Protumor vs Antitumor Functions of IL-17

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Protumor vs Antitumor Functions of IL-17

Gopal Murugaiyan* and Bhaskar Saha2†

Inflammation appears to be a necessity for both metastasis and elimination of tumor cells. IL-17, a proinflammatory cytokine produced by Th17 cells, contributes to both processes by playing a dual role in the antitumor immunity. On one hand, IL-17 promotes an antitumor cytotoxic T cell response leading to tumor regression. On the other hand, by facilitating angiogenesis and egress of tumor cells from the primary focus, IL-17 promotes tumor growth. Thus, the therapeutic application that uses IL-17 needs to be refined by minimizing its protumor functions. The Journal of Immunology, 2009, 183: 4169–4175.

Chronic inflammation is associated with increased tumor metastasis, but the mechanism of the association remains unknown. Hypoxia is proposed to be the triggering factor. As the tumor cells grow in mass, the core of the tumor suffers from hypoxia that triggers a chain of events leading to increased intratumoral vasculature. These vessels function as countercurrent conduits, helping the tumor cells metastasize out of the tumor and supplying not only nutrients but also immune cells into the tumor mass (1). Thus, the inflammation serves two counteracting functions: promoting tumor growth and antitumor immunity. Effective antitumor immunity depends primarily on T cells. Although IFN-γ, a cytokine produced by Th1 cells, and IL-10-secreting regulatory type 1 (Tr1) cells dampen immune responses against tumors, the other T cell subsets such as Foxp3-expressing regulatory T cells (Treg)3 and IL-10-secreting regulatory type 1 (Tr1) cells dampen immunity to tumor-associated Ags and represent the main hurdle in successful antitumor immunotherapy (2–4). In addition, the IL-17-secreting Th subset (Th17) promotes inflammation and thus may promote both tumor growth and tumor regression. Similarly, CD40, a costimulatory receptor that plays important roles in the induction of Th1 cells and CTLs (5–9) is also shown to play dual role not only in tumors (10–12) but also in Leishmania infection (13, 14). Thus, any factors that play dual roles, such as CD40 or IL-17, in promoting both tumor growth and antitumor immunity need to be studied in depth to minimize their protumor effects and thereby enhance the antitumor effects.

Although CD40-induced IL-12 is required for the induction of Th1, the inflammatory Th subset, lack of CD40 did not seem to impair Th1 response as much as expected and mediated the autoimmune encephalomyelitis (EAE). In contrast, p19-deficient mice are deficient in functional IL-23 and are resistant to EAE (17). Further investigation into these discrepancies led to the discovery of IL-17-producing CD4+ T cells that were later named Th17 cells. In this review, we will discuss how IL-17 also contributes to the antitumor immunity rather dually, although its major function may be to mediate inflammation.

IL-17, IL-17 receptors, and Th17 cells

The cytokine IL-17, originally termed CTLA-8, was isolated as a CD4-specific transcript from a rodent cDNA library (18). Later on, human IL-17 and the IL-17 receptor, IL-17R, were discovered (19–21). With the discovery of new cytokines that resemble it, IL-17 became the founding member of a new cytokine family composed of six cytokines and five receptors (Table 1 and Refs. 22–25). IL-17 is secreted primarily by Th17 cells as a homodimer and can be both nonglycosylated and N-glycosylated. In addition to Th17 cells, IL-17 can also be produced by cells other than Th cells, such as invariant NKT cells, CD8+ T cells, and γδ-T cells (26–28). The cytokine has pleiotropic functions with multiple targets. IL-17R has a single trans-membrane domain with a long cytoplasmic tail, implying the existence of multiple regulatory domains such that receptor signaling may trigger diverse functions. Discrepancies between IL-17 binding constants and the concentrations needed to evoke biological responses imply an additional subunit in IL-17R signaling (22, 23, 25). Although IL-17R expression is ubiquitous, most of the studies have been performed on fibroblasts, osteoblasts, and epithelial cells. However, the structure-function relationship is not available for either the cytokine or its receptor.

