Tc17 cells in autoimmune diseases

Yong Peng1, Xiang Deng1, Qiuming Zeng2, Yandan Tang1

Abstract
Multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE), a pathologically similar disease used to model MS in rodents, are typical CD4+ T cell-dominated autoimmune diseases. CD4+ interleukin (IL)-17+ T cells (Th17 cells) have been well studied and have shown that they play a critical role in the pathogenesis of MS/EAE. However, studies have suggested that CD8+IL17+ T cells (Tc17 cells) have a similar phenotype and cytokine and transcription factor profiles to those of Th17 cells and have been found to be crucial in the pathogenesis of autoimmune diseases, including MS/EAE, psoriasis, type I diabetes, rheumatoid arthritis, and systemic lupus erythematosus. However, the evidence for this is indirect and insufficient. Therefore, we searched for related publications and attempted to summarize the current knowledge on the role of Tc17 cells in the pathogenesis of MS/EAE, as well as in the pathogenesis of other autoimmune diseases, and to find out whether Tc17 cells or Th17 cells play a more critical role in autoimmune disease, especially in MS and EAE pathogenesis, or whether the interaction between these two cell types plays a critical role in the development of the disease.

Introduction
Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS), which typically causes serious disability.[1] In the past few decades, MS and experimental autoimmune encephalomyelitis (EAE), a disease similar to that used to model MS in rodents, have been considered typical CD4+ T cell-mediated autoimmune diseases. However, increasing evidence supports the view that CD8+ T cells also play a critical role in the pathogenesis of MS/EAE.[2,3]

A subset of CD8+ T cells, namely, CD8+ interleukin (IL)-17+ (Tc17) cells, plays a critical role in the pathogenesis of MS.[4,5] In EAE, CD8+ T cells have been shown to invade the blood-brain barrier (BBB) and produce granzyme B, perforin, interferon (IFN)-γ, and IL-17. This showed that Tc17 cells can assist CD4+ IL-17+ (Th17) cells in the CNS and induce EAE. Additionally, once IL-17A is produced by Th17 cells, Tc17 cells can also produce IL-17A. This is shown to be the case in MOG35-55-induced EAE mice, as well as in active MS lesions, as confirmed by immunohistochemistry and in-situ hybridization. The present study aims to investigate whether Tc17 cells, Th17 cells, or an interaction between the two cell types plays a more critical role in MS and EAE pathogenesis. Currently, this remains unanswered. Thus, we reviewed the latest evidence in this field in an attempt to clarify these points.

Brief Biology of Type 17 T Cells
The Th17 subset was identified as a unique cell type of CD4+ T cells, which secrete several cytokines, such as IL-17A, IL-17F, IL-21, IL-22, and granulocyte macrophage colony-stimulating factor (GM-CSF).[6] Retinoic acid receptor-related orphan nuclear receptor gamma (RORγT) is the key transcription factor (TF) but not the prototypical master regulator for the differentiation of Th17 cells, because RORγT itself is influenced by environmental cues, resulting in the relative instability and functional plasticity of Th17 cells.[7] For example, a subset of Th17 cells secreted both IL-17 and IFN-γ and were named Th17.1 cells or IFN-γ+ Th1-like cells. Another example is that TGFB and IL-6 driven Th17 cells secrete both IL-17 and IL-10 and were named IL-10-producing Tr1 cells.[8] Both Th17.1 cells and IL-10-producing Tr1 cells were almost losing IL-17 production. Therefore, the question arises as to what kind of role Th17 cells play: Protection or pathogenesis? In addition, some people called Th17 cells as “two-side swords” suggesting that the different roles of Th17 cells depend on the subset, and the phenotype of Th17 cells should be deeply studied.
Tc17 cells secrete IL-17 and a high plasticity switch toward the cytotoxic T lymphocytes (CTL) or Tc2 phenotype, similar to Th17 cell function. Tc17 cells are thought to have protective or pathological roles in different mouse and human tissues,[9-11] as well as in different diseases and animal models, such as lethal fungal pneumonia,[12,13] gastrointestinal tract-associated cancers,[14-16] melanoma, psoriasis, and MS.[17,18]

**Cytokines, TFs, and genetic factor profiles on Type 17 T cells**

Different cytokines respond to different functions of Th17 cells: IL-21 for differentiation, survival, and expansion; IL-23 for expansion and maintenance; IL-12, IFN-γ, and IL-4 inhibit Th17 polarization; and low doses of TGF-β plus IL-6 induce Th17 polarization. Evidence between TGF-β and Th17 cells has been confirmed both in vitro and in vivo.

Th17 cells secrete IL-9, IL-17, IL-21, and IL-22.[6] With TGF-β, Th17 cells secrete IL-9,[19] which confirms IL-9 contributions to Th17-related autoimmune diseases, expansion, and survival. Murine Th17 differentiation depends on T cell receptor (TCR) stimulation of naive CD4+ T cells, resulting in the recruitment of basic leucine zipper TFATF-like (BATF) and IRF4 to the IL-17A locus, followed by RORγ binding to activate IL-17A.[7] Moreover, Th17-specific chromatin looping mechanisms contribute to the regulation of murine IL-17A expression.[20] Some genes are related to the stability of Th17 cells, such as GATA3. Interestingly, the chromatin landscape of Th17 cells is similar to that of Th1 cells. Furthermore, the IFN-γ locus in Th17 cells drives these cells toward a Th1 phenotype in humans, which might explain the reason for Th17.1 cells or IFN-γ Th1-like cells,[6] which is confirmed by 3D genome topology.

Tc17 cells can express cytokines IL-5, IL-13, IL-17, IL-21, IL-22, IFN-γ, TNF-α, and GM-CSF.[11,21] Similar to Th17 cells, Tc17 cells are induced by TGF-β along with IL-6, IL-21, and IL-1, and maintained by IL-23.[10] IL-6, via signal transducer and activator of transcription 3 (STAT3), induces RORγt and IL-17 expression and enhances IL-23R expression. Additionally, interferon regulatory factor (IRF) 4 acts through comosederin (EOMES) and forkhead-box-protein P3 (FOXP3) to activate RORγ and RORα, resulting in the regulation of the development of Tc17 cells. Cytotoxic T lymphocyte antigen (CTLA)-4 moderates STAT3, IL-17, IL-21, and RORγ activity, ultimately affecting Tc17 development.

