the type 17 context, such as GM-CSF, IL-6, and TNF can be produced to initiate a positive feedback loop in cellular crosstalk between cancer cells and immunosuppressive compartments in the environment. On the other hand, IL-17 mediated fostering of anti-tumor immunity was also demonstrated in several instances. For example, IFN- γ , TNF- α co-production from type 17 T-cells was often correlated with improved overall survival and better sensitivity to cancer therapy. Additionally, the presence of certain types of IL-17⁺ T-cells enhanced dendritic cell (DC) and CTL recruitment into the tumor bed, which boosts tumor-specific T-cell responses (25,106,107).

TISSUE-SPECIFIC NICHE DIVERSIFIES TYPE 17 RESPONSES

Cancer cells, tumor-derived fibroblasts, and Ag-presenting cells secrete several key cytokines for Th17 differentiation such as IL-1 β , IL-6, IL-23, and TGF- β . In the tumor, IL-1 β , probably produced by tumor-associated macrophages, was shown to be critical for the expansion of memory Th17 cells in ovarian and breast cancers (58,59). In mammary gland tumors, Prostaglandin E2 (PGE2)-induced IL-23 production led to Th17 cell expansion (108). In addition, IL-17 can signal epithelial cells and fibroblasts to produce a diverse array of chemokines and growth factors, which depending on the tissue-niche can either foster cancerous development, or assist in anti-tumor activities. For example, IL-17 was shown to induce the production of angiogenic factors such as VEGF, CXCL1, or CXCL8 in colorectal cancer and NSCLC patient samples (109,110), whereas the same cytokine induced secretion of angiostatic CXCL9 and CXCL10 chemokines in ovarian cancer, which in turn recruited effector CTL and NK cells (59). Therefore, the tissue-specific niche can be another factor that augments the diversity and function of type 17 cells. The following briefly summarizes studies that investigated the link between type 17 cells and cancers by tissue-type.

Gut: intestinal type 17 cells

Th17 cells act to support the integrity and homeostasis of the intestinal barrier in a non-inflammatory manner. These tissue-resident homeostatic Th17 cells are elicited by the commensal flora, and function to control their composition (111). Considering the close associations of certain commensals with intestinal cancers, it is possible to postulate homeostatic Th17 cells obtaining pathogenicity in inflammatory sites of precancerous lesions. The contributions of both adaptive (Th17) and innate ($\gamma\delta$ T17) type 17-driven mucosal immunity to oncogenic commensal-promoted colon carcinogenesis have been demonstrated in mouse models (14,28,112). Ab-blockade of IL-17 ameliorated tumorigenesis and growth, demonstrating a STAT3- and type 17-dependent pathway for commensal-induced colon carcinogenesis. IL-23, another type 17 cytokine, was shown to be secreted by tumor-associated myeloid cells activated by microbial products in colon cancer models (113). IL-23 has been suggested to be the driver of *de novo* gut carcinogenesis via the activation of IL-23R⁺ ILC3s (114). Similarly, it is well-known that *Helicobacter pylori*-associated gastritis is a major risk factor for gastric cancer. Such pathogenesis has shown to be correlated with a type 17-driven response (115). As such, the gut can foster a niche-specific type 17 response that is important in the initial stages of cancerous transformations.

Intestinal commensal-type 17 axis has been shown to exert pro-tumorigenic effect in distal tissues. In pancreatic cancer, the intestinal microbiome was shown to induce IL-17 expression from Th17 cells and promote pancreatic oncogenesis (14,116). Ablation of the microbiome with antibiotics reduces cancer growth in an IL-17-dependent fashion, which supports the protumoral role of bacteria and IL-17 in the early stages of oncogenesis in distal tissues (14,21). Whether the impact of dysbiosis on cancer growth is due to a specific gut microbe, or depletion of commensal flora in general remains to be studied.