Because Th17 cells produce large quantities of IL-17A, most Th17-mediated effects are attributed to this cytokine. Many factors are required for the induction and stabilization of Th17 cells. Of these, TGF-β and IL-6 are the most crucial cytokines for its differentiation. IL-6 induces the production of IL-21, which subsequently favors Th17 differentiation in an autocrine manner (29, 30). These cells require CD40-induced IL-23 to

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3 Abbreviations used in this paper: Treg, regulatory T cell; DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; ROR, retinoic orphan receptor; VEGF, vascular endothelial growth factor.

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maintain their Th17 phenotype in vivo. The differentiation of Th17 cells that secrete IL-17 requires the expression of the transcription factor ROR-γt (where ROR is retinoic orphan receptor; Ref. 31). The induction of ROR-γt is dependent on STAT-3, which is preferentially activated by IL-6, IL-21, and IL-23. STAT-3-deficient T cells impair Th17 differentiation, whereas overexpression of a constitutively active form of STAT-3 increases IL-17 production. STAT-3 affects ROR-γt expression and binds to the IL-17 and IL-21 promoters. Thus, STAT-3 and ROR-γt regulate IL-17 production in a coordinated manner (Fig. 1).

It has been shown that Th17 cells are gradually increased in the tumor microenvironment during tumor development. In addition, Th17 cells have been found in various tumors, including mycosis fungoides, Sézary syndrome, prostate, and gastric cancer (Table II; Refs. 32–52). Many factors released by the tumor cells and the tumor stroma or molecules secreted by tumor-infiltrating immune cells such as TGF-β, IL-6, PGE2, IL-21, IL-23, osteopontin, IL-1β, and TNF-α can play major roles in the induction of Th17 differentiation (53–56) (Fig. 2). Interestingly, some of these factors are transcriptionally regulated by IL-17, thus creating positive feedback regulation of Th17 differentiation.

Regulation of Th17 differentiation in tumors

It has become clear that IL-17-producing Th17 cells and Treg cells share a common pathway. Although TGF-β favors differentiation of naive T cells into Tregs, simultaneous presence of both TGF-β and IL-6 promotes the differentiation of Th17 cells. Given the tight association of TGF-β and IL-6 with tumor incidence and progression, naive T cells entering an established tumor are more likely to be exposed to conditions favoring Th17 differentiation. TGF-β favors tumor growth by antagonizing Th1 differentiation and CTL functions such as perforin production (57). Upon stimulation with TGF-β and IL-6, CD8⁺ T cells not only lose their cytotoxic ability but are also induced to secrete IL-17 (58). Th1 or CD8⁺ T cell-expressed IFN-γ inhibits angiogenesis and induces MHC class I molecules in tumor cells, thus favoring immune recognition and the subsequent arrest of tumor growth (59). In contrast, IL-17 favors angiogenesis and tumor growth; therefore, replacing IFN-γ with IL-17 in the tumor microenvironment may have severe consequences for immune recognition and surveillance. Indeed, the presence of a tumor secreting both IL-6 and TGF-β causes local polarization or expansion of CD8⁺ T cells into an IL-17 secreting state (Tc17). Because IL-17 could potentially promote tumor cell survival, it is possible that the IL-17-producing CD8⁺ T cells may promote tumor growth (53).

In a developing tumor, IL-17 production is further enhanced by the reciprocal regulation of IL-12 and IL-23 by PGE2, the most abundant prostanoid in epithelial cell tumors (60). Although IL-12 production is decreased, IL-23 production is increased in tumors (61). Administration of PGE₂ resulted in higher expression of IL-23 and Th17 cells in the inflamed tissue. PGE₂ inhibits the induction of IL-12 and IL-27, which induce IFN-γ but inhibit IL-17 production from T cells (62). PGE₂, inducing and working with IL-23, favors the expansion of human Th17 cells and enhances IL-23-induced IL-17 production by memory T cells (56). Belonging to the IL-12 family, IL-23 performs protumor functions. In contrast to the antitumor role of IL-12, IL-23 up-regulates inflammatory processes, including matrix metalloproteinase expression and angiogenesis, and reduces infiltration and function of CTLs (63), thus contributing to tumor growth. Indeed, the IL-23/p19-deficient mice are completely resistant to carcinogen-induced tumors (63). The absence of tumor formation in these mice correlated with the absence of various markers that are indicative of tumor-associated inflammation, confirming the role of IL-23 and IL-17 in tumor-promoting inflammation. In fact, IL-23

