Tc17 cells in autoimmune diseases

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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.
Keywords: Tc17; Autoimmune diseases; Multiple sclerosis; Experimental autoimmune encephalomyelitis; Retinoic acid receptor-related orphan receptor gamma; Th17

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 and treatment of MS and 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 MOG$_{37-50}$-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 (RORγ) is the key transcription factor (TF) but not the prototypical master regulator for the differentiation of Th17 cells, because RORγ 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 TGFβ 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.

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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 TGFβ 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, such as MOG-induced EAE by IL-9 neutralization or IL-9R deficient mice. IL-21 contributes to Th17 cell differentiation, expansion, and survival. Murine Th17 differentiation depends on T cell receptor (TCR) stimulation of naïve 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 eomesodermin (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)1hi, T-BETlo, and EOMESlo 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, RORγ, 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 chemo-attraction 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-RORγ taxes, regulate Tc17 cell development in the thymus but not in the periphery.[27] IL-17A regulates Th cell polarization. IL-17A is inactivated in naïve or Th1 cells, and is activated only under Th17 differentiation initiated by epigenetic transformation, with promoter 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.[27] Interferon regulator 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 Th17cells 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 theCNS[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 autoimmunity.[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.[9]

The plasticity of Tc17 and Th17 cells in type 2 immune responses has been reported. RORγt+GATA3+DP

CD4+cells secrete cytokines IL-17, IL-22, IL-4, IL-5, and IL-13 and shows high pathogenesis in asthma.[35] In contrast, in tissue damage, Tc17 switches to the Tc2 phenotype by secreting IL-5 and IL-13 production, resulting in a protective immune response.[11]

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.[9]

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.[36] 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.[37] Th17 cells are induced by IL-23, RORγt, and RORα.[38] 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, gpr65, toso, and plzp.[39,40]

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.[41] In EAE mice, IL-17A, IFN-γ, and GM-CSF are co-expressed in CNS-infiltrating CD4+ T cells.[42,43] 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-1RI-/-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.[44] 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 Th-17 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 Th-17 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.[45] Similarly, other reports have confirmed that TGFβ inhibits differentiation into Th17 cells in EAE, healthy people, and experimental autoimmune uveitis.[46]

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.[47]

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.[48,49] In addition, secukinumab has also been approved as a treatment for psoriatic arthritis (PsA) and ankylosing spondylitis.[37,49-53] However, clinical trials of other anti-IL-17 antibodies, ustekinumab and briakinumab, for use in MS have either been terminated or have failed.[54,55] 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.[56] This showed that IFN-γ-/- or anti-IFN-γ-treated mice were susceptible to EAE due to enhanced IL-17 and GM-CSF production.[57]

Furthermore, IL-1β, IL-23, and GM-CSF resulted in encephalitogenic Th17 cells in EAE.[42,58,59] 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.[60] In addition, IFN-β, fingolimod, and hematopoietic stem cell transplantation have shown clinical improvement in patients with MS by attenuation of Th17 responses.[61]

Development, Differentiation, and Phenotype of Tc17 Cells

Development and differentiation of Tc17 cells

Tc17 T cells have a cytokine profile that is similar to that of Th17 cells; this suggests that Tc17 cells have development and differentiation conditions similar to that of Th17 cells, despite the fewer reports on Tc17 in comparison with Th17 cells.[10] 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 Tc17 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+ Tc17 cells. In addition, the addition of TGF-β and IL-21 or a cocktail containing TGF-β, IL-6, IL-1, IL-2, IL-21, IL-23, anti-IL-4, and anti-IFN-γ with or without IL-2 resulted in 19% and 64% differentiation into Tc17 cells and IFN-γ+Tc17 cells, respectively. However, few studies have been conducted on human Tc17 cells. When human naïve CD+ 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 naïve CD$^+$ 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.[62]

TGF-β inhibits various functions of IFN-γ$^+$CD$^+$ 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 orrposite effect, that is, it promotes the induction of Tc17 cells.[63] 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[64] and those performed using TGF-βRIIDN mice,[65] 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.
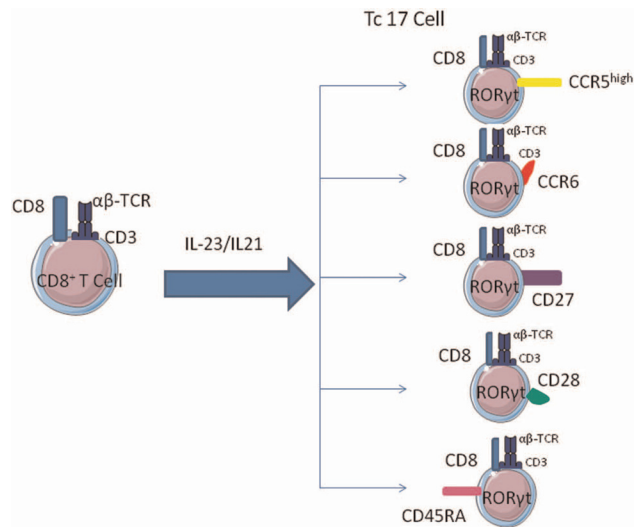
Phenotype of Tc17 cells

