REVIEW

When worlds collide: Th17 and Treg cells in cancer and autoimmunity

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The balance between Th17 cells and regulatory T cells (Tregs) has emerged as a prominent factor in regulating autoimmunity and cancer. Th17 cells are vital for host defense against pathogens but have also been implicated in causing autoimmune disorders and cancer, though their role in carcinogenesis is less well understood. Tregs are required for self-tolerance and defense against autoimmunity and often correlate with cancer progression. This review addresses the importance of a functional homeostasis between these two subsets in health and the consequences of its disruption when these forces collide in disease. Importantly, we discuss the ability of Th17 cells to mediate cancer regression in immunotherapy, including adoptive transfer and checkpoint blockade therapy, and the therapeutic possibilities of purposefully offsetting the Th17/Treg balance to treat patients with cancer as well as those with autoimmune diseases.

Keywords: autoimmunity; cancer; immunotherapy; Th17; Treg

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INTRODUCTION

$CD4^+$ T cells play a critical role in regulating human health and disease by orchestrating the immune system to contend with danger induced by foreign antigens, such as infections or cancer formation. Proper function of the $CD4^+$ T cell compartment relies on an adjustable equilibrium among various T cell subsets, which help trigger the host's immune system in defense against threat. While the division of CD4 support was previously hypothesized to be dominated solely by Th1 and Th2 helper subsets, mounting evidence over the past decade reveals that Th17 cells and regulatory T cells (Tregs) also play important roles in regulating health and exacerbating autoimmunity and cancer. Herein, we will discuss the delicate balance between Th17 and Treg cells in maintaining a healthy, functioning immune environment, as well as the harmful effects that transpire when homeostasis is disturbed and their therapeutic implications. Finally, we discuss the possibilities of harnessing a Th17 response against cancer in adoptive transfer and checkpoint blockade therapy, thus highlighting an approach whereby therapeutically and purposefully offsetting the Th17/Treg balance could be effective in treating human cancers.

Basics of T helper subsets

Before the 1980s, helper T cells were believed to be a single subset among T lymphocytes[1]. Increasing evidence now suggests that there are at least seven distinct T helper subsets differentiated in response to particular combinations of cytokines. These subsets are also controlled by different transcription factors to produce a characteristic milieu of cytokines and exert an effector function against self and foreign antigens. These subsets are described below and summarized visually in Fig. 1.

$CD4^+$ T cells differentiate into subsets such as Th1, Th2, Th17, Treg, Th9, Th22, and T follicular helper cells[2]. Th1 cells rely on the expression of T-bet and eliminate intracellular pathogens through IFN-γ production, which activates macrophages[2–4]. Th2 cells play a role in the presentation of allergens; promote immunity against parasites through production of IL-4, IL-5, and IL-13, and are regulated by transcription factor GATA3[5]. Interestingly, Th2 differentiation is also mediated by IL-4, creating a positive feedback loop to bolster proliferation[2,6]. Th17 cells secrete IL-17A, IL-17F, IL-21, IL-22, and CCL20, express master transcription factor RORγt, encoded by *Rorc*[7], and promote inflammation in response to infections[8–10]. Regulatory T cells (Tregs) suppress effector function through secretion of inhibitory cytokines such as IL-10 and TGF-β or through cell-mediated engagement of inhibitory checkpoint molecules such as TIGIT and CTLA-4[11]. The relevance of Th17 cells has been documented in promoting autoimmunity, carcinogenesis, and antitumor immunity, whereas Treg cells are essential for immune tolerance and have been shown to dampen autoimmunity and antitumor immunity[6,12,13].

Most recently, Th9, Th22, and T follicular helper cells (Tfh) have been described as distinct helper populations. As such, knowledge of the programming cytokines and master transcription factors for these subsets is still somewhat under debate. Th9 cells differentiate in response to IL-4 and TGF-β[14–16] and produce IL-9 under control of the transcription factors STAT6, PU.1[17], IRF4[18], BATF[19], and FOXO1[20]. IL-9 recruits lymphocytes and mast cells as effectors[21–23] and is enhanced under the influence of IL-1β and transcription factor IRF1[24]. Th22 cells are polarized by IL-6 and TNF-α to secrete IL-22[25] and have been shown to exacerbate psoriasis in patients[26]. Which transcription factor(s) control Th22

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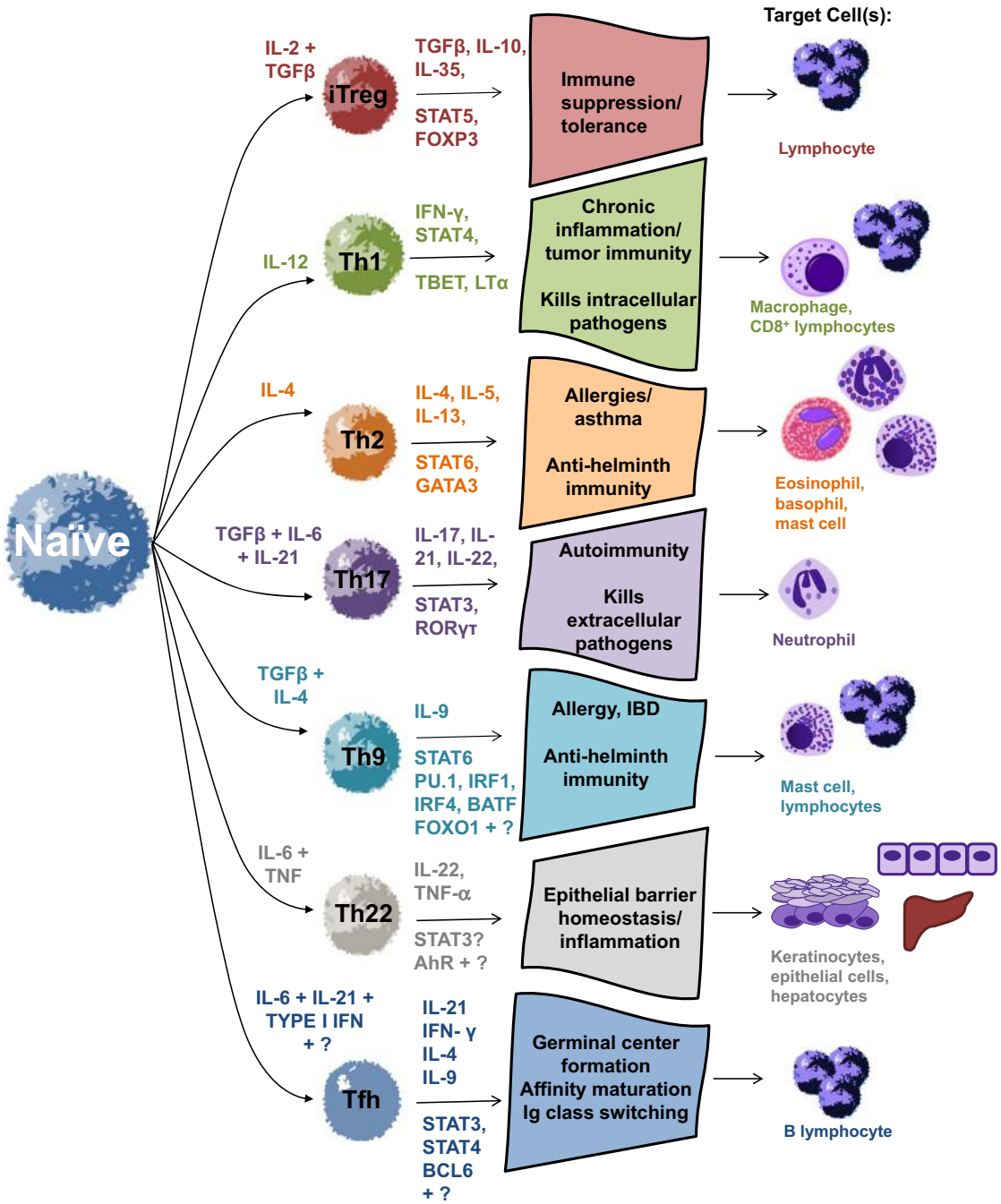