Lung: pulmonary type 17 cells

In LSL-K-ras^{G12D} murine lung cancer model, inflammatory macrophage-Th17 cell axis was critical for tumorigenesis (117), highlighting the tissue-specific context that shapes the cellular interactions of Type 17 cells. Tissue specific niche also can change the functional role of type 17 cells. Commensal bacteria have shown to shape the efficiency of immune surveillance in lung mucosal tissues via the induction of homeostatic $\gamma\delta$ T17 cells (20). The

tissue-specific niche also seems to vary the degree to which IL-17 can affect early stages of cancer angiogenesis, especially tissues in which type 17 cells play a homeostatic role (36,68,118).

Murine models of lung cancer have demonstrated conflicting roles of IL-17. In a murine model of oncogenic mutation-driven lung cancer, Th17 cells accumulated in the tumor, and Th17-derived IL-17 regulated the recruitment of Gr-1⁺ CD11b⁺ myeloid cells to the tumor, thereby exerting a pro-tumorigenic role (23). In another recent study, lung commensal microbiota was shown to promote lung cancer development via induction of inflammatory tissue-resident $\gamma\delta$ T17 cells (24). Tumor burden was correlated with local bacterial load in the airway. Interestingly, bacterial intratracheal inoculation led to accelerated tumor growth and enhanced neutrophil expansion. A positive feedback loop seemed to be the important tumor-initiating mechanism, whereby oncogenic tumor initiating genes act to stimulate local microbiota. Anti-tumor properties of endogenous IL-17 have also been reported using IL-17-deficient mouse systems (13,106). Mechanistically, anti-tumor Th17 cells have been suggested to enhance the activation of tumor-specific CD8⁺ T-cells in the tumor in TCR-transgenic mouse models, but whether the same phenomenon occurs in human lung cancers remains to be determined.

Skin: cutaneous type 17 cells

Type 17 response in the skin acts to efficiently mediate wound healing and repair in cases of injury. A recent study illustrated how such intrinsic wound healing signaling can be hijacked by cancerous skin cells in tumorigenesis. Mechanistically, IL-17 receptor signaling can transactivate epidermal growth factor receptor (EGFR) in skin epithelial cells for tumorigenesis (119). IL-17 signaling seems to be important also in tumorigenesis via its direct capability to induce STAT3 activation in skin epithelial cancer cells. IL-17 deletion was associated with reduced tumorigenesis in a chemically-induced skin tumor model, with lower expression of STAT3-mediated chemokine expression, and lower infiltration of myeloid cells into the tumor (26).

Skin-commensal associated inflammatory Th17 response has shown to trigger skin cutaneous T-cell lymphoma progression. Markedly lower tumor burdens in STAT3-hyperactive mutant mouse group housed in germ-free conditions were observed compared to those in specific-pathogen free facilities (120).

Cancer-intrinsic IL-17 signaling: IL-17 acts as mitogenic stimulant

Both cancerous and healthy non-immune cells express functional IL-17 receptors (121,122). Whether cancer cells show elevated levels compared to healthy cells is unclear. IL-17 signaling directly activates the early stages of cancer cell proliferation via STAT3 signaling. Along with it, the downstream activation of transcription factors (NF- κ B, STAT, and AP-1), kinases (MAPK), tissue remodeling matrix metalloproteinases (MMPs), and anti-apoptotic proteins (Akt, Erk, mTOR, Bcl-2, and Bax) are also stimulated in a myriad of cancers (123–125). For example, IL-17 ligation stimulates the proliferation and self-renewal of ovarian cancer stem cells in a dose-dependent fashion via the NF- κ B and MAPK pathways (126). IL-17RA expression and engagement has shown to directly promote colonic tumorigenesis within transformed colonic epithelial cells (30).