**Plasticity or stability of Tc17 cells**

Lack of CTLA-4 drives Tc17 cells to downregulate RORγt and IL-17 expression and to shift toward CTL phenotype, which referred to as the so-called “plasticity of Tc17 cells.”[22] On the other hand, some studies reported the stability and non-plasticity of Tc17 cells. In a mouse model, Tc17 cells express a stable phenotype and mediate protection against fungi[13,23] and bacteria.[24] In addition, Tc17 cells act as IL-17-producing memory cells without switching to secrete IFN-γ in T cell factor (TCF)1+Tc17 cells, T-BET+Tc17, and EOMES+ mouse models.[13] The stability of Tc17 cells was attributed to T cell-intrinsic expression of myeloid differentiation antigen (MyD) 88, which maintains IL-17 production via activation of the AKT1-mTOR pathway.[25] Tc17 also showed Tc2-like responses in a mouse model. In the skin, Tc17 and Th17 cells co-express RORγt and GATA-3. However, it is only under tissue challenges that Tc17 and Th17 cells can produce IL-1, IL-18, and IL-33, resulting in the secretion of type 2 cytokines IL-5 and IL-13, and simultaneously promoting local immunity and tissue repair.[11] RORγt via STAT3 regulates IL-6 and IL-23 production, and via epigenetic mechanisms, regulates IL-17A, IL-17F, IL-23R, and IL-21 productions.[6] BATF, IRF4, fos-relatedantigen2, RORα, and aryl hydrocarbon receptor contribute to Th17 cell differentiation. STAT3, RORγt, and RORα contribute to the secretion of Th17-related cytokines. Promyelocytic leukemia zinc finger protein contributes to the Th17 phenotype and regulates the chemokine receptor CCR6, which responds to chemoattraction of Th17 cells via its ligand CCL20.[26]

At the double-positive (DP) stage in the thymus, TCF-1 (encoded by Tcf7) suppresses the transcriptional regulator MAFBZIP TF (MAF). MAF, via the RORγt and MAF-RORγt taxes, regulate Tc17 cell development in the thymus but not in the periphery.[27] IL-17A regulates Th17 cell polarization. IL-17A is inactivated in naive or Th1 cells, and is activated only under Th17 differentiation initiated by epigenetic transformation, with promotor activation and DNA demethylation occurring and several GREs involved.[28]

**Difference in the regulation of Tc17 and Th17 cells**

In the thymus, TCF-1 suppresses Tc17 cells only at the DP stage and suppresses Th17 cells before the stage of expression of the CD4 coreceptor.[23] Interferon regulatory factor 3 (IRF3) via RORγt inhibited Tc17 cell development much more than it did on Th17 development.[29] Moreover, dimethyl fumarate (DMF), a preferential suppressive drug on MS, effects IL-17 production in murine and human Tc17 cells, but much less on Th17 cells. It might be that there are different requirements for Tc17 and Th17 cells in AKT-m TOR signaling and divergent metabolic requirements,[18] such as glycolysis,[30] oxidative phosphorylation, and lipid metabolism.[18,27] Finally, the plasticity and related functions of Tc17 and Th17 cells are different. Th17 cells switch to a Th1-like phenotype, resulting in a more pathogenic profile and were confirmed by pathologic inflammation in the CNS[31] and in the intestine during bacterial infection or colitis.[32-34] In contrast, Tc17 cells shift to the Tc1-like phenotype only in CNS autoimmune.[18] Above all, it suggested that with regard to the plasticity toward type 1 phenotype, the functional specificity of Tc17 and Th17 cells are different.[19]

The plasticity of Tc17 and Th17 cells in type 2 immune responses has been reported. RORγt*GATA3*DP
Th17 cell differentiation causes EAE, whereas differentiation into Th2 phenotype by secreting IL-5 and IL-13 production, resulting in a protective immune response.

Altogether, these studies showed the differences in molecular and metabolic factors, and functional impact of plasticity on type 1 and type 2 immunity between Tc17 and Th17 cells. However, the underlying mechanism is still unclear, and it is worth investigating autoimmunity, allergy, and cancer.

**Th17 Cells in MS/EAE**

**Development, differentiation, and phenotype of Th17 cells in MS/EAE**

Studies have suggested that Th17 cells contribute to the pathogenesis of EAE in mice and MS in human patients. The contributory effect of Th17 in the pathogenesis of EAE and MS is further evidenced by the fact that IL-17+ mice are resistant to EAE and by the presence of Th17 cells in the demyelinating plaques, cerebrospinal fluid (CSF), and blood of patients with MS. In addition, secukinumab, an anti-IL-17 antibody, has been found to significantly reduce MS lesions on brain MRI. Th17 cells are induced by IL-23, RORγt, and RORα. This relationship is supported by the high expression of IL-23 mRNA and protein in the macrophages and microglia in lesions of patients with MS and the fact that RORγt mice are resistant to EAE. As a key factor in Th17 cells, RORγt is modulated by STAT3, BATF, IRF4, gpr63, toso, and plzp. Th17 cells from EAE mice and patients with MS have been found to secrete IL-17A, IL-17F, IL-21, IL-22, IL-26, TNF-α, IFN-γ, and GM-CSF. In EAE mice, IL-17A, IFN-γ, and GM-CSF are co-expressed in CNS-infiltrating CD4+ T cells. IL-1β expression induces IL-23 expression, which in turn leads to the activation and expansion of Th17 cells. The results from experiments with IL-1R−/− mice support the existence of this cascade.

There is some evidence for the involvement of TGF-β in EAE. TGF-β1 or TGF-β3 has been shown to drive the differentiation of naïve CD4+ T cells into Th17 cells in EAE. Moreover, investigators found that TGF-β played a critical role not only in the development of EAE but also in the absence of Th17 cells, even when Th1 cells infiltrated the spinal cord. This suggests that Th17 cell infiltration might be the key factor in recruiting enough Th1 cells to the spinal cord, resulting in the induction of EAE. Furthermore, only local treatment with anti-TGF-β antibody prevented Th17 cell differentiation and the onset of EAE.

In contrast, other investigators have shown that IL-6 driven Th17 cell differentiation causes EAE, whereas differentiation into Th17 cells driven by TGF-β1 or TGF-β3 and IL-6 does not. Similarly, other reports have confirmed that TGFβ inhibits differentiation into Th17 cells in EAE, healthy people, and experimental autoimmune uveitis.

In addition to the presence of Th1 cells, Th17-induced EAE is characterized by neutrophil infiltration, high expression of the chemokine receptor CCR6 on Th17 cells, and migration of Th17 cells to the brain parenchyma. This is confirmed by the fact that CCR6 is critical for the pathogenesis of EAE and rheumatoid arthritis (RA) in humans. However, multiple studies have found that CCR6 is dispensable for EAE and Th17 trafficking.