Fig. 1 $CD4^+$ cell differentiation and effector function. $CD4^+$ T cells differentiate based on the presence of various cytokines. Under the influence of IL-2 and TGF-β, Treg cells develop and express transcription factors STAT5 and Foxp3 and cytokines TGF-β and IL-10. IL-12 influences Th1 cell development and promotes immunity upon the presence of IFN-γ, STAT4, T-bet, and LTα. Th2 cell differentiation is induced by IL-4, during which cytokine release may manifest in allergies or asthma. Th17 cell development occurs following the influence of TGF-β, IL-6, and IL-21. IL-1β and IL-23 maintain Th17 cell stabilization during clonal expansion. Upon differentiation, Th17 cells are most commonly classified by their expression of RORγt and STAT3. Th9, Th22, and Tfh cells have been most recently described, and transcription factors controlling their differentiation remain under debate

differentiation is less clear[27,28]. However, several groups have identified aryl hydrocarbon receptor (AHR) as having a vital role in Th22 differentiation[25,28–30], while the role of T-bet is more controversial[25,30]. Tfh cells classically secrete IL-21 for B cell development in germinal centers, as well as IFN-γ and IL-4 to aid B-cell immunoglobulin class-switching to IgG and IgE in the lymphoid follicle[31]. They also secrete IL-9 to promote B cell memory and differentiation of plasma cells[31,32]. Although Bcl6 has been the widely accepted transcription factor controlling differentiation of Tfh cells, there are also recent reports suggesting STAT4 and T-bet[33], c-Maf[34], IRF4[35], and Batf[36] are important to differentiation of this lineage.

T helpers in opposition

Our current understanding of T helper function revolves around a theory that subsets are in a state of equilibrium[37]. Upon activation of one particular subset, other subsets are modulated or inhibited in order to promote the most specific effector response in defense

against imminent threat[37,38]. Historically, this discussion began with the Th1/Th2 hypothesis of distinct opposing T helper subsets, formulated after searching for a T cell responsible for helping antibody production versus one responsible for tissue damage in delayed-type hypersensitivity (DTH)[39,40]. Early studies claimed that Th1 cells mediated tissue damage in DTH, not the antibodies in serum, and would likely be the cell responsible for mediating tissue damage in various autoimmune diseases[40]. After several failed attempts to show that tissue damage in murine experimental autoimmune encephalitis (EAE) was mediated by Th1 cells and their effector cytokine, IFN-γ, the characterization of a novel subset called Th17 cells emerged[41–45]. The Th1/Th17 balance developed, recognizing that IFN-γ and IL-17 have antagonistic properties, as blockade of IFN-γ results in increased IL-17 production by T cells[46,47]. Finally, an antagonistic relationship between Th17 cells and Tregs has been described, as their differentiation is stimulated by similar cytokines yet they have different functions[48–50]. Th17 cells serve as an effector lymphocyte population, while Tregs are suppressor cells[48–50]. Herein, we will focus on the particular Th17/Treg balance of opposing forces in autoimmunity and cancer and the roles of each subset in both promotion of and protection from these pathogenic phenotypes.

The YIN: Th17 cells

Differentiation. The emergence of the distinct Th17 lineage can be attributed to studies of central nervous system autoimmunity. Early studies involving the EAE model revealed that IL-23 knockout (KO) mice were resistant to developing EAE, while IL-12 KO mice remained susceptible[51]. This surprising series of experiments signified that Th1 polarization was not critical to the autoimmune phenotype, as was previously posited[51]. IL-23 was subsequently discovered to drive polarization of a pathogenic $CD4^+$ T cell subset characterized by production of IL-17A and IL-17F, which could induce EAE upon adoptive transfer, while IFN-γ producing Th1 cells could not[52].

These IL-17 producing cells were considered a distinct lineage, when the milieu of cytokines supporting their differentiation was shown to be independent of the environment of cytokines required for Th1 and Th2 development[47,53]. In fact, the in vitro differentiation of naive $CD4^+$ T cells to Th17 cells is suppressed by Th1/Th2 cytokines IFN-γ and IL-4[53] and relies on costimulation by CD28 and ICOS[47]. The cytokines most important to Th17 differentiation are TGF-β, IL-6, and IL-1β, and the phenotype is maintained long term in the presence of IL-21 and IL-23[54,55]. The role of each of these individual cytokines is discussed below.