Table I. IL-17 and IL-17 receptor superfamily: ligands, receptors, and functions

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Chromosomes</th>
<th>Cellular Sources</th>
<th>Receptors</th>
<th>Major Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A (CTLA8)</td>
<td>6p12</td>
<td>Memory T cells</td>
<td>IL-17RA, IL-17RC</td>
<td>Neutrophil recruitment, cytokine induction, inflammation</td>
</tr>
<tr>
<td>IL-17B</td>
<td>5q32-34</td>
<td>Multiple tissues</td>
<td>IL-17RB</td>
<td>Inflammation</td>
</tr>
<tr>
<td>IL-17C</td>
<td>16q24</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Modulation of Th1 cytokine production</td>
</tr>
<tr>
<td>IL-17D</td>
<td>13q12.11</td>
<td>Multiple tissues</td>
<td>Unknown</td>
<td>Cytokine secretion</td>
</tr>
<tr>
<td>IL-17E (IL-25)</td>
<td>14q11.2</td>
<td>Th2</td>
<td>IL-17RB</td>
<td>Modulation of Th2 cytokines</td>
</tr>
<tr>
<td>IL-17F (ML-1)</td>
<td>6p12</td>
<td>CD4+ T cells, monocytes</td>
<td>IL-17RA, IL-17RC</td>
<td>Angiogenesis</td>
</tr>
</tbody>
</table>

Table II. List of identified tumor type with IL-17⁺ or Th17 infiltrating cells

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>33, 42–44</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>36, 45</td>
</tr>
<tr>
<td>Myeloma</td>
<td>39</td>
</tr>
<tr>
<td>Melanoma</td>
<td>46</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>35, 38, 47</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>37</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>40, 49, 50</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>41</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>34</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>32, 48</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>51</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>52</td>
</tr>
</tbody>
</table>
FIGURE 2. Paradoxes in the antitumor functions of Th17. Initial infiltration of immune cells into the tumor mass results in TNF-α production and activation of the local and newly recruited APCs, inducing TGF-β, IL-6, IL-23, IL-12, and IL-10. TGF-β alone induces regulatory T cells (Tregs), which are anti-inflammatory, but the same cytokine with IL-6 induces IL-17-secreting Th17 cells, which are proinflammatory. Although IL-23 stabilizes, iTr and IL-10 inhibit Th17 cells. On one hand, PGE2 supports Th17 cells and, on the other, promotes Th2 differentiation, which is possibly triggered by the NK1.1⁺ T cell-secreted IL-4. Th2 cells secrete IL-4 and inhibit Th17 cells. Thus, PGE2 seems to play dual roles by promoting both inflammatory Th17 and the counteracting Th2 cells. Th17 cells induce inflammation in the tumor so that the T cells and other infiltrating cells destroy the tumor. Paradoxically, IL-17 increases angiogenesis that helps the tumor cells metastasize. Thus, multiple factors act in concert, some synergistically and some counteractively, to regulate the Th17-mediated control of tumor growth or regression. Perhaps the conditioning of the respective cell types involved in the response and their temporal regulation are crucial to this control.

Promotes the production of IL-17 by activated T cells (64). IL-23 is not required for triggering Th17 differentiation but is crucial for the function, survival, and propagation of this T cell population in the inflamed environment. In contrast to the protumor functions of IL-23, several reports have described the antitumor effects of IL-23. IL-23-overexpressing tumors show reduced growth and metastasis (65–69). The antitumor effects of IL-23 in these studies were found to be mediated through the enhancement of CD8⁺ T cell response. In addition, intratumoral injection of IL-23-overexpressing dendritic cells (DCs) resulted in a similar phenotype (70). Artificial overexpression of IL-23 induced potent antitumor immunity through various mechanisms. For example, IL-23 can mediate myeloid infiltration consisting of DCs, macrophages, and granulocytes, which contribute to the inhibition of tumor growth and boost an immune reaction to these immune-sensitive tumors. In addition, IL-23 overexpression is likely to increase systemic IL-23 levels, leading to the growth and survival of CD8⁺ memory T cells.