**Therapeutic implications of Th17 cells in MS/EAE**

There is a large gap between preclinical animal studies of EAE and clinical trials of patients with MS targeting Th17 cells. Three antibodies, either targeting the IL-17 or IL-17 receptor (IL-17R), namely, secukinumab, ixekizumab, and brodalumab, have been recently approved for use in the clinical treatment of plaque psoriasis. In addition, secukinumab has also been approved as a treatment for psoriatic arthritis (PsA) and ankylosing spondylitis. However, clinical trials of other anti-IL-17 antibodies, ustekinumab and briakinumab, for use in MS have either been terminated or have failed. These results do not align with the successful use of anti-IL-12/IL-23p40 in EAE models of MS or the successful use of ustekinumab in treating psoriasis and Crohn’s disease. This showed that IFN-γ−/− or anti-IFN-γ-treated mice were susceptible to EAE due to enhanced IL-17 and GM-CSF production.

Furthermore, IL-1β, IL-23, and GM-CSF resulted in encephalitogenic Th17 cells in EAE. Despite this, the first anti-IL-23p19 antibody has been approved for the treatment of plaque psoriasis, but not for the treatment of MS. However, clinical trials on two anti-IL-23 p19 antibodies, tildrakizumab and guselkumab, are underway. In a phase I trial, MOR103, an anti-GM-CSF antibody, was used to determine its efficacy in treating MS. Many studies have shown that the presence of combinations of in-vitro factors, such as IL-6, TGF-β, and IL-21, can lead to the expansion of murine Th17 cells. Studies have also shown that the addition of TGF-β and IL-6 can lead to the expansion of the population of murine IFN-γ−/− Th17 cells. In addition, the addition of TGF-β and IL-21 or a cocktail containing TGF-β, IL-6, IL-1, IL-21, IL-23, anti-IL-4, and anti-IFN-γ with or without IL-2 resulted in 19% and 64% differentiation into Th17 cells and IFN-γ+Th17 cells, respectively. However, few studies have been conducted on human Th17 cells. When human naïve CD4+ T cells were incubated with TGF-β, IL-6, IL-1 β, IL-23, and anti-IFN-γ monoclonal antibodies for 5 days, and IL-2 was...
subsequently added to this mix for a further 4 days, only 0.11% differentiated into Tc17 cells; on the other hand, when human naive CD8+ T cells were incubated with TGF-β and IL-6 for 3 days, it resulted in low ELISA detection of IL-17 and the percentage differentiation into Tc17 cells was not documented.

TGF-β inhibits various functions of IFN-γ/CD8+ T cells (Tc1 cells), including their ability to produce IFN-γ and express the cytolytic marker granzyme B, as well as their ability to undergo proliferation and division. However, when combined with IL-6, TGF-β has been shown to have the opposite effect, that is, it promotes the induction of Tc17 cells, TGF-β in combination with a cocktail containing IL-6, IL-1, IL-2, IL-21, IL-23, anti-IL-4, and anti-IFN-γ antibodies with or without IL-2 produced very high percentages (ranging from 39%-54%) of Tc17 cells in vitro. In-vivo experiments, such as those investigating TGF-β neutralization and those performed using TGF-βRII/DN mice provide additional support for the role of TGF-β in Tc17 differentiation. Numerous sources also indicate that IL-21 and IL-23 influence Tc17 differentiation. This suggests that other unknown cytokines may contribute to in-vivo Tc17 development and differentiation.

Phenotype of Tc17 cells

Murine Tc17 cells are known to exhibit phenotypic similarities with Th17 cells. However, the profile of human Tc17 cells is still unclear, although a report has shown that some cytokines, such as IFN-γ, tumor necrosis factor alpha (TNF-α), IL-21, IL-22, GM-CSF, RORγt, and its subfamily homolog RORα, are co-expressed with IL-17 in cultured Tc17 cells. RORγt is a key factor in the development, maintenance, and function of IL-17-producing cells and plays a role in regulating thymopoiesis. Indeed, clinical trials of several RORγt inhibitors in patients are ongoing. The anti-psoriatic potential of a novel, potent RORγt inhibitor, S1-000003, markedly inhibited the development of psoriatic skin inflammation by suppressing all subsets of IL-17-producing cells. Other TFs, including STAT3, IRF3, and IRF4, also promote Tc17 cell differentiation. However, there is also a report suggesting that IRF3 is a negative regulator of Tc17 cells that acts by inhibiting RORγt [Figures 1 and 2].

Furthermore, Tc17 cells express several surface markers, such as CD161, as well as various cytokine and chemokine receptors, including CCR5 (CD1 3), CCR6 (CD196), IL-23 receptor (IL-23R), and CD27+CD28+CD45RA− or CT27−CT28−CT45RA+ [Table 1].

Tc17 cells recognize autoantigens, including LL-37 antimicrobial peptide expressed by keratinocytes, mela-nocyte-derived antigen ADAMTS-like protein5, and keratin 17. Di Meglio et al reported that epidermal Tc17 cells increased the frequency of CD4+ T cells in AGR mice and was associated with the onset of psoriasis. These Tc17 cells secreted a single IL-17A or IL-17A/IFN-γ or IL-17A/IL-22 double profile, with increased proliferation of keratinocytes and onset of papillomatosis. Moreover, it showed that psoriasis was completely inhibited by the
depletion of CD8+ T cells. All data suggest that Tc17 cells play a critical role in the pathogenesis of psoriasis.[71]

These findings are consistent with those of two clinical investigations. Matos et al[72] reported that Tc17 cells with unique TCR sequences were enriched in the epidermis of resolved psoriatic lesions in patients. Cheuk et al[73] showed that tissue-resident memory cells secreted high IL-17 with CD8+CD103+CD49a phenotype in patients with acute psoriatic lesions.

This revealed that myeloid antigen presenting cells (APCs), such as Tc17/IFN-γ cells, strongly support the induction of Tc17 cells, and that this capacity of APCs was highly increased in patients with psoriasis. IFN-γ was found to be elevated in psoriatic blood and skin and programmed myeloid APCs induce Tc17 cell generation via IL-1 and IL-23. Moreover, IFN-γ stimulated APC production of CCL20, thus supporting the migration of Tc17 cells into lesional skin and cooperating with IL-17 to produce IL-1, IL-23, CCL20, and β-defensin-2 in APCs and keratinocytes. This consequently resulted in increased Tc17 cell recruitment and enhanced proliferation of keratinocytes and Tc17 cells, which are thought to accelerate the development of psoriasis.[74]

In addition, examination of activated CD8+ T cells from the epidermis of patients with psoriasis revealed that a substantial percentage of Tc17 cells produce IL-22.[75] Moreover, at least in vitro, daughter cells from IL-17A-producing Tc17 cells could lose their capacity to express IL-17A and develop into IL-22 single-producing Tc22 cells.[75] These findings may provide important insights into the pathogenesis of psoriasis because of the keratinocyte proliferation-promoting activity of cytokine IL-22.[74] These findings suggest that Tc17 cells play an important role in autoimmune diseases.