Along with IL-6, TGF-β is well known as a critical cytokine for inducing RORγt in naive $CD4^+$ T cells, which in turn drives their differentiation to a Th17 phenotype. However, new findings have provided insight into exactly how TGF-β regulates RORγt. Interestingly, TGF-β was shown to modulate the SKI–SMAD4 complex[56]. The SKI–SMAD4 complex suppresses RORγt, as the SKI protein inhibits acetylation of the *Rorc* locus[56]. However, in the presence of TGF-β, SKI is degraded, permitting RORγt expression in $CD4^+$ T cells and ultimately driving Th17 differentiation[56]. Low doses of TGF-β1 also inhibit IL-2-mediated activation of STAT5 and reduce T-bet and GATA3 expression, which inhibits Th1/Th2/Treg differentiation while promoting the Th17 lineage[57]. Recent findings have also demonstrated that phosphatase and tensin homolog (PTEN) in Th17 cells suppresses IL-2 signaling, reducing STAT5 and the Treg pathway while upregulating STAT3, a transcription factor that supports the Th17 pathway[58]. It is also important to appreciate that TGF-β and IL-6 induce the IL-23 receptor (IL-23R) in Th17 cells[59]. IL-23 further activates STAT3, RORα and RORγt in Th17 cells to maintain their long term proinflammatory signature[6,7,59,60]. Thus, naive $CD4^+$ T cells cultured with TGF-β and IL-6 but without IL-23 still produce IL-17 but also produce anti-inflammatory cytokine IL-10[61,62]. These non-pathogenic Th17 cells do not induce EAE and have compromised persistence and phenotypic maintenance in vivo [62].

Recent reports have also shed new light on the role of IL-1β and IL-21 in regulating Th17 cells. IL-1β induces alternative splicing of Foxp3, inhibiting Treg differentiation and promoting IL-17A production[55]. Finally, IL-21 activates STAT3 downstream and can induce Th17 differentiation even in the absence of IL-6[63]. As Th17 cells also produce IL-21, this autocrine signaling amplifies the Th17 response and aids in their maintenance. Globally, transcription factor JunB also supports the Th17 phenotype while repressing alternate $CD4^+$ Th1 and Treg phenotypes[64]. Collectively, this mounting body of work reveals that various cytokines and key transcription factors are critical for inducing Th17 differentiation and maintaining their function and phenotype long term.

Function. At homeostasis, Th17 cells promote gut barrier defense, granulopoiesis, granulocyte chemotaxis, and immunity against extracellular pathogens. Most Th17 cells reside within the lamina propria of the gut in healthy individuals but are induced at other mucosal sites upon exposure to danger signals, such as infection[65]. To maintain gut defense, IL-17 upregulates claudins for tight junction formation in the intestinal barrier and IL-22 plays a role in epithelial maintenance[66,67]. IL-17 induces granulopoeisis indirectly through stimulation of epithelial cells, endothelial cells, and fibroblasts to secrete GM-CSF, IL-6, IL-8, and MIP-2[68,69]. In turn, IL-8, and MIP-2 enhance chemotaxis of neutrophils[70]. Mice deficient in IL-17R have an impaired ability to repopulate these immune cells after irradiation[71]. Th17 cells and IL-17 have been implicated in immunity against extracellular pathogens, such as *Klebsiella pneumoniae*[69], *Staphylococcus aureus*[72], *Salmonella enterica* serovar Enteriditus[73], and *Shigella flexneri*[74] among other bacterial species. Th17 cells have also been shown to augment Th1 recruitment in *Mycobacterium tuberculosis* infection, which is critical to granuloma formation and sequestration of bacteria[75]. These collective Th17 functions are critical in preserving the health of the host and when compromised can lead to various disease symptoms, as discussed below.

Mutations that result in loss of Th17 cell function manifest in disorders such as Job's syndrome, also named hyper-IgE syndrome, and chronic mucocutaneous candidiasis (CMC) disease. Job's syndrome is caused by an autosomal dominant STAT3 inactivating mutation and results in increased susceptibility of patients to *S. aureus* and *Candida albicans*[76]. Phenotypically, this disease presents as a triad of eosiniphilia, eczema, and recurrent skin and pulmonary infections[77]. CMC disease, manifested by chronic infection of the skin, nails, and mucosa by *C. albicans*, is related to any of four inheritable gene defects in IL-17RA, IL-17RC, IL-17F, or ACT1[78]. These mutations impair the host Th17 response and increase susceptibility to infection with extracellular pathogens. Thus, Th17 cell function plays a critical role in regulating immune responses in health and in disease within the host. Based on these findings, translational researchers and physician scientists have been actively investigating methods to regulate the Th17 pathway in patients to treat both autoimmunity and infectious disease.

The Yang: Regulatory T cells

Effector functions of the adaptive immune response provide the ability to fight and clear invading pathogens while generating memory against those pathogens for a rapid recall response. Such effector functions, while vital for survival, can be damaging if engaged for too long, driving chronic inflammation, or if directed against self-tissue, causing autoimmunity[38]. As such, effector T cells must be regulated to prevent immune cell defense from turning to offense.

The discovery and recognition of a distinct T cell subset functioning to suppress immune responses was controversial in the late 20th century, and some debate over lineage still exists today. The first discovery that T cells could dampen immune

responses was made in 1970, and thereafter, these cells were termed "suppressor" cells[79]. These cells were defined by their expression of the "I-J" molecule, which was claimed to be important to suppressive function[80]. Controversy arose when the I-J coding region could not be identified on murine major histocompatibility complex (MHC) and due to a lack of other concrete identifying markers led to the collapse of the "suppressor" T cell movement[81].

Around that time, it was separately noted that immune tolerance could be broken from the beginning of development. Neonatal thymectomy of mice resulted in destruction of the ovaries, which was later correlated with tissue damage in other organs[82,83]. Identification of two types of "regulatory" T cells followed—one naturally occurring in the thymus and responsible for clonal deletion of T cells specific to self-antigens and one in the periphery, inducible from naive $CD4^+$ T cells.