IL-23 can be induced in Propionibacterium acnes-conditioned dendritic cells upon re-stimulation with CD154 (71). In a model of the P. acnes infection, CD40-deficient animals had impaired IL-17 but not IFN-γ response. The CD40 stimulation was instrumental in inducing IL-23 and IL-6, of which the latter alone proved essential for Th17 differentiation, delineating sequential requirements for DC expression of CD40 and production of IL-6 during Th17 polarization and revealing distinct costimulatory requirements for Th1 vs Th17 generation (72). It has been shown in an EAE model that strong antigenic stimulation of T cells up-regulated CD154 expression, which, in concert with certain microbial stimuli (i.e., cytokine phosphate guanine, curdlan, and zymosan), synergistically increased DC IL-6 production and Th17 polarization. CD40 deficiency reduced the cytokine release, impaired Th17 development, and substantially reduced EAE. Thus, CD40-CD40L cross-talk is important for Th17 development by translating strong TCR and microbial stimuli into IL-6 production (73). Considering the above observations in different models of infection and autoimmunity, it is possible that in a growing tumor, MHC class II and CD40 expression may be low (74) due to the prevalence of IL-4 and IL-10. IL-10 inhibits CD40 signaling as well. Expression of both IL-23 and IL-6 together may be reduced to lower Th17 differentiation in tumors, but the same process provides an intratumoral TGF-β-rich milieu that skews the Treg/Th17 reciprocity toward Treg dominance.

Reciprocity between Treg and Th17 and the functional plasticity of the CD4⁺ T cells

Although a predominant TGF-β production in tumors causes Treg differentiation, the addition of IL-6 shifts the Th differentiation to Th17 cells, identifying IL-6 as a crucial factor in determining the Treg/Th17 reciprocity. Recent observations suggest that IL-2, which promotes Treg expansion, inhibits the generation of Th17 cells (75). Conversely, mice lacking IL-2 or STAT-5, which is required for IL-2R signaling, had fewer Tregs but more Th17 cells. Retinoic acid metabolite, secreted by DCs in tumors, can reduce Th17 but not Th1 cell differentiation through the inhibition of IL-6 signaling and promote Treg cell generation by enhancing TGF-β-induced Foxp3 promoter activity (76). Foxp3 can bind to ROR-γ and ROR-α to regulate each other’s activity counteractively (77). Conditional deletion of Foxp3 recovered ROR-γ activity and Th17 differentiation. Even though Foxp3 alone inhibits IL-17 expression, recent studies suggest that there exists a functional plasticity between these two cell types (reviewed in Refs. 78 and 79). The differentiated Treg cells can be converted into Th17 cells under the influence of strong inflammatory conditions. It has been shown that under IL-6 and TCR stimulation, Tregs from both the thymus and the periphery that down-regulated Foxp3 are converted to Th17 cells (80). STAT3-deficient T cells failed to repress Foxp3 upon IL-6 stimulation, consistent with the requirement for STAT3 suppression of Foxp3 in developing Th17 cells (81). Moreover, adoptive transfer of Tregs into lymphopenic hosts resulted in the loss of Foxp3 expression, and the Foxp3-negative cells could produce strong proinflammatory cytokines including IL-17 and IFN-γ. In addition, Foxp3⁺ IL-17⁺ CD4⁺ T cells have been observed both in vitro, after polarization in the presence of TGF-β and IL-6, and in vivo in mice (82, 83). Circulating human Foxp3⁺ IL-17⁺ T cells have in vitro suppressive activity (83). Although the origin and function of these coexpressers are currently unknown, it is possible that these cells are in transition during early Treg or Th17 differentiation. Accumulating evidence has demonstrated that Tregs exist in markedly higher proportions within PBMCs, tumor draining lymph nodes, and tumor-infiltrating lymphocytes of patients with cancer (84). Although Tregs represent the largest population...
of CD4⁺ T cells in progressing tumors, IL-17-positive T cells accumulate in parallel with Tregs within tumor tissues in mice as well as in blood and ascites of various tumor tissues, and both populations reached maximal levels in advanced tumors. Thus, the conversion of Treg cells into an IL-17-producing phenotype in the tumor microenvironment may further amplify inflammation as they control active immune responses against tumors. All of these observations suggest that in the tumor microenvironment, the regulation of Treg and Th17 proportion dictates the growth or regression of tumors. However, Th17 cells themselves contribute to the paradox, because part of their activities can both promote and regress tumors.