In Cd40lg transgenic mice, Loser et al[77] found that damage-associated molecular pattern molecules, myeloid-related protein 8 (Mrp8), and Mrp14 via TLR-4 signaling-induced activated Tc17 cells, as well as activating CD40-CD40L DC, which upregulates TFs Rorc and Runx1. Solimani et al[78] showed similar results, demonstrating that Tc17 cells were in lichen planus, an inflammatory skin and mucous membrane, by targeting the IL-23-IL-17 axis, which was also confirmed by Chiricuzzi et al,[79] who reported clinical successes in the treatment of psoriasis.

**Tc17 cells and type I diabetes (T1D)**

In the streptozotocin (STZ)-induced diabetes model, the frequencies of Th17 and Tc17 cells were detected in the pancreatic lymph nodes. In addition, IL-17R knockout mice demonstrated reduced levels of progression to STZ-induced diabetes.[80] A study using a mouse model of T1D reported an increased frequency of splenic Tc17 cells during the initial phase of disease development compared to that in healthy controls, indicating a key role for Tc17 cells in the initiation of autoimmune diabetes. Similar results showed that the percentage of Tc17 cells in patients who had T1D for <5 years was higher than that in patients who had T1D for >5 years and healthy controls.

Using an experimental model of T1D, Saxena et al[81] investigated the diabetogenic potential of Tc17 cells and reported that following transfer to mice, Tc17 cells maintained strong CCR7 expression, which allowed preferential homing of these cells to the pancreatic lymph nodes rather than pancreatic islets, without causing any pancreatic infiltration or tissue destruction. However, the transfer of Tc17 cells and a subdiabetogenic dose of Th1 cells promoted disease progression and drove the destruction of β-islet cells, causing hyperglycemia and ultimately death. In this context, Tc17 cells accumulated in pancreatic islets, and a considerable fraction of Tc17 cells underwent a phenotypic shift to become IFN-γ-producing Tc17 cells. Unexpectedly, it is thought that the IFN-γ produced by Tc17 cells may play a critical role in diabetes potentiation. This is in line with the similar disease exacerbation seen when Tc17 cells were transferred, together with Tc1 cells, from IFN-γ-deficient mice. One possibility is that the converted Tc17 cells in vivo could drive the aggravation of diabetes through a direct cytotoxic effect on β-islet cells.[81]

Alternatively, these cells exert their pathogenic potential through the secretion of pro-inflammatory cytokines other than IFN-γ. It has been reported that Tc17/IFN-γ+ cells rapidly proliferate in mesenteric lymph nodes in a CD8+ T cell transfer colitis model. In this case, IL-17 likely cooperated with IFN-γ to induce various colitogenic responses, such as the

---

**Table 1: A comprehensive phenotype of cytokine-based subsets within CD4+ and CD8+ T-aβ cells.**

| Items                          | CD4 | CD8 |
|-------------------------------|-----|-----|
| Extracellular                 |     |     |
| CD138 (CXCR3)                 | +   |     |
| CD161                         |     | +   |
| CD194 (CCR4)                  |     | +   |
| CD196 (CCR6)                  |     | +   |
| IL-23R                        | +   | +   |
| Intracellular                 |     |     |
| RORγt                         |     | +   |
| T-bet                         |     | +   |
| IRF4                          |     | +   |
| IRF3                          |     | +   |
| Intracellular upon cell       |     |     |
| stimulation                   |     |     |
| IFN-γ                         |     |     |
| IL-2                          |     |     |
| IL-4                          |     |     |
| IL-9                          |     |     |
| IL-17                         |     |     |
| IL-21                         |     |     |
| IL-22                         |     |     |
| IFN-α                         |     | +   |
| GM-CSF                        |     |     |

References [66,102,103] [103-105] [116] [67,74,105]

Boxes marked negative (−) indicate antigens, TFs, or cytokines which are not expressed or produced by the corresponding subset; +: Positive. An empty box indicates that this is not used for the discrimination of a specific subset. GM-CSF: Granulocyte macrophage colony-stimulating factor; IFN: Interferon; IL: Interleukin; IRF3: Interferon regulator factor 3; TF: Transcription factor.
migration of effector CD8+ T cells and other inflammatory cells into the colon.

Tc17 cells and RA, SLE, and other autoimmune disease

Compared to patients with inactive SLE, the frequency of Tc17 cells was increased in the peripheral blood (PB) of patients with active SLE.[82] Furthermore, although there was no correlation with the SLE disease activity index, the frequency of Tc17 cells in patients with SLE was significantly higher than that in healthy volunteers.

The instability and heterogeneity of Tc17 cells in patients with RA were similar to those in patients with SLE, and peripheral Tc17 cells from patients with SLE have been shown to produce IFN-γ and TNF-α, in addition to IL-17.[80] Production of IFN-γ and TNF-α by Tc17 cells may have important functional implications, as they exhibit a potent pro-inflammatory synergy with IL-17.

Memory Tc17 cells were increased and shared Tc17 and Tc1 transcriptional profiles in the synovial fluid (SF) of patients with SpA/PsA, and were associated with disease severity and bone erosion.[83,84] Furthermore, Steel et al.[83] reported that these Tc17 cells secreted IFN-γ, TNF-α, and GM-CSF.

Menon et al.[84] reported that in patients with PsA, the frequency of Tc17 cells in SF was significantly higher than that in PB. In addition, the percentage of Tc17 cells in SF was positively correlated with the presence of inflammatory markers, including erythrocyte sedimentation rate, C-reactive protein, and a disease activity score of 28 joints, and was significantly increased in patients with erosive disease. Furthermore, the frequency of Tc17 cells in SF was significantly associated with power Doppler ultrasound scores of the PsA knee joints, which is a marker of active synovitis. Peripheral Tc17 cells from patients with RA have been shown to preferentially produce type 1 cytokines, as evidenced by the high frequencies of IFN-γ and TNF-α-producing Tc17 cells.[74]

Idiopathic thrombocytopenic purpura is an autoimmune disease characterized by a low platelet count, which results from increased platelet destruction and insufficient platelet production. It has recently been established that the percentage of Tc17 cells in newly diagnosed patients is significantly higher than that in healthy controls.