Differentiation and function

Several cornerstone discoveries about Tregs include the identification of IL-2Rα (CD25) as a functional marker, the importance of IL-2 for tolerogenic function, and designation of Foxp3 as the master transcriptional regulator. In mice, CD25 marks a population of $CD4^+$ T cells that normalize immune function and prevent lethal autoimmunity[84,85]. Reconstitution of the neonatally thymectomized mice with $CD4^+$ $CD25^+$ T cells, but not with $CD25^-$ cells, prevented autoimmune development[86]. IL-2 is critical for Treg development and function, as IL-2Rα KO, IL-2Rβ KO, and neutralization of IL-2 induce severe autoimmunity[87–89]. Very recent reports by Dwyer et al. have further revealed that the level of IL-2 signaling is vital to proper Treg function, as chronically reduced IL-2 signaling compromised peripheral tolerance and led to accelerated onset of type 1 diabetes in NOD mice[90]. Despite its necessity for function, CD25 is not exclusively on Tregs and does not mark the Treg population as effectively in humans as it does in mice. Other Treg surface molecules include glucocorticoid-induced TNF receptor (GITR), PD-1, CTLA-4[85], TIGIT[91], and GARP[92], though these markers are also not exclusive to Treg cells. The master transcriptional activator of Tregs is Foxp3, which is a more specific marker for Tregs[93] and is important for Treg development and maintenance of function[12,94–97]. Foxp3 is enhanced by Helios expression[98], which correlates with GARP expression and marks a regulatory cell with greater immunosuppressive characteristics[99]. Bluestone and coworkers found that Foxp3 expression also correlates inversely with CD127 (IL-7Rα) expression, identifying the phenotype of $CD4^+CD25^+CD127^{lo/-}$ as more representative of human Tregs[100]. Foxp3 is present in natural and peripheral Tregs, although the exact mechanism of generating peripheral Tregs in the context of antigen specificity is still somewhat under debate[101].

Cellular development of Th17 and Treg cells shares a common cytokine, TGF-β, which is needed to induce Foxp3 and RORγt in Treg and Th17 cells, respectively. TGF-β with IL-2 can induce $Foxp3^+$ Treg differentiation peripherally from naive $CD4^+$ T cells, whereas TGF-β plus IL-6 (secreted by the innate immune arm, such as activated dendritic cells) induces the Th17 lineage (Fig. 1)[48,49,102]. As mentioned previously, IL-6 and IL-21 induce STAT3, which inhibits Foxp3, while IL-2 induces STAT5, which reduces STAT3 binding and inhibits Th17 differentiation[59,103–105]. Supplemental IL-2 as therapy for autoimmune disease may augment Treg function and boost self-tolerance. The notion is now well appreciated that generating a regulatory response is closely related to differentiating an effector Th17 response against pathogens. Collectively, the immune system tightly regulates Th17/Treg homeostasis via the TGF-β/IL-2 and IL-6 cytokine axis.

Defects in Treg function lead to unregulated immune responses to self-tissue. Treg function depends heavily on migratory activity—during an immune response, Tregs migrate from blood to lymph nodes and tissues, and the ratio of Treg/non-Treg $CD4^+$ cells in those compartments increases[106]. Recent reports have shown that Treg migration is regulated by bioenergetics. Specifically, glucokinase-dependent glycolysis in Tregs was found to prevent the effector response from generating excess

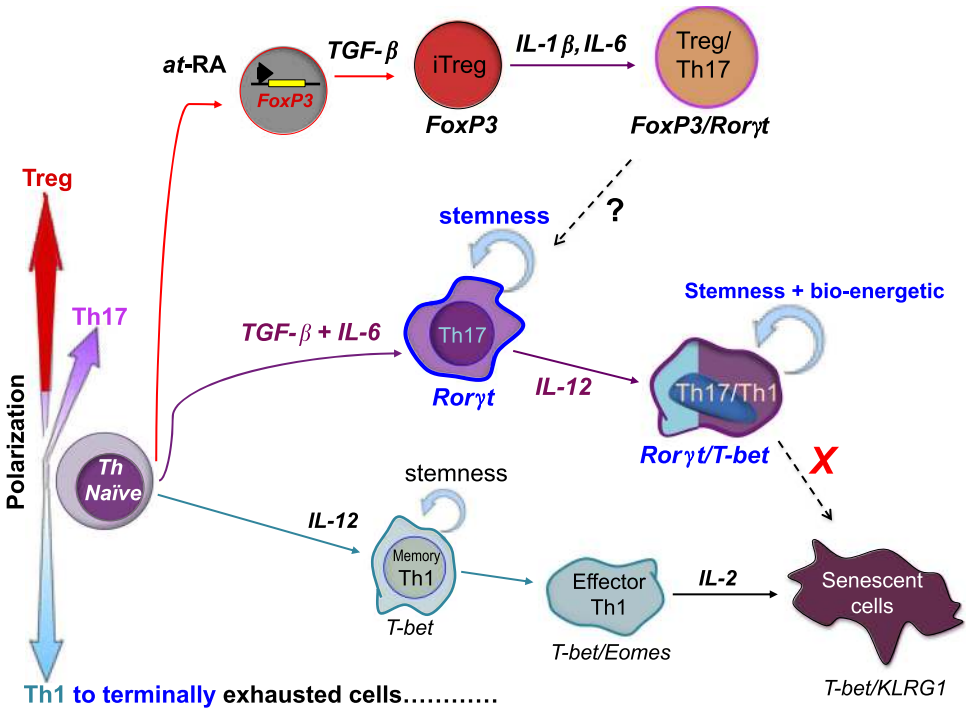

Fig. 2 Cytokines induce functional plasticity of Th17s and Tregs. Both Th17 cells and Tregs exhibit the ability to acquire characteristics of other helper subsets. The presence of Th17-type cytokines IL-1B and IL-6 can generate Treg-producing IL-17. The ability of Th17 to differentiate into a Treg-like phenotype is less well described at this time. Similarly, a Th17 cell reactivated in the presence of IL-12 generates an ex-Th17 or non-classical Th1 cell with self-renewing abilities compared to a classical Th1 cell that progressively differentiates into senescence