Oncogenic mutations have shown to activate intrinsic IL-17 signaling in pancreatic neoplasia (116). During cancer angiogenesis, cancer cells become directly responsive to IL-17 signaling (68). IL-17 promoted tumor graft development and directly inhibited apoptosis in several

breast cancer cell-lines in a TGF- β dependent manner (16). Furthermore, this anti-apoptotic effect was reversed after IL-17R suppression, indicating intrinsic signaling at play. IL-17-mediated prostate cancer promotion was demonstrated to occur through epithelial to mesenchymal transition as a result of enhanced MMP7 expression (127).

Cancer stage seems also change the dominant type-17 mechanism(s) at play. Regardless of the mechanism by which IL-17 promotes tumor growth, the protumoral properties of IL-17 via STAT3 signaling in cancer cells impact the early stages of oncogenesis rather than the later stages in an established tumor (27,128,129). Additionally, the extrinsic tumor microenvironment is a dynamic one that changes along with the progression of cancer. CCR4 expression among intratumoral Th17 cells has been reported to be higher than in blood Th17 in HCC patients (45). The frequency of CCR4⁺ intratumoral Th17 subset was shown to correlate positively with the stage of hepatocellular carcinoma patients (45).

TYPE 17 CELLS AS PROGNOSIS FACTORS AND THERAPEUTIC TARGETS

Despite the universal presence of tumor-infiltrating type 17 cells across many cancer types, the relative functions of these cells and the overall prognostic factors associated is an on-going effort that remains to be fully elucidated. **Table 2** simply summarizes the current findings of the correlation between IL-17 producing T-cells and their overall prognosis of survival in various cancer types. Others have more comprehensively and systemically summarized the correlations between the presence of tumor-infiltrating type 17 cells and disease progression (130). It is important to highlight the distinction that needs to be made between IL-17 and type 17 cells. As demonstrated in lung adenocarcinoma, the presence of Th17 cells in the MPEs was associated with improved overall survival (48), while IL-17 levels in the same anatomical location were correlated with poor overall survival (56) Nevertheless, the following sections aim to outline the mechanistic insight of IL-17 producing T-cells in the tumor microenvironment in response to current therapy, and how current efforts aim to utilize type 17 axis for clinical remission (**Fig. 2**).

Role of type17 cells in conventional therapy resistance

Resistance mechanisms against conventional chemo- or irradiation therapy are rather well-studied (131). Several reports have documented the involvement of IL-17 cytokine in the cancer-intrinsic acquisition of therapy resistance. Chemotherapy can trigger local inflammation, and such release of inflammatory cytokines could curtail the drug's anti-tumor effect. Indeed, treatment of 5-fluorouracil (5-FU) has shown to increase the production of IL-17 in the local tumor microenvironment (30). IL-17 secretion promotes the development of chemoresistance in breast and colon cancers by suppressing the expression of pro-apoptotic signals (132,133). Immunochemotherapy reagents and irradiation can also promote IL-17 secretion and induce resistance (11). In breast cancer patient samples, tumor-infiltrating lymphocytes (TILs) were demonstrated to be the main source of IL-17 (132), although in other cases autocrine IL-17 signaling seemed to be the more dominant mechanism. Tumor resistance mechanism to anti-angiogenic agents, such as anti-VEGF neutralizing Ab, has been shown to be triggered by IL-17 signaling as well. Tumor-infiltrating Th17 cells and IL-17 induced the expression of G-CSF from tumors through NF- κ B and ERK signaling. This led to immature myeloid-cell mobilization and recruitment into the tumor microenvironment, thereby desensitizing the tumor microenvironment from the effects of anti-VEGF therapy