Tc17 Cells in MS/EAE

Tc17 cells were detected in the CSF and PB of patients with MS and in the CNS infiltrates of MCMV-infected BALB/c mice.[83] In contrast to Tc1 cells, Tc17 cells are non-cytotoxic and downregulate the expression of T-bet and Eomes, which are important for the development of CD8+ T cells and regulation of the expression of IFN-γ, granzyme B, and perforin.[86]

Tc17 cells in EAE

Huber et al.[17] investigated the function of Tc17 cells in EAE. Their results showed that IL-17A produced by Tc17 cells accelerated the encephalitogenicity of Th17 cells by inducing aberrant Th17 production of IL-17A and by enhancing the recruitment of Th17 cells to the CNS. This activity could potentially be dependent on direct cell-cell interactions, since it could not be replaced by exogenous soluble IL-17A. Moreover, a direct, cell-contact-dependent interaction between Tc17 and CD4+ T cells was shown to assist in the development of the type 17 transcriptional profile in CD4+ T cells and in the production of IL-17A in vitro. These data collectively suggest that Tc17 cells contribute to the initiation of CNS autoimmunity by enhancing Th17 pathogenicity. In this setting, IL-17A is primarily an effector molecule of Tc17 cells, whereas in Th17 cells, IL-17A can be considered a marker of encephalitogenicity.

In EAE, mesenchymal stem cells (MSCs) enhanced the Tc1-like phenotype but strongly inhibited the production of IL-17A and Tc17 polarization in vitro.[87] MSC treatment of EAE revealed that MSCs enhanced the IFN-γ-CTL-like phenotype but strongly inhibited the production of IL-17A and the polarization of Tc17 cells in vitro. These observations are underscored by differential MSC modulation of T cell activation, proliferation, and upregulation of signature TFs. In addition, effector CD81 T cells co-cultured with MSCs exhibited increased production of IL-2, a molecule known to enhance IFN-γ production and suppress IL-17A production. The effects of MSCs on CD81 T cells in vitro also affected the severity of EAE. For this purpose, mice were immunized with MOG37-50, a CD8-targeted epitope. The results revealed worsening of the disease, consistent with the in-vitro stimulation of CTL cells. These findings highlight the emerging duality of MSCs in immune modulation and provide implications for future applications of MSCs in immune-related diseases.[87]

Tc17 cells in MS

In MS, activated T cells migrate to the BBB, and as the integrity of the BBB is impaired, inflammatory cells and T cells can enter the CNS. Resident microglia become activated, and myelin antigens are present in T cells. Microglia secrete IL-1β, IL-6, and IL-21, which then amplify Tc17 cell responses. GM-CSF secretion by Tc17 cells enhances inflammatory myeloid cell IL-17 secretion, leading[88] to a CTL phenotype and elevated IFN-γ secretion.[89] Furthermore, Tc17 cells induce apoptosis in oligodendrocytes. This can eventually result in decreased axon myelination and potentially contribute to MS pathogenesis [Figure 3].[88] Tc17 cells, as the target cell population of DMF, repair microglial DNA to protect the myelin sheath of nerve cells through the PI3K-Akt-FoxO1-T-bet and STAT5 pathways, inhibit the differentiation of T lymphocytes to Tc17 cells, and reduce the secretion of inflammatory mediators, thus providing a novel therapeutic approach for targeting Tc17 cells in MS and other IL-17-mediated diseases.[17] The enrichment of Tc17 cells in active lesions of patients with MS has been demonstrated previously. In patients with MS, treatment with DMF reduced the frequency of Tc17 in PB mononuclear cells, decreased the ratio of RORC to TBX21, and decreased the ratio of CD8+ T cells to express cytotoxic T lymphocyte
Interferon; IL: Interleukin; MS: Multiple sclerosis; TNF-

cells induce apoptosis in oligodendrocytes. This can result in decreased axon myelination,
secretion, leading to a CTL phenotype and elevated IFN-

responses. GM-CSF secretion by Tc17 cells enhances in

T cells. Microglia secrete IL-1

enter the CNS. Resident microglia become activated and myelin antigens become present

PB of patients with relapsing-remitting MS (RRMS) in

(MAIT), was identi-

and were present in active areas of acute and chronic

ment have been identi-

IL-17-producing cell subsets within the T cell compart-

EAE in IL-17, ROR
t, and STAT5-signaling.

differentiation of Tc17 cells

Evidence has shown that both Tc17 and Th17 cells

contribute equally to the pathogenesis of MS/EAE. It is

also evident that the two cell types cooperate. This is

confirmed by the co-existence of these cell types in active

lesions and inactive lesion areas of patients with MS, as

well as by the fact that IL-17A secreted by Tc17 cells

enhances the pathogenicity of Th17 cells in EAE. Huber et al.[1] showed that IRF4 is vital for the
differentiation of Tc17 cells in vitro and in vivo during

CNS autoimmunity, and that IRF4-deficient mice play a

previously unknown cooperation between Tc17 and Th17 cells
to facilitate EAE induction. The pathogenic interplay
between Tc17 cells and Th17 cells requires IL-17A, but

not CCR6, for CD8+ T cells and CCR6, but not IL-17A,

for CD4+ T cells. In addition, in-vitro experiments have shown that direct cell contact-mediated helper activity of

Tc17 cells is necessary for Th17 differentiation. Further-
more, increased Tc17 cell numbers are detectable in the

CSF of patients with early stage MS, suggesting that Tc17
cells contribute to the progression of MS in humans. Since

the CSF of patients with early stage MS contains a greater

number of Tc17 cells than PB, these cells are considered to be

required for the accumulation of Th17 cells in the CNS in

MS.[17]

Above all, there was some evidence concerning the role of

Tc17 cells and interaction between Tc17 and Th17 cells in

MS/EAE. Unfortunately, the evidence for this point is

indirect and insufficient. Of course, this scanty evidence

still provides clues that can be used for carrying out further

and deeper studies; examples include following the well-

known protocol of studies on Th17 cells in MS/EAE,

comparison of Tc17 with Th17 cells point by point, and

also adopting different combinations of the mixture of

Tc17 and Th17 cells. On the another hand, it will be

interesting to carry out an in-vivo study of the role of Tc17
cells and interaction between Tc17 and Th17 cells on MS/

EAE in IL-17, RORyt, and STAT5-signaling gene-knock

out mice, as well as in wide-type mice.

Conclusion and Perspectives

In this review, we focused on the updated information of

Tc17 cells and highlighted the development, differentia-
tion, phenotype, cytokine and TF profiles, plasticity or

stability, and pathogenesis of autoimmune diseases,
especially MS/EAE. Interestingly, unlike the stability of CTL or Tc2 cells, Tc17 cells are not stable and can easily switch their cytokine profile to CTL or Tc2 phenotype under different stimulation conditions. However, to keep Tc17 cells at stable status only under fungal and bacterial infection, there are no reports of autoimmune diseases, especially MS/EAE. This suggests that Tc17 cells are difficult to control in the future therapy of MS/EAE due to their plasticity, and even Tc17 cells will have good evidence for the treatment of MS/EAE.