Table 1. Th17/Treg role in pathogenesis and therapy for autoimmune diseases

	Th17 role in pathogenesis	Treg role in pathogenesis	Therapeutic intervention		References
			Th17-related	Treg-related	
MS	↑ IL-17 in CSF and chronic lesions	nL Frequency	Ustekinumab showed no benefit	Baltimore VA looks to induce myelin-specific Tregs	126–128
	IL-23 KO mice resist EAE	↓ Function	Secukinumab may show benefit		
Psoriasis	↑ IL-17, IL-23, IFN-γ in lesions stimulate keratinocyte proliferation	↓ Function Increased Treg plasticity to Th17-like phenotype	Secukinumab Ustekinumab Guselkumab	None	130–139
RA	↑ Th17 frequency	↓ Frequency	No benefit over standard of care with Secukinumab or Ustekinumab	Tocilizumab restores Th17/Treg imbalance	119,141–144
	↑ Th17 migration to synovium	nL Function	Tociluzumab has shown efficacy alone or in combination with methotrexate		
IBD	↑ IL-17 in serum and mucosa	↓ Frequency	Ustekinumab showed no benefit over placebo; showed efficacy in patients who failed anti-TNF-α therapy	Anti-CD3 shows benefit in UC; may result from accumulation of IL-10^{+} Tregs in colon	145–148
	IL-23 mediated pathology	nL Function			
SLE	↑ IL-17 compared to healthy controls	↓ Frequency	None	MSCT/HSCT induces remission	121,149–151
	IL-23R KO mice show reduced severity of nephritis	↓ Function, migration			

MS multiple sclerosis, *nL* normal, *RA* rheumatoid arthritis, *IBD* inflammatory bowel disease, *UC* ulcerative colitis, *SLE* systemic lupus erythematosus, *KO* knockout, *MSCT* mesenchymal stem cell transplant, *HSCT* hematopoietic stem cell transplant

inflammation[107]. Without the ability to migrate, Tregs cannot relocate to the site of inflammation, as shown by their reduced ability to suppress allograft rejection[107].

Similarly, inheritable mutations that render Tregs dysfunctional cause lethal autoimmunity. Mutations in Foxp3 result in a disease known as IPEX, which is characterized by immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome[108]. This disorder generally presents early after birth with severe dermatitis or psoriaform lesions, watery diarrhea, excessive cytokines, thyroiditis and hypothyroidism and frequently leads to death early in childhood[108]. This mutation impairs the regulatory host response and permits rampant inflammation from other unopposed immune cell compartments.

Th17/Treg plasticity

Both Th17 and Treg cells have been described as exhibiting the property of plasticity. Plasticity is defined by the unique ability to adapt to signaling cues in a changing environment. For example, as shown in Fig. 2, Th17 cells can acquire Th1-like characteristics after activation, a property that likely plays a role in enhancing autoimmunity and antitumor immunity. Termed ex-Th17 cells, or non-classical Th1 cells, these cells lose their ability to secrete IL-17 while gaining the capacity to secrete IFN-γ in the presence of proinflammatory signals, such as TCR-triggering or exposure to IL-12 or IL-23[109]. Although ex-Th17 cells acquire a Th1 profile, they can still be distinguished from classic Th1 cells via unique surface markers, including CD161, CCR6, and IL-17RE[110]. Moreover, these cells are functionally distinct from classic Th1 cells, secreting more TNF, IL-2, GM-CSF, and IFN-γ[111]. Interestingly, proliferation of ex-Th17 cells is not suppressed by Treg cells in direct contrast to classical Th1 and Th17 cells, which are inhibited by Treg cells[111]. These data implicate a possible role for these cells in an unbalanced Th17/Treg autoimmune response. The observed plasticity of Th17 cells occurs only in the direction of Th17 to Th1, as Th1 cells have not been shown to convert to Th17-like T cells[112].

As also displayed in Fig. 2, Tregs are able to reacquire characteristics of Th17 cells under a cytokine-driven influence. When Foxp3^{+} Tregs are exposed to IL-6 with or without IL-1β and IL-23, Foxp3 becomes down-regulated in favor of expressing Th17 genes including IL-17, IL-22, IL-23R, and RORγt[113]. Such ex-Foxp3 cells have been implicated in the pathogenesis of autoimmune arthritis because they have a reduced ability to suppress cytotoxic CD8^{+} and effector Th17 cells[114]. Conversely, the transition to Th17 cells acquiring Treg-like characteristics is less well described but has recently been shown in ovarian and colorectal cancer model. Over time, tumor-infiltrating cells that produce IL-17 and are Foxp3^{-} transdifferentiate into IL-17A^{neg}-Foxp3^{+} cells, termed "ex-Th17 Tregs"[115]. It is hypothesized that this conversion is controlled by TGF-β and prostaglandin E2 (PGE2)[115]. This dynamic functionality by Th17s and Tregs reveals the complexity of manipulating these subsets therapeutically.

Th17/Treg in Autoimmunity

Th17 cell-mediated immunity is important for maintaining mucosal and hematopoietic homeostasis. However, too strong of a Th17 cell response can induce autoimmunity. Likewise, a lack of Tregs can result in lethal autoimmunity in humans. As detailed in Table 1, the altered homeostasis between Th17 and Treg has been implicated in several autoimmune diseases, including multiple sclerosis[116,117], psoriasis[118], rheumatoid arthritis[119], inflammatory bowel disease[120], and systemic lupus erythematosus[121]. Thus, the relationship between effector Th17 cells and Tregs must remain balanced to preserve functional immunity and health of the host. Some important examples of this Th17/Treg balance in patients are discussed in various

autoimmune manifestations below. In addition, recent therapeutics that have been used to reduce the severity of these diseases by modulating the Th17/Treg axis are discussed below.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease involving destruction of myelin in central nervous system white matter. This disease presents in patients as deficits in sensory or motor function, unilateral vision loss, diplopia, gait disturbance, or loss of bladder control, among other varied symptoms of nervous system malfunction. As discussed previously, the experimental mouse model of MS is EAE, from which came the discovery of Th17 cells and their role in neuroinflammation. In MS patients, myelin-reactive T cells not only secrete IL-17 but also secrete IFN-γ and GM-CSF in contrast to T cells from healthy individuals[122]. These data suggest, as in the EAE animal model, that Th17 cells play a role in MS in human patients. These data also suggest that these Th17 cells are pathogenic due to their ability to cosecrete multiple cytokines. IL-17 levels have been reported to be increased in the CSF of MS patients during symptomatic relapse[123], as well as in chronic lesions[116]. Interestingly, Th17 cells from patients with active symptoms of MS secrete less IL-10 compared to those who are clinically stable[124]. These data further suggest that Th17 cells from MS patients with stable disease are non-pathogenic with a regulatory property that might protect the host from aberrant cytotoxic responses against self.