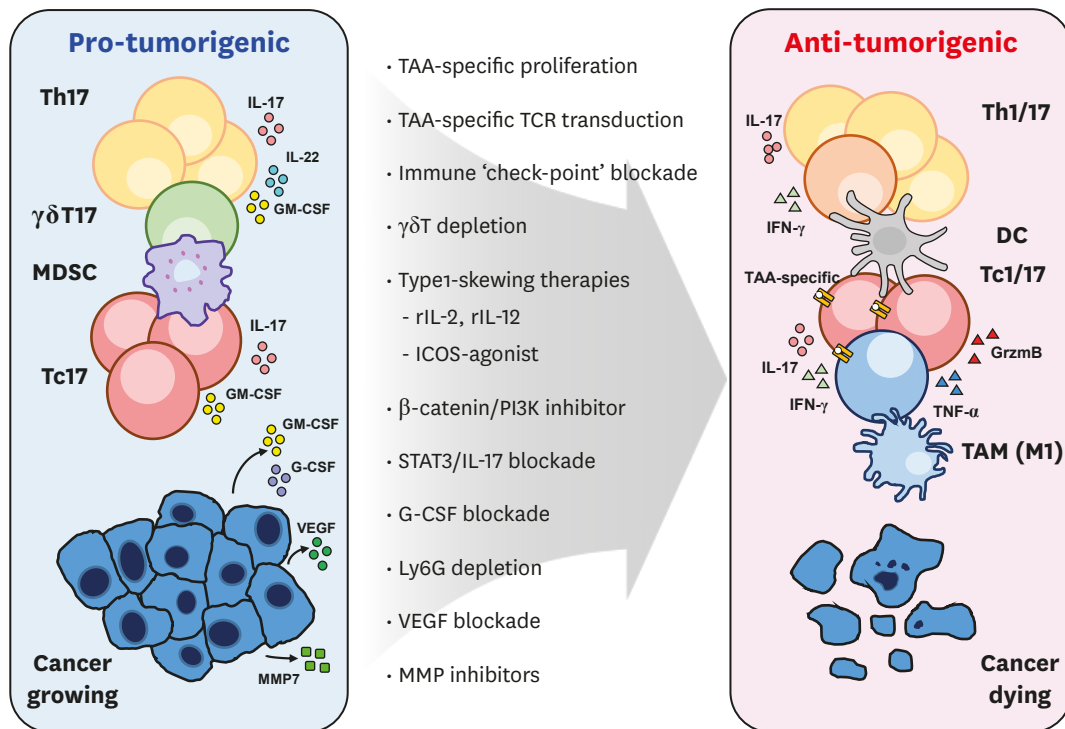


Figure 2. Developing strategies to utilize type 17 axis for anti-cancer therapy. Currently developing strategies to transform the type 17 landscape within the tumor microenvironment for successful cancer elimination are illustrated. TAM, tumor-associated macrophage.

(134). As such, current findings uniformly illustrate that in response to conventional cancer therapies, IL-17 secretion—whether it is secreted from cancer cells or tumor-infiltrating immune cells—contributes to the development of cancer resistance.

Therapeutic opportunities: tumor-specific Th17 adoptive cell transfer

Tumor-specific *in vitro* expanded Th17 cells have shown to eradicate cancer in melanoma models either by directly converting to Th1 cells (12) or assisting in Th1 recruitment into the tumor bed (135). In fact, tumor-specific Th17 cells have been reported to eradicate melanoma better than Th1 cells by recruiting DCs and CTLs to the tumor environment (106). This, along with a series of other proof of concept studies using mouse models of cancer, have demonstrated that type 17 cells can be potentiated to exhibit anti-tumor properties if the cells are exploited properly (136). Recent breakthroughs in chimeric Ag receptor (CAR) and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 technologies have made cancer-targeting cellular therapies become a reality (137). The most practical cellular platform for these technologies are currently the patient's own PBMC-derived T-cells that are transduced, expanded *ex vivo* and then transfused back to the patient. However, the fundamental limitation to this method is that often times the patient's own T-cells exhibit phenotypic and/or functional exhaustion, and are not 'fit' enough to survive and function *in vivo* when transferred back into the patient (138). As a potential alternative, several research groups have attempted to take advantage of the plastic nature of type 17 cells to convert into IFN- γ -co producing hybrid-like cells *in vivo* after adoptive transfer (75). Compared to the type 1 counterpart, type 17-skewed cells display enhanced capacity for self-renewal and durable persistence, which can be potentiated to be less easily exhausted and more resistant to apoptosis than its Th1 or Tc1 counterparts (77).