Another interesting finding is the difference between Tc17 and Th17 cells, including development, differentiation, and the condition and direction of plasticity, as well as the different roles and co-operations in MS/EAE. The question is the difference from their basic phenotype: CD8 vs. CD4, or Tc17 vs. Th17 cells themselves. Numerous studies have addressed the role of Th17 cells in MS and EAE, including studies that examine how Th17 cells develop and differentiate and how they may contribute to the phenotype and pathogenesis of MS and EAE. However, the role of Tc17 cells in MS and EAE remains unclear. Although some studies have indicated that Tc17 cells may share some characteristics with Th17 cells, considerable research is required to fully characterize their role in MS and EAE.

Recently, investigators reported some interesting points on Th17 of MS and EAE, which might be showing the future direction for the studies on Tc17 of MS and EAE. Qian et al.\(^ {899} \) showed that deletion of Zinc finger E-box-binding homeobox (ZEB1) delayed the development of EAE by inhibiting pathogenic Th1 and Th17 differentiation. The possible mechanism might be that ZEB1 inhibits miR-101-3p, and then reduces JAK2 expression and STAT3/STAT4 phosphorylation, resulting in inhibiting miR-101-3p, and then reduces JAK2 down-regulation decreases pathogenic cytokines expression in T cells from MS patients.\(^ {99} \) Falcon et al.\(^ {100} \) showed that Diazepam (DZ) treatment inhibited allogeneic Th1 and Th17 responses in vitro by preventing lipopolysaccharide-induced DC ability, and also that DZ reduced the release of IFN-γ and IL-17 from splenocytes from untreated sick mice in vitro. Bae et al.\(^ {101} \) showed that CKD-506, a novel HDAC6-selective inhibitor, downregulated the expression of IFN-γ and IL-17A in MOG35-55-re-stimulated splenocytes, and also reduced the levels of pro-inflammatory cytokines in the blood of EAE mice.

**Funding**

This work was supported by grants from the Fund for Creative Research Group of Affiliated First Hospital of Hunan Traditional Chinese Medical College, China (No. 2021B-003), Key Plans of Hunan Administration Traditional Chinese Medicine, China (No. 2019151), Natural Science Foundation of Hunan Province, China (No. 2018J6043), Health and Family Planning Commission of Hunan Province, China (No. B20180815), and Technology Plan Project of Zhuzhou City, Hunan Province, China (No. 2021-003).

**Conflicts of interest**

None.

**References**

1. Amankwa N, Marrie RA, Bancej C, Garner R, Manuel DG, Wall R, et al. Multiple sclerosis in Canada 2011 to 2031: results of a microsimulation modelling study of epidemiological and economic impacts. Health Promot Chronic Dis Prev Can 2017;37:37–48. doi: 10.24095/hpcdp.37.2.02.

2. Peng Y, Zhu FZ, Chen ZX, Zhou JX, Gan L, Yang SS, et al. Characterization of myelin oligodendrocyte glycoprotein (MOG) 35-55-specific CD8+ T cells in experimental autoimmune encephalomyelitis. Chin Med J 2019;132:2934–2940. doi: 10.1097/CM9.000000000000555.

3. Wagner CA, Roqué PJ, Mileur TR, Liggitt D, Governm JM. Myelin-specific CD8+ T cells exacerbate brain inflammation in CNS autoimmunity. J Clin Invest 2020;130:203–213. doi: 10.1172/JCI132531.

4. Salou M, Nicol B, Garcia A, Baron D, Michel L, Elong-NGono A, et al. Neuropathologic, phenotypic and functional analyses of mucosal associated invariant T cells in multiple sclerosis. Clin Immunol 2016;166:167–1–11. doi: 10.1016/j.clim.2016.03.014.

5. Nicol B, Salou M, Vogel T, Toque V, Ruffley J, Bae JS. The intermediate level of CD161 expression defines a novel activated, inflammatory, and pathogenic subset of CD8+ T cells involved in multiple sclerosis. J Autoimmun 2018;88:61–74. doi: 10.1016/j.jaut.2017.10.005.

6. Stadhouder R, Lubberts E, Hendriks RW. A cellular and molecular view of T helper 17 cell plasticity in autoimmunity. J Autoimmun 2018;87:1–15. doi: 10.1016/j.jaut.2017.12.007.

7. Ciofani M, Madar A, Galan C, Sellars M, Mace K, Pauli F, et al. A validated regulatory network for Th17 cell specification. Cell 2012;151:289–303. doi: 10.1016/j.cell.2012.09.016.

8. Gagliani N, Vesely MCA, Iseppon A, Brockmann L, Xu H, Palm NW, et al. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. Nature 2013;523:221–225. doi: 10.1038/nature14452.

9. Luckel C, Picard FSR, Huber M. Tc17 biology and function: novel concepts. Eur J Immunol 2020;50:1257–1267. doi: 10.1002/eji.202048627.

10. Srenathan U, Kaams K, Taams LS. IL-17+ CD8+ T cells: differentiation, phenotype and role in inflammatory disease. Immunol Lett 2016;178:20–26. doi: 10.1016/j.imlet.2016.03.001.

11. Harrison OJ, Linehan JL, Shih HY, Bouladoux N, Han SJ, Smelkinson M, et al. Commensal-specific T cell plasticity promotes rapid tissue adaptation to injury. Science 2019;363:eaat6280. doi: 10.1126/science.aat6280.

12. Naik S, Bouladoux N, Linehan JL, Han SJ, Harrison OJ, Wilhelm C, et al. Commensal-dendritic-cell interaction specifies a unique protective skin immune signature. Nature 2015;520:1042–1049. doi: 10.1038/nature14052.

13. Nanjappa SG, McDermott AJ, Fites JS, Galles K, Wüthrich M, Deepe GS Jr, et al. Antifungal Tc17 cells are durable and stable, persisting as long-lasting vaccine memory without plasticity towards IFNγ. PLOS Pathog 2017;13:e1006356. doi: 10.1371/journal.ppat.1006356.

14. Zhuang Y, Peng LS, Zhao YL, Shi Y, Mao XH, Chen W, et al. CD8 (+) T cells that produce interleukin-17 regulate myeloid-derived suppressor cells and are associated with survival time of patients with gastric cancer. Gastroenterology 2012;143:951–962. e8. doi: 10.1053/j.gastro.2012.06.010.

15. Chellappa S, Hugenschmidt H, Haggens M, Subramani S, Melum KD, et al. RORγt and T-bet are functionally impaired and expand in patients with distal bile duct cancer. J Immunol 2017;198:1729–1739. doi: 10.4049/jimmunol.1600061.

16. Kuang DM, Peng C, Zhao Q, Wu Y, Zhu LY, Wang J, et al. Tumor-activated monocytes promote expansion of IL-17-producing CD8+ T cells in hepatocellular carcinoma patients. J Immunol 2010;185:1544–1549. doi: 10.4049/jimmunol.1009049.