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.[66] 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 RORγ 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,[66,67] 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 asCD161, as well as various cytokine and chemokine receptors, including CCR5 (CD1 3), CCR6 (CD196), IL-23 receptor (IL-23R), and CD27$^+$CD28$^+$CD45RA$^-$ or CT)27$^-$CT)28$^+$CT)45RA$^-$[Table 1].[66,68]

## Tc17 Cells and Autoimmune Disease Excluding MS/EAE

Autoimmune diseases are a group of complex diseases caused by the loss of immunological tolerance to self-antigens, leading to immune-mediated destruction of tissues and organs. The pathogenic role of Tc17 cells correlates with the development of many autoimmune diseases, including diabetes, RA, systemic lupus erythematosus (SLE), and psoriasis.

Figure 1: Phenotype of murine and human Tc17 cell subsets. Tc17: IL17$^+$CD8$^+$ cells. Mouse IL-17$^+$ CD8$^+$ T cells express CCR6 and IL-23R and can produce the pro-inflammatory cytokines IL-17A, IFN-γ, TNF-α, IL-21, IL-22, and GM-CSF. Human IL-17$^+$ CD8$^+$ T cells express CCR6, CD161, CCR5, and IL-23R and can produce IL-17A, IFN-γ, TNF-α, IL-21, and IL-22. GM-CSF: Granulocyte macrophage colony-stimulating factor; IFN: Interferon; IL: Interleukin; RORγt: Receptor-related orphan nuclear receptor gamma t; TCR: T cell receptor; TNF-α: Tumor necrosis factor alpha.

Tc17 cells and psoriasis

Tc17 cells recognize autoantigens, including LL-37 antimicrobial peptide expressed bykeratinocytes,[69] mela-nocyte-derived antigen ADAMTS-like protein5,[70] and keratin 17. Di Meglio *et* al[71] 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
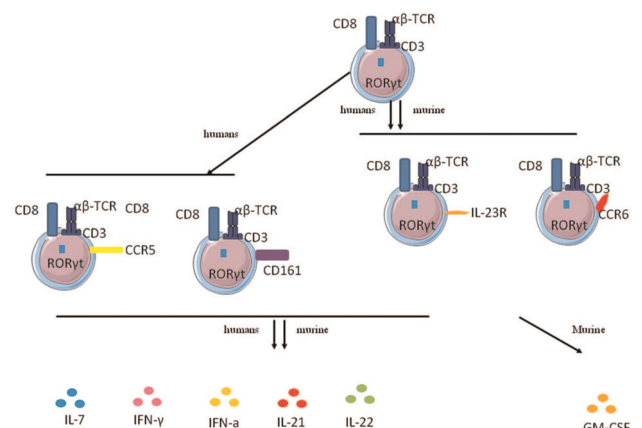
Figure 2: Effect of transcriptional regulators on major CD8$^+$ T cell subsets. CD8$^+$ cytotoxic T-αβ (Tc) cell subsets CCR5^{high}, CCR6, CD161, IL-23R, and CD45RA. Discriminative surface proteins are visualized on the cell surface, and TFs are expressed as squares. GM-CSF: Granulocyte macrophage colony-stimulating factor; IFN: Interferon; IL: Interleukin; RA: Rheumatoid arthritis; RORγt: Receptor-related orphan nuclear receptor gamma t; TCR: T cell receptor; TF: Transcription factor.

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

Items	CD4		CD8	
	Th1	Th17	Tc1	Tc17
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.