Additionally, other type 17 cell compartments such as $\gamma\delta$ T, or iNKT cells, although less attractive than T-cell platforms due to the sheer quantity of cells that can be extracted from PBMC, can be suggested as alternatives for cellular therapies (139,140). As such, it will be important to understand how type 17 lymphocytes are regulated in the tumor microenvironments.

Immunotherapies targeting type 17 responses

Many immuno-modulating therapies, most notably immune check-point blockade Abs, have shown clinical efficacy in cancer therapy. Therapeutic agents that regulate the type 17 response within the tumor microenvironment such as ROR γ agonists have also shown preclinical efficacy (77) and one candidate has already shown to be clinically safe (141). Currently, a phase Ib study is underway for assessing clinical and biological activity of the agonist in combination with anti-PD1 blockade (NCT03396497). Mechanisms and clinical efficacy remains to be determined. In a mouse model of melanoma, PI3K and β -catenin inhibition unleashed potent antitumor Th17 responses via conversion to an effector phenotype (142,143). Inducible T-cell co-stimulator (ICOS) agonistic signaling in a CAR-T construct also optimally expanded tumor-specific Th1/Th17 hybrid-like cells, with enhanced persistence *in vivo* compared to conventional CAR constructs (144). ICOS stimulation, PI3K inhibition, and other immunotherapeutic agents that can potentiate tumor-specific Th17 responses should be considered in the future.

On the other hand, treatment with an antagonistic IL-17 Ab has shown to block the development of pancreatic cancer metastasis in a murine xenograft model, indicating that IL-17 alone can be protumorigenic in the tumor microenvironment. In early stages of cancer development, anti-IL-17 Abs have shown to potentiate anti-VEGF therapy and prevent the progression of pancreatic intraepithelial neoplasia and pancreatic cancer metastasis. As such, consideration of protumorigenic and anti-tumor properties of type 17 cell types and developing therapeutic strategies to make the tumor environment more favorable for anti-tumor cell types seems to be an important focus point in future research.

Other small molecule agents that target STAT3 inhibition in cancer cells can also indirectly bring about the inhibition of type 17 responses in the tumor microenvironment (145). Several clinical trials have been conducted, at phase I/II levels, most notable of which are STAT3 inhibitors modulate STAT3 activity in cancer cells directly in advanced and solid cancers, as well as in cutaneous T-cell lymphomas (OPB-31121, OPB-51602, Otsuka Pharmaceutical, Tokyo, Japan; AZD9150, ISIS Pharmaceuticals Inc., Carlsbad, CA, USA). Clinical efficacy of these agents, and whether they work via the type 17 axis, remains to be determined.

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite the complexity of the matter, therapeutic opportunities are being explored to either remove the immunosuppressive effects elicited by IL-17 signaling via Ab blockade, or drive type 17 cells towards cancer elimination via skewing towards the IFN- γ -producing cytotoxic type 1 subset. On-going efforts aim to better understand if and how the variously employed immunotherapeutic approaches and cancer resistant mechanisms are associated with type 17 responses. Seemingly contradictory results in the function of type 17 cells, even within the same cancer type, illustrate that the therapeutic approach targeting the type 17 axis should be individually adjusted according to cancer type, stage, and the resulting dominant type 17 mechanism at work.

ACKNOWLEDGEMENTS

This work was supported by the research grant (2017R1A2B3007392; to YC), the Basic Science Research Program (2016R1A6A3A11933284; to Kim BS), and the Global Ph.D. Fellowship Program (2017H1A2A1042662; to Kuen DS) from the National Research Foundation of Korea (NRF) funded by the Ministry of Education of Korea.

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