17. Huber M, Heinik S, Pagenstecher A, Reinhard K, Ritter J, Visekruna A, et al. IL-17A secretion by CD8+ T cells supports...
A novel subset of CD4(+)/CD8(+) T(H)2 memory/effector cells that produce inflammatory IL-17 cytokine and promote the exacerbation of chronic allergic asthma. Exp Med 2010;207:2479–2491. doi: 10.1084/jem.20101376.

Mohme M, Hotz C, Stevanovic S, Binder T, Lee JH, Okomieki M, et al. HLA-DRA13-derived self-peptides are involved in increased autologous T cell proliferation in multiple sclerosis. Brain 2013;136:1793–1798. doi: 10.1098/brain.2013.11.

Havrdova E, Belova A, Goloborodko A, Tisserant A, Wright A, Wallstroem E, et al. Activity of secukinumab, an anti–IL-17A antibody, on brain lesions in RRM3: results from a randomized, proof-of-concept study. J Neurol 2016;263:1287–1295. doi: 10.1007/s00415-016-8128-x.

Hirota K, Durante JH, Veldhoen M, Hornsy E, Li Y, Cui DJ, et al. Fate mapping of IL-17-producing T cells in inflammatory responses. Nat Immunol 2011;12:253–263. doi: 10.1038/ni.1993.

Gaulthomme JT, Yosef N, Lee Y, Gartner RS, Yang LV, Wu C, et al. Single-cell genomics uncovers critical regulators of Th17 cell development. Cell 2015;163:1401–1412. doi: 10.1016/j.cell.2015.11.009.

Yang C, Yosef N, Gaulthomme J, Wu C, Lee Y, Chib CB, et al. CD5L/aim regulates lipid biosynthesis and restrains Th17 cell pathogenicity. Cell 2015;163:1413–1427. doi: 10.1016/j.cell.2015.10.068.

Broux B, Zandee S, Gowd E, Charabati M, Lécuyer MA, Tastet O, et al. Interleukin-26, preferentially produced by Th17 lymphocytes, regulates CNS barrier function. Neuroimmunol Neuroinflamm 2020;7:870. doi: 10.1212/NXI.0000000000000870.

Cadorri L, Gyulveszi G, Tosevski V, Hesse L, Fontanà A, Magnenat L, et al. RORC drives production of the drug GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. Nat Immunol 2011;12:560–567. doi: 10.1038/nm.2627.

Ronchi F, Bassio C, Prete S, Reboldi A, Baumjohann D, Perlini L, et al. Experimental priming of encephalitogenic Th1/Th17 cells requires pertussis toxin-driven IL-1β production by myeloid cells. Nat Commun 2016;7:11341. doi: 10.1038/ncomms11341.

Lee Y, Awasthi A, Yosef N, Quintana FJ, Xiao S, Peters A, et al. Induction and molecular signature of pathogenic Th17 cells. Nat Immunol 2012;13:991–999. doi: 10.1038/ni.2416.

Lee PW, Yang Y, Racke MK, Lovett-Racke AE. Analysis of TGF-β1 and TGF-β3 as regulators of encephalitogenic Th17 cells: implications for multiple sclerosis. Brain Behav Immun 2015;46:44–49. doi: 10.1016/j.bbi.2014.12.007.

Ghoreschi K, Laurence A, Yang XF, Tato CM, McGeehny MJ, Konkel JE, et al. Generation of pathogenic Th17 cells in the absence of TGF-β signalling. Nature 2010;467:967–971. doi: 10.1038/nature09477.

Kara EE, McKenzie DR, Bastow CR, Gregor CE, Fenix KA, Olgunmy D, et al. Interleukin-26, preferentially produced by T(H)17 lymphocytes, regulates CNS barrier function. Neuroimmunol Neuroinflamm 2020;7:e870. doi: 10.1212/NXI.0000000000000870.

Doroudian D, Monahan S, Blouin N, Marzouk E, Fontanà A, Magnenat L, et al. RORC drives production of the drug GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. Nat Immunol 2011;12:560–567. doi: 10.1038/nm.2627.

Ronchi F, Bassio C, Prete S, Reboldi A, Baumjohann D, Perlini L, et al. Experimental priming of encephalitogenic Th1/Th17 cells requires pertussis toxin-driven IL-1β production by myeloid cells. Nat Commun 2016;7:11341. doi: 10.1038/ncomms11341.

Lee Y, Awasthi A, Yosef N, Quintana FJ, Xiao S, Peters A, et al. Induction and molecular signature of pathogenic Th17 cells. Nat Immunol 2012;13:991–999. doi: 10.1038/ni.2416.
60. Constantinescu CS, Asher A, Fryze W, Kozubski W, Wagner F, El-Behi M, Ciric B, Dai H, Yan Y, Cullimore M, Safavi F, Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Dungan LS, McGuinness NC, Boon L, Lynch MA, Mills KHG.

58. Bittner S, Wiendl H. Neuroimmunotherapies targeting T cells: a review. Immunity 2015;43:502–12. doi: 10.1016/j.immuni.2015.03.010.

57. Dungan LS, McGuinness NC, Boon L, Lynch MA, Mills KHG. Induction of a distinct CD8 Tnc17 subset by transforming growth factor-β mediates tolerance to human antibody to GM-CSF, in multiple sclerosis. Neurol Immunol Neurol 2011;2:e117. doi: 10.1212/NXI.0b013e3182176f7f.

56. Solimani F, Pollmann R, Schmidt T, Schmidt A, Zheng X, Savai R, et al. Therapeutic targeting of Th17/Tc17 cells leads to clinical improvement of Lichen Planus. Front Immunol 2019;10:1808. doi: 10.3389/fimmu.2019.01808.

55. Menon B, Gullick NJ, Walter GJ, Rajasekhar M, Garrood T, et al. Polynuclear functional, proinflammatory, tissue-resident memory phenotype and function of synovial interventional CD8+ T cells in psoriatic arthritis. Arthritis Rheumatol 2020;72:435–447. doi: 10.1002/art.41156.

54. Arakawa A, Sievert K, Stolz J, Besgen P, Kim SM, Rühl G, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 2015;212:2203–2212. doi: 10.1084/jem.20151093.

53. Orthmann-Murphy JL, Calabresi PA. Therapeutic application of monoclonal antibodies in multiple sclerosis. Clin Pharmacol Ther 2017;101:52–64. doi: 10.1002/cpt.547.

52. Di Meglio P, Villanova F, Navarini AA, Mylonas A, Tosi I, Nestle FO, et al. Targeting CD8(+) T cells prevents psoriasis development. J Allergy Clin Immunol 2016;138:274–276. e6. doi: 10.1016/j.jaci.2015.10.046.

51. Matos TR, O’Malley JT, Lowry EL, Hamm D, Kirsch IR, Robins HS, et al. Clinically resolved psoriatic lesions contain psoriasis-specific IL-17-producing αβ T cell clones. J Clin Invest 2017;127:4031–4041. doi: 10.1172/JCI93396.