Treg frequency and function have also been studied in MS. Although the frequency of Tregs is generally accepted as unaltered in MS patients[117,125], Tregs from MS patients show impaired ability to suppress proliferation and cytokine secretion of other $CD4^{+}CD25^{-}$ T cells compared to healthy individuals[117]. Both the upregulation of IL-17 and down-regulation of Treg-mediated immunity likely contribute to the pathogenesis of MS in humans.

Due to these Th17/Treg-related causes of MS, therapies that target these pathways are of great interest to the medical community. However, intriguingly, recent trials with IL-12/23 blockade (ustekinumab) did not show efficacy against the disease[126]. However, blockade of IL-17 with secukinumab showed some efficacy over placebo[127]. These preliminary findings will need to be evaluated more robustly in future trials. There is also growing interest in inducing suppressive Tregs in patients to reduce the severity of MS. For example, there is a new study led by Jewell at the Baltimore VA Medical Center that seeks to use nanotechnology to program myelin-specific Tregs in lymph nodes through exposure to myelin and toll-like receptor suppressive ligands, but data are not available from this investigation at this time (NIH Award 1I01BX003690-01)[128]. Perhaps targeting a combination of both Th17 and Treg pathways through IL-17 blockade and a boost of functional Tregs is necessary for disease control in patients with multiple sclerosis.

Psoriasis

MS is not the only disease where pathogenic Th17 cells have been shown to exacerbate autoimmune manifestations. Psoriasis is a chronic inflammatory skin disorder where the over-production of IL-23 by keratinocytes supports pathogenic Th17 cells in the dermis[129]. Hallmark features of psoriasis include various factors: parakeratosis, elongation and bulbous widening of the rete ridges with thinning of suprapapillary plates, dilated blood vessels and rouleaux formation in the papillary dermis[118]. Patients with psoriasis have more IL-17 and IL-22-producing cells in their peripheral blood than healthy individuals[130]. Moreover, psoriatic lesions have been discovered to contain increased IL-17A, IL-17C, and IL-17F compared to non-lesioned skin biopsies[131–133] and are populated with more Th17 and Th1 cells[134]. T cell recruitment and proliferation are induced by CCL20 and IL-23 (secreted by APCs), while IFN-γ and various isoforms of IL-17 stimulate keratinocyte proliferation and APC activation in a cyclic manner[134–137].

In addition to the strong link to Th17 hyperactivity, psoriasis has also been associated with altered Treg functionality. Patients have comparable Treg frequency compared to healthy individuals, but suppression of effector T cell function is impaired, similar to what has been shown in MS[138]. Treg cells from psoriasis patients produce more IL-17 and progressively lose Foxp3 expression more frequently than healthy controls, demonstrating a plasticity in Treg cells that further exacerbates disease pathology[139].

Therapeutic options for patients include topical corticosteroids or phototherapy for mild disease, systemic immunosuppression, or TNF-α inhibitors (adalimumab, etanercept). More recently, interventions that target Th17 cells have been FDA approved and include blockade of IL-17 (secukinumab) or IL-12/23 (ustekinumab). A new drug that selectively blocks IL-23 called guselkumab was FDA approved July 2017. This drug was approved based on improved response to selective IL-23 blockade versus adalimumab and ustekinumab[140]. Therapies that may bolster or correct the faulty Treg function in these patients may also yield improved effects, but such therapies are not currently available. It is possible that modulation of low dose IL-2 or TGF-β could also bolster the generation of suppressive Treg cells in these patients while concomitantly suppressing Th1 or Th17 cells.

Other autoimmune diseases impacted by Th17/Treg axis: RA, IBD, SLE

Similar to MS and psoriasis, it has become clear that the pathogenesis of rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE) are also influenced by an imbalance in Th17/Treg function. These autoimmune diseases are summarized in Table 1. Clinical investigations are underway to understand how drugs that block the IL-17 and IL-23 pathway or potentiate Treg function impact RA, IBD, and SLE. More information on these findings is outlined in these references[119,141–151].

A pinch of salt to reduce autoimmunity?

While an obvious way to treat autoimmunity in patients is by blunting the Th17 pathway via IL-17 or IL-23 blockade with FDA-approved drugs, holistic strategies involving simply changing the patient's diet or modulating the microbiota to dampen Th17-mediated diseases are becoming increasingly more appreciated. A high-salt diet has been shown to induce Th17 cells and exacerbate EAE[152]. This concept is supported by a recent report by Wilck and team, who found that a high-salt diet triggers an increased number of pathogenic Th17 cells in the peripheral blood of mice, correlating with destruction of the *Lactobacillus* species in the gut microbiome and hypertension[153,154]. Repopulating the gut with *Lactobacillus* species was shown to mitigate the severity of EAE and hypertension[152,153]. The high-salt diet similarly led to an increase in peripheral circulating Th17 cells in a healthy human cohort[153]. In a preclinical arthritis model, the gut microbe segmented filamentous bacterium (SFB) was also found to support Th17 cells and exacerbate autoimmunity[155]. While antibiotics have been shown to reduce SFB and lessen the pathogenesis of Th17 cells, thus reducing these autoimmune diseases, it is less clear how altering the salt intake or administering probiotics in human patients could impact disease outcome. Regardless, it is now clear that modulating the microbiome can also play a major role in shaping the biology of the Th17/Treg axis. As discussed below, we will review the important role of Th17 cells and Tregs in cancer progression as well as ways to manipulate these two subsets to augment cancer immunotherapy.

Th17/Treg in Cancer

The relative contribution of Th17 and Treg cells in carcinogenesis is often related to chronic inflammation. It was first posited in 1863 that tissue injury and resulting cell proliferation could lead to

cancer[156]. Today, it is widely accepted that chronic infection with bacteria, such as *Helicobacter pylori*[157], or viruses, such as human papilloma virus[158], can cause cancer. Although present day evidence for the role of Th17 cells in cancer is contradictory, excess inflammation from Th17 cells or too much immunosuppression induced by Treg cells may lead to carcinogenesis.