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.[76] 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 Tc17 cells, as well as activating CD40-CD40L DC, which upregulates TFs *Rorc* and *Runxl*. 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 Chiricozzi 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

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.[85] 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 high-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 to a CTL phenotype and elevated IFN-γ secretion.[18] 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.[18] 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
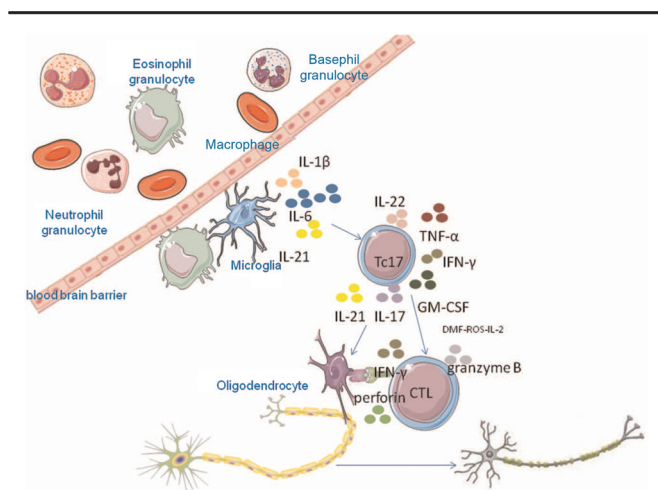
Figure 3: In MS, activated T cells migrate toward the BBB. In MS, activated T cells migrate to the BBB, and as the integrity of the BBB is impaired, inflammatory cells and T cells can enter the CNS. Resident microglia become activated and myelin antigens become present in T cells. Microglia secrete IL-1 β, 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 to a CTL phenotype and elevated IFN-γ secretion. Furthermore, Tc17 cells induce apoptosis in oligodendrocytes. This can result in decreased axon myelination, potentially contributing to MS pathogenesis. BBB: Blood-brain barrier; CNS: Central nervous system; GM-CSF: Granulocyte macrophage colony-stimulating factor; IFN: Interferon; IL: Interleukin; MS: Multiple sclerosis; TNF-α: Tumor necrosis factor alpha.

gene. These effects are likely to be mediated by the inhibitory effect of the PI3K-AKT-FOXO1-T-BET pathway on IL-17, RORγt, and STAT5-signaling.[18]

IL-17-producing cell subsets within the T cell compartment have been identified, and numerous studies support the idea that Tc17 cells play a pivotal role in the pathogenesis of several autoimmune diseases. Peelen et al[8] reported that the percentage of Tc17 cells in the PB of patients with relapsing-remitting MS (RRMS) in remission was significantly higher than that in the PB of healthy individuals and that patients with RRMS in remission with elevated Tc17 levels often had a proportionally expanded Tc17/IFN-γ-cell population. In contrast, an increased proportion of Tc17 cells in the CSF, but not in the PB, of patients with clinically isolated syndrome and early MS was observed. In addition, they demonstrated that there was no significant difference in the percentages of Tc17 cells or Tc17/IFN-γ-cells between untreated patients with RRMS in remission and those in relapse, indicating that there is no significant correlation between the percentages of these cells and disease activity.[88] However, one report showed significantly elevated Tc17 levels in active MS lesions compared to those in inactive MS lesions. Tc17 cells increased frequencies in CSF at early MS stages[17] and were present in active areas of acute and chronic MS lesions. Moreover, Tc17 frequencies in PB from DMF-sensitive MS patients were reduced after DMF therapy.[18]

A unique Tc17 subset, mucosal-associated in variant T (MAIT), was identified.[89] MAIT cells are effector memory cells, phenotyping CD8+CD4− and CD8−CD4−, expressing a semi-invariant TCR (Vα7.2-Jα33/12/20 in humans), and restricting to the non-classical MHC class I-related protein 1 (MR1).[90-93] MAIT secrete IL-17 only after non-specific PMA/ionomycin stimulation.[91,94,95] They also exert cytotoxic effects against cells co-cultured with different bacteria by secreting granzyme B, perforin, and granulysin, a function similar to Th1 cells.[96,97] Finally, MAIT cells express a wide range of homing receptors, such as CCR5, CCR6, and VLA4 (α4β1), suggesting an ability to migrate to inflamed tissues.[91] Indeed, MAIT cells are present in MS lesions, representing approximately 5% of infiltrating CD8+ T cells.[98] Finally, transcriptional over expression of MR1 is overexpressed and presents cognate antigens to MAIT cells, resulting in the secretion of IL-18 and IL-23 in MS lesions.[4]

Relationship of Tc17 and Th17 cells in MS/EAE

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.[17] 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. Furthermore, 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, RORγt, 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, differentiation, 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*[99] 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 the expression of IL-17 and IFN-γ. And also, ZEB1 and JAK2 down-regulation decreases pathogenic cytokines expression in T cells from MS patients.[99] Falcon *et al*[100] showed that Diazepam (DZ) treatment inhibited alloge-neic 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 by 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 MOG$_{35-55}$-re-stimulated splenocytes, and also reduced the levels of pro-inflammatory cytokines in the blood of EAE mice.

Conflicts of interest

None.

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