50. Cheuk S, Schlums H, Sérézal IG, Martini E, Chiang SC, Marquardt N, et al. CD49a expression defines tissue-resident CD8(+) T cells poised for cytotoxic function in human skin. Immunity 2017;46:287–300. doi: 10.1016/j.immuni.2017.01.009.

49. Raychaudhuri SK, Abria C, Mitra A, Raychaudhuri SP. Functional significance of MAIT cells in psoriatic arthritis. Cytokine 2020;128:338–352. doi: 10.1016/j.cyto.2019.1281.050.

48. Skepner J, Ramesh R, Trocha M, Schmidt D, Baloglu E, Lobera M, et al. Pharmacologic inhibition of RORγt regulates Th17 signature gene expression and suppresses cutaneous inflammation. J Immunol 2014;194:2564–2575. doi: 10.4049/jimmunol.1302190.

47. Magliozzo R, Howell OW, Nicholas R, Cruciani C, Castellaro M, Romualdi C, et al. Immunofluorescence, tissue and corneal damage in multiple sclerosis. Ann Neurol 2018;83:739–755. doi: 10.1002/ana.25197.

46. Kos M, Szentiványi Á, Szirmai A, Kádár A, Varga L, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. J Invest Dermatol 2014;134:2218–2228. doi: 10.1038/jid.2014.0293-y.

45. Sebastián I, del Barrio D, Perales J, del Campo E, Bódalo S, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 2015;212:2203–2212. doi: 10.1084/jem.20151093.

44. Aranda D, Del Rio M, Villalba A, Miranda G, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 2015;212:2203–2212. doi: 10.1084/jem.20151093.
89. Salou M, Nicol B, Garcia A, Baron D, Michel L, Elong-Ngono A, et al. Neuropathologic, phenotypic and functional analyses of Mucosal Associated Invariant T cells in multiple sclerosis. Clin Immunol 2016;166-167:1-11. doi: 10.1016/j.clim.2016.03.014.
90. Walker LJ, Kang YH, Smith MO, Tharmalingham H, Rammurthy N, Fleming VM, et al. Human MAIT and CD8aa cells develop from a pool of type-17 precommitted CD8+ T cells. Blood 2012;119:422-433. doi: 10.1182/blood-2011-05-333789.
91. Dusseaux M, Martin E, Serraart N, Péguelleti I, Premel V, Louis D, et al. Human MAIT cells are xenobiotic-resistant, tissue-targeted, CD161hi IL-17-secreting T cells. Blood 2011;117:1250-1259. doi: 10.1182/blood-2010-08-303339.
92. Patel O, Kjer-Nielsen L, Le Nours J, Eckle SBG, Birkinshaw R, Beddoe T, et al. Recognition of vitamin B metabolites by mucosal-associated invariant T cells. Nat Commun 2013;4:2142. doi: 10.1038/ncomms3142.
93. Reantragoon R, Corbett AJ, Sakala IG, Gherardin NA, Furness JB, Chen Z, et al. Antigen-loaded MR1 tetramers define T cell receptor heterogeneity in mucosal-associated invariant T cells. Nat Commun 2013;4:2142.
94. Le Bourhis L, Martin E, Péguillet I, Guihot A, Froux N, Coré M, et al. Antimicrobial activity of mucosal-associated invariant T cells. Nat Immunol 2010;11:701-708. doi: 10.1038/ni.1890.
95. Lepore M, Kalinichenko A, Colone A, Paleja B, Singhal A, et al. Parallel T-cell cloning and deep sequencing of human MAIT cells reveal stable oligoclonal TCRB repertoire. Nat Commun 2014;5:3866. doi: 10.1038/ncomms4866.
96. Le Bourhis L, Dusseaux M, Bohineust A, Besoises S, Martin E, Premel V, et al. MAIT cells detect and efficiently lyse bacterially-infected epithelial cells. PLoS Pathog 2013;9:e1003681. doi: 10.1371/journal.ppat.1003681.
97. Kurioka A, Usher JE, Cosgrove C, Clough C, Ferguson JR, Smith K, et al. MAIT cells are licensed through granzyme exchange to kill bacterially sensitized targets. Mucosal Immunol 2015;8:429-440. doi: 10.1038/mi.2014.81.
98. Willing A, Leach OA, Ufer F, Attfield KE, Steinbach K, Kursawe N, et al. CD8+ MAIT cells infiltrate into the CNS and alterations in their blood frequencies correlate with IL-18 serum levels in multiple sclerosis. Eur J Immunol 2014;44:3119-3128. doi: 10.1002/eji.201344160.
99. Qian Y, Arellano G, Ifergan I, Snowden C, Kim T, et al. ZEB1 promotes pathogenic Th1 and Th17 cell differentiation in multiple sclerosis. Cell Rep 2021;36:109602. doi: 10.1016/j.celrep.2021.109602.
100. Falcon CR, Hurst NF, Vivinetto AL, Lopez PHH, Zurita A, Gatti G, et al. Diazepam impairs innate and adaptive immune responses and ameliorates experimental autoimmune encephalomyelitis. Front Immunol 2021;12:682612. doi: 10.3389/fimmu.2021.682612.
101. Bae D, Lee JY, Ha N, Park J, Baek J, Sub D, et al. CKD-506: A novel HDAC6-selective inhibitor that exerts therapeutic effects in a rodent model of multiple sclerosis. Sci Rep 2021;11:14466. doi: 10.1038/s41598-021-93232-6.
102. Li H, Rostami A. IL-9: basic biology, signaling pathways in CD4+ T cells and implications for autoimmunity. J Neuroimmune Pharmacol 2010;5:198-209. doi: 10.1007/s11481-009-9186-y.
103. Beriou G, Bradshaw EM, Lozano E, Costantino CM, Hastings WD, Orban T, et al. TGF-beta induces IL-9 production from human Th17 cells. J Immunol 2010;185:46-54. doi: 10.4049/jimmunol.1000356.
104. Kalyan S, Kabelitz D. Defining the nature of human γδ T cells: A biographical sketch of the highly empathetic. Cell Mol Immunol 2013;10:21-29. doi: 10.1038/cmi.2012.44.
105. Maggi L, Santarlasci V, Capone M, Peited A, Frosali F, Crone SQ, et al. CD161 is a marker of all human IL-17-producing T-cell subsets and is induced by RORC. Eur J Immunol 2010;40:2177-2181. doi: 10.1002/eji.200940257.

How to cite this article: Peng Y, Deng X, Zeng Q, Tang Y. Tc17 cells in autoimmune diseases. Chin Med J 2022;135:2167-2177. doi: 10.1097/CM9.0000000000002083