Th17 cells are found in human tumors[159,160]. IL-17A promotes the proliferation of malignant cells and induces angiogenic constituents by stimulating fibroblasts to upregulate vascular endothelial growth factor (VEGF), resulting in tumor neovascularization[161,162]. Whether Th17 cells promote or inhibit cancer development depends on the phenotype of the tumor. Pro-tumorigenic neutrophils, recruited by IL-17, have been reported in breast cancers[163]. High IL-17A and RORγt expression correlated with reduced disease-free survival rates in patients with colorectal cancer[164]. In pancreatic cancer, increased IL-22 production by Th17 cells is associated with decreased survival rates in patients[165]. In non-small cell lung cancer, patients were found to have a greater ratio of Th17/Treg frequencies compared to healthy controls, which correlated with the levels of carcinoembryonic antigen (CEA)[166]. In breast cancer, though, IL-22 production correlates with decreased tumor formation and a positive prognosis[167]. In ovarian cancer, increased tumor-associated IL-17 predicted improved patient survival[160].

Treg cells, however, are often associated with tumor progression and reduced survival in cancer patients[168,169]. GARP expression in tumors has been shown to enhance active TGF-β and support Treg induction in the cancer microenvironment, thus hindering immune responses[170]. Treg presence in the tumor microenvironment has been associated with more advanced stage of malignancy, presence of invasion, and worsened prognosis[168,169]. Depletion of live Tregs in the murine tumor microenvironment prevented immunosuppression of tumor-infiltrating $CD8^+$ T cells, allowing improved anti-tumor efficacy of endogenous effector T cells[171]. Apoptotic Tregs in the tumor, however, may also contribute to immune evasion. Recent work by the Zou lab revealed that oxidative stress in the tumor microenvironment induces Treg apoptosis, releasing large amounts of ATP, which is metabolized to immunosuppressive adenosine and signals through the A2a receptor (A2aR)[172]. This work suggests that selective depletion of Tregs in a patient's tumor with inhibition of the A2aR pathway could circumvent the immune-evasive tumor microenvironment and thus increase immunity to human malignancies[173].

Immunotherapy: a shift in the paradigm?

Despite the evidence suggesting a pro-tumorigenic role of Th17 cells and related cytokines, recent advances in the field of immunotherapy for treating cancer have suggested that Th17 cells may play a powerful role in antitumor immunity. In this case, tipping the Th17/Treg scale towards a dominant Th17 cell influence could be beneficial for patients with aggressive tumors. Herein, we will discuss preclinical and clinical findings that support further investigation of Th17 cells in therapeutically modulating tumor regression.

Adoptive cell transfer

Adoptive T cell transfer therapy (ACT) uses the patient's own T cells to target and kill tumor cells. In the clinic, T cells can be obtained and logarithmically expanded from the tumor (called tumor-infiltrating lymphocytes or TIL) or can be rendered antigen-specific via genetically engineering peripheral blood T cells using Chimeric Antigen Receptor (CAR) or T cell receptor (TCR) constructs[174]. Much of ACT has focused on using $CD8^+$ T cells to treat cancer patients; however, $CD8^+$ T cells tend to progressively lose antitumor function as they expand, showing reduced ability to persist and clear tumors in vivo[175]. Recent clinical trials have now shown that $CD4^+$ tumor-reactive T cells polarized to a Th1 subset are able to regress tumors in humans[176], and in recently published work, human $CD4^+$ T cells that express high levels of CD26 were found to cosecrete IL-17 and IFN-γ and be even more effective than $CD8^+$ T cells when infused into mice bearing large human tumors[177]. However, based on preclinical work, efficacy may ultimately depend on the particular type of T helper subset infused into the cancer patient[178–181].

Numerous laboratories have now discovered that Th17 cells can cause tumor regression to a greater extent than Th1 cells when transferred into mice[178,179,182,183]. While the mechanism by which Th17 cells regress tumors is not fully understood, they may kill tumor cells through synergism with $CD8^+$ T cells or by themselves via direct lysis[180,181]. The enhanced ability of Th17 to ablate tumors has been attributed to a variety of characteristics. In culture, Th17 cell polarization is known to generate a more differentiated effector memory phenotype ($CD62L_{lo}$, $CCR7_{lo}$); However, paradoxically, after transfer, Th17 cells express high CCR7, *Lef1*, and *Tcf7*, indicating a durable stem memory phenotype[179]. In adoptive transfer therapy, it is interesting to note that the ability of Th17 cells to convert to a Th1-like phenotype and generate IFN-γ in vivo is critical for antitumor response[178,179]. However, compared to their Th1 counterpart, Th17 cells persist far longer and at greater frequencies in the host[179]. Th17 cells are also resistant to apoptosis, which permits them to oppose activation-induced cell death (AICD)[184]. Finally, Bowers et al. recently reported that Th17 cells retain their antitumor efficacy and resist senescence compared to Th1 cells even after long term ex vivo expansion for nearly one month[185]. Given that a large number of T cells are needed to mediate curative responses in mice with large tumors, the fact that Th17 but not $CD8^+$ T cells can expand to ample numbers without losing their therapeutic potency has significant implications for clinical translation.

Despite preclinical success with murine and human Th17 cells, this powerful lymphocyte population has not yet been transferred into patients. One current barrier to successful antitumor response in the clinic includes use of exhausted T cells that do not persist in the blood. Through use of Th17-polarizing conditions in vitro in the clinic, Muranski et al.[179] could generate a population that displays improved persistence and long-lived immunity. As many cytokines are needed to generate human Th17 cells, investigators seek to find other methods to effectively enrich and expand these cells without such cumbersome protocols. Most recently, it was demonstrated that CD26, a multifunctional ectoenzyme with costimulatory properties, was associated with enhanced Th17 cell function and activation[177]. In this work by Bailey and team, high levels of CD26 could be used to enrich human T cells with a type 17 phenotype[177,186]. T cells with a high expression of CD26 are multifunctional, have enhanced migratory and stem-like properties, resist apoptosis, and have been shown to regress multiple tumors[177]. Conversely, T cells with low CD26 expression were regulatory T cells, as demonstrated by their high expression of classic hallmark molecules such as high CD25, low CD127 and high expression of Foxp3 and Helios[177]. While such characteristics of CD26 could be capitalized upon therapeutically by inducing $CD26^{high}$ Th17 cells while concomitantly ablating $CD26^{low}$ Tregs, the possibility of Th17-induced autoimmunity dictates caution for the safe translation of this putative exciting, and perhaps more effective therapy.