The paradox of the protumor and antitumor functions of IL-17

Protumor functions of IL-17. Many functions of IL-17 in the tumor microenvironment contribute to tumor progression. Apart from a minor direct effect on the proliferation and survival of tumor cells (34), as not all tumor cells express IL-17 receptor and respond to IL-17, the major protumor role of IL-17 in inflammation-associated cancer relies on its proangiogenic property of surrounding endothelial cells and fibroblasts. For example, IL-17-overexpressing human cervical cancer cells and nonsmall cell lung carcinoma cells show greater ability to form tumors in immunocompromised mice compared with control cells not overexpressing IL-17 (85, 86). In addition, IL-17 overexpression in fibrosarcoma cells enhances their tumorigenic growth in syngenic mice, owing primarily to the proangiogenic activity of IL-17. Moreover, the levels of Th17 cells were positively correlated with microvessel density in tumors (87). By acting on stromal cells and fibroblasts, IL-17 induces a wide range of angiogenic mediators (88, 89), including vascular endothelial growth factor (VEGF), that markedly promote inflammatory and tumor angiogenesis (90). IL-17 is able to up-regulate VEGF production by fibroblasts and therefore promote fibroblast-induced new vessel formation in inflammation and tumors. The IL-17-VEGF loop that modulates angiogenesis includes another angiogenic factor, TGF-β (91). TGF-β enhances the VEGF receptivity of endothelial cells by increasing VEGF receptor expression (92). IL-17 also induces IL-6 and PGE₂ and enhances ICAM-1 expression in fibroblasts. All of these molecules were known to have a major role in angiogenesis and tumor invasion (Fig. 3). IL-17 appears to stimulate production of IL-8 (93). IL-8 signaling promotes angiogenic responses in endothelial cells, increases proliferation and survival of endothelial and cancer cells, and potentiates the migration of cancer cells and infiltrating neutrophils at the tumor site. Accordingly, IL-8 expression correlates with the angiogenesis, tumorigenicity, and metastasis of tumors in numerous xenograft and orthotopic in vivo models (94). Moreover, IL-17 was found to induce IL-1β and TNF-α in macrophages, and these cytokines can further synergize...
with IL-17 to activate neutrophil-specific chemokines, thereby recruiting neutrophils to the site of inflammation (95).

Recently, the transcription factor NF-κB has been identified as a potential molecular bridge between inflammation and cancer (96). However, IL-17R signaling via ERK1, ERK2, JNK, and p38 MAPKs results in the activation of NF-κB, albeit weakly (97–100). Although proinflammatory cytokines (e.g., IL-6 and TNF-α), chemokines (e.g., IL-8), PGE₂, matrix metalloproteinase, and several adhesion molecules are reported to require NF-κB-mediated transcriptional activation (reviewed in Refs. 24 and 101), the role of the same transcription factor in the IL-17-mediated inflammatory responses remain to be established. Although IL-17-mediated cytokine expression is regulated primarily by NF-κB, the same cytokines can further stimulate NF-κB-mediated transcription of their own in tumor cells and tumor-associated stromal cells, thereby creating a sustained chronic inflammatory state within the tumor microenvironment (Fig. 3). In support of this notion, enhanced cervical cancer growth elicited by IL-17 was associated with increased expression of IL-6 and macrophage recruitment to the tumor sites (86). Therefore, IL-17 might also function through IL-6 to promote tumor development.