Checkpoint blockade

Monoclonal antibodies that inhibit suppressive regulatory receptors (checkpoints) on T cells regress various tumors in patients including melanoma, bladder, breast, renal cell, ovarian, lung, and colorectal cancers[187]. The role of Th17 cells or other IL-17-producing immune cells has not been fully described in the mechanism for checkpoint blockade therapy, yet immune-related adverse events (irAEs) are frequent toxicities reported with this

therapy. Anti-PD-1 therapy has been associated with exacerbated degrees of colitis, pneumonitis, endocrinopathy, lichenoid reactions, eczema, vitiligo, psoriasis, and pemphigoid in patients[188–199]. Anti-CTLA-4 therapy with ipilumimab has been reported to induce even more toxic side effects than anti-PD-1 therapy, including colitis, arthritis, dermatitis, hepatitis, and endocrinopathies, with less frequent incidence of uveitis, myopathy, and nephritis[199–201]. Combination therapy with CTLA-4 and PD-1 blockade (ipilimumab and nivolumab, respectively) can result in tumor regression with concurrent autoimmune toxicities related to a secondary immune response and epitope spreading[202]. PD-1 blockade with nivolumab as a monotherapy in advanced melanoma has been shown to be nearly as effective as combination therapy with ipilumumab; both therapies show significantly increased overall survival compared to ipilumumab alone[203,204]. Since the combination therapy induces a higher frequency of adverse events, treatment benefits should be weighed against risk of toxicity[205].

For many patients, these toxicities are not without benefit. Fortunately, irAEs are often self-limiting or can be managed with high dose corticosteroids or hormone replacement, and especially with ipilumimab, may correlate with antitumor response[200,201]. Toxicities with ipilumimab have been associated with a greater likelihood of objective response in melanoma. Importantly, it should be noted that use of corticosteroids to treat irAEs has not significantly affected antitumor response[206–210]. Thus, it is important to understand the underlying reason why irAEs may be associated with better treatment outcome in cancer patients. These adverse events have prompted the search for immune system biomarkers predictive of therapy success. Interestingly, higher baseline IL-17 before treatment with ipilumimab has been associated with more advanced grade III irAEs[211]. Higher pretreatment serum levels of Th17 lineage related cytokines TGF-β and IL-6 have been associated with lack of melanoma progression and regression free survival with ipilumimab and interferon-α2b treatments, respectively[211,212]. Thus, autoimmune toxicities have been correlated with IL-17 levels, while antitumor responses have been associated with autoimmune toxicity. Mounting evidence from these various findings warrants future investigations that precisely uncover the role of Th17 cells in modulating these toxic and antitumor events.

Two recent reports suggest that Th17 cells and IL-17 may play an important role in both the efficacy and toxicity of checkpoint blockade therapy in cancer patients. This concept was demonstrated in a 50-year-old male with a history of mild psoriasis and Crohn's disease who received PD-1 blockade (pembrolizumab) for metastatic colon cancer. The first two rounds of this therapy resulted in a remarkable 50% reduction in CEA[213]. Interestingly, after the third cycle of pembrolizumab, the patient displayed a severe psoriatic rash that covered 75% of his body along with increased abdominal pain and stool frequency. To resolve the skin manifestations, the patient was treated with secukinumab, an FDA-approved IL-17A blockade indicated for treatment of psoriasis. Although IL-17 blockade improved the symptoms of psoriasis and gastrointestinal pain, the anti-tumor activity was reduced as serum CEA returned to pretreatment levels[213]. Similarly, in a recent analysis of melanoma patients receiving PD-1 therapy, the frequency of IL-17-producing T helper cells was increased in responders to therapy versus non-responders, though monocytes were most predictive of response to therapy[214]. Given that several preclinical studies have suggested that Th17 cells and IL-17 may enhance or support tumor immunity, these clinical reports underscore the importance of studying the antitumor qualities of these effector Th17 cells in treating human patients.

The ultimate goal of the immunotherapy field is to uncouple toxicity from durable antitumor immunity. In the future, it is possible that the Th17/Treg axis could be effectively manipulated to augment tumor immunity while suppressing adverse immune side effects to healthy tissue. For example, it is possible that low dose IL-2 therapy following adoptive transfer of Th17 cells could mitigate prolonged autoimmunity once tumors have been cleared by elevating self-antigen-specific Tregs while still supporting antitumor Th17 and $CD8^+$ T cells. Additionally, depletion of Tregs along with inhibition of the adenosine A2aR pathway could empower infiltrating effector immune cells to overcome the immunosuppressive tumor microenvironment. The potential in this field to treat and cure patients could be further enhanced through careful manipulation of both sides of this Th17/Treg balance.

CONCLUSIONS

The balance between Th17 and Treg T cells is critical for maintaining homeostasis. A Th17 dominance or dysfunctional Treg surveillance is associated with autoimmune disorders such as MS, psoriasis, RA, IBD, or SLE. Th17 cells and related cytokines can promote either tumorigenesis or tumor suppression, although this role is poorly understood. Future work in the field of immunotherapy in terms of adoptive transfer, vaccines and checkpoint blockade may provide new insights into the power of Th17 cells in regressing tumors, further enhancing our ability to harness the immune system against cancer. Future clinical trials may also use Tregs to quench immune responses to self-tissue without disturbing antitumor Th17 or $CD8^+$ T cell responses in order to maximize efficacy and minimize toxicity in caring for cancer patients. Indeed, these are exciting times in the field of cancer immunotherapy and mounting evidence is converging on the potential to exploit the Th17/Treg axis to profoundly impact the life of patients with cancer and autoimmunity.

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ADDITIONAL INFORMATION

Competing interest: The authors declare that they have no competing interest.

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