Chemokines can stimulate or inhibit proliferation and chemotaxis of endothelial cells of the blood vessels that serves tumors. The balance between angiogenic and angiostatic chemokines in the tumor microenvironment can determine tumor survival. When a tumor or tumor-infiltrating immune cells secrete more of an angiogenic chemokine than an angiostatic chemokine, angiogenesis is stimulated and leads to new blood vessel formation and continued tumor growth. In contrast, an excess of angiostatic chemokines in the tumor microenvironment can inhibit neovascularization and cause the subsequent arrest of tumor growth (102, 103). IFN-γ is a potent inducer of angiostatic cytokines (e.g., CXCL10) from a variety of cells, including fibroblasts, endothelial cells, and tumor cells (104). In contrast, IL-17 has been shown to selectively enhance the production of angiogenic chemokines such as CXCL1, CXCL5, CXCL6, and CXCL8 in tumor cells and epithelial cells (85, 105). In addition, IL-17 is also known to inhibit angiostatic chemokine secretion by fibroblasts (85). Thus, IL-17 may shift the local biologic balance between angiogenic and angiostatic chemokines toward a predominance of angiogenic chemokines to enhance the net angiogenic activity.

Antitumor functions of IL-17. Although IL-17 seemed to us to be a potential tumor-promoting cytokine, a sizeable number of reports have described tumor-inhibitory effects of IL-17. Th17-polarized cells were found to be more effective than Th1 cells in eliminating large established tumors (106). However, the Th17-mediated tumor responses were highly dependent on IFN-γ. Indeed, the effects of Th17-polarized cells were completely abrogated by the administration of IFN-γ-depleting Abs and not by IL-17- or IL-23-depleting Abs. The Th17-polarized cells also secreted cytokines associated with the Th17 phenotype, such as IL-17F, IL-22, IL-21, and CCL20. In addition, IL-17 has been shown to inhibit the growth of hematopoietic tumors such as mastocytoma and plasmacytoma by enhancing CTL activity (107). Different mechanisms have been proposed for the IL-17 enhancement of tumor-specific CTLs. IL-17 has been shown to induce IL-6 from variety of cells. Moreover, IL-17 stimulation can induce IL-12 production from macrophages (108). Both IL-6 and IL-12 have been associated with the induction of tumor-specific CTL induction. IL-17 promotes the maturation of DC progenitors as indicated by increased expressions of costimulatory molecules, MHC class II Ags, and allostimulatory capacity (109). This may lead to further improvement in T cell priming by tumor cells producing IL-17 (Fig. 3). In addition, IL-17-transduced fibrosarcoma cells induced tumor-specific antitumor immunity by augmenting the expression of MHC class I and class II Ags (110). These studies were focused on the effects of exogenous IL-17 in established mouse tumor cell lines. A recent demonstration shows that tumor growth in subcutaneous tissue and lung tumor metastasis are enhanced in IL-17-deficient mice. The effect is accompanied by reduced IFN-γ levels in tumor-infiltrating NK cells and T cells (111). Although this study emphasizes the importance of endogenous IL-17 in tumor immunity in one particular model, it remains to be determined whether endogenous IL-17 is involved in regulating tumor immunity in other tumor models, and the involvement of other Th17-associated molecules such as IL-17F and IL-22 in determining tumor growth must also be studied. Although IL-17 has been shown to promote tumor growth by inducing angiogenesis, the same process provides the channel through which the immune cells can invade and inflict an assault on the relatively inaccessible tumor cells at the core of the solid tumor mass. Thus, IL-17-induced angiogenesis might also promote antitumor immunity by being a supply channel for immune cells to reach and attack the inner mass of solid tumor.

Conclusions
IL-17 secreting Th cells, termed Th17 cells, can either stimulate or inhibit tumor growth and progression. Many of the inflammatory functions of IL-17 can initially benefit the host, but with the altered tumor microenvironment, IL-17 starts promoting tumor growth. The pro-tumor vs anti-tumor effects of IL-17 are thus functions of the IL-17-induced inflammatory mediators and, perhaps, the mediators that counter-regulate IL-17 production, all operating in tandem. These factors regulate the plasticity of the T cell differentiation—from cytotoxic CD8⁺ T cells to IL-17-producing inflammatory CD8⁺ T cells or from Treg to Th17 or vice versa—by reprogramming the switching of gene expressions in T cells (112–114). Therefore, to formulate a more efficient therapeutic strategy, we need to better understand the role of the factors that regulate T cell plasticity.

Disclosures
The authors have no financial conflict of interest.

References


