Journal of Translational Medicine

REVIEW

Open Access

An angel or a devil? Current view on the role of $CD8^+$ T cells in the pathogenesis of myasthenia gravis

Yong Peng[1,2*], Huan Yang[3], Quan Chen[1,2], Hong Jin[1,2], Ya-hui Xue[1,2], Miao-qiao Du[1,2], Shu Liu[1,2] and Shun-yu Yao[1,2]

Abstract

Background Myasthenia gravis (MG) and the experimental autoimmune MG (EAMG) animal model are characterized by T-cell-induced and B-cell-dominated autoimmune diseases that affect the neuromuscular junction. Several subtypes of $CD4^+$ T cells, including T helper (Th) 17 cells, follicular Th cells, and regulatory T cells (Tregs), contribute to the pathogenesis of MG. However, increasing evidence suggests that $CD8^+$ T cells also play a critical role in the pathogenesis and treatment of MG.

Main body Herein, we review the literature on $CD8^+$ T cells in MG, focusing on their potential effector and regulatory roles, as well as on relevant evidence (peripheral, in situ, cerebrospinal fluid, and under different treatments), T-cell receptor usage, cytokine and chemokine expression, cell marker expression, and Treg, Tc17, $CD3^+CD8^+CD20^+$ T, and $CXCR5^+$ $CD8^+$ T cells.

Conclusions Further studies on $CD8^+$ T cells in MG are necessary to determine, among others, the real pattern of the Vβ gene usage of autoantigen-specific $CD8^+$ cells in patients with MG, real images of the physiology and function of autoantigen-specific $CD8^+$ cells from MG/EAMG, and the subset of autoantigen-specific $CD8^+$ cells (Tc1, Tc17, and IL-17^+IFN-γ^+CD8^+ T cells). There are many reports of CD20-expressing T (or CD20 + T) and $CXCR5^+$ CD8 T cells on autoimmune diseases, especially on multiple sclerosis and rheumatoid arthritis. Unfortunately, up to now, there has been no report on these T cells on MG, which might be a good direction for future studies.

Keywords Myasthenia gravis, Experimental autoimmune myasthenia gravis, $CD8^+$ T cells, Effector T cells, Regulatory T cells

Introduction

Myasthenia gravis (MG) and its animal model, experimental autoimmune MG (EAMG), are T-cell-driven, autoantibody (Ab)-mediated disorders affecting transmission in neuromuscular junctions [1–5]. As the treatment of MG has remained a burden for patients, finding better treatments is necessary [6]. Abs in patients with MG are against the muscle nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK), and lipoprotein-related protein 4 [1, 3, 5, 7], and are secreted by B cells and plasma cells with assistance from $CD4^+$ T cells [1, 8], resulting in complement anti-AChR

*Correspondence:
Yong Peng
1779342446@qq.com
[1] Department of Neurology, Affiliated First Hospital of Hunan Traditional Chinese Medical College, Zhuzhou 412000, Hunan, China
[2] Department of Neurology, The Third Affiliated Hospital of Hunan University of Chinese Medicine, Zhuzhou 412000, Hunan, China
[3] Department of Neurology, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

antibodies damaging the neuromuscular junctions and inducing MG symptoms such as ptosis, dysphagia, limb weakness, and even dyspnea [4, 9].

A possible mechanism of MG might be that these autoreactive Abs bind to functional molecules in the postsynaptic membrane, impairing signal transmission in these synapses [10]. Currently, a few new Abs have been confirmed to affect patients with MG in several clinical trials. Regarding existing treatments, eculizumab has been approved in many countries [11–13], zilucoplan has shown better results than eculizumab in a phase II clinical trial [14], and efgartigimod has been successful in a phase III clinical trial [15]. Moreover, immunomodulatory drugs, such as terifunomide [16, 17], have also shown benefits for MG treatment in EAMG [16].

Many subtypes of $CD4^+$ T cells contribute to the pathogenesis of MG, including T helper 1 (Th1), Th17, Th22, follicular Th (Tfh), Th_{CD103}, and regulatory T (Treg) cells; however, previous reports focused on $CD4^+$ T cells [18–30]. Major histocompatibility complex (MHC) class I-restricted $CD8^+$ T cells act as both effectors and/or regulators in various autoimmune diseases, such as multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE) [31–33], and animal models of uveitis—experimental autoimmune uveitis (EAU) [34]. However, in Theiler's murine encephalomyelitis virus-induced demyelination, $CD8^+$ T cells played a regulatory role predominantly. MHC class I and $CD8^+$ T cell deficiency in $\beta2\text{-}m^{-/-}$ mice inhibited clinical scores in an animal model of type I diabetes and Ab-mediated autoimmune disease, such as systemic lupus erythematous disease.

Indeed, increasing evidence supports that $CD8^+$ T cells also play a critical role in the pathogenesis and treatment of MG [13, 35, 36] and EAMG [37], even though this evidence is fragmented and unsystematic [38]. Herein, we investigate $CD8^+$ T cells in MG, focusing on their potential effector and regulatory roles, as well as on evidence (peripheral, in situ, cerebrospinal fluid (CSF), and under different treatments), T-cell receptors (TCR) usage, cytokine and chemokine expression, cell marker expression, regulatory T cells, and Tc17 cells.

Evidence of $CD8^+$ T cells in patients with MG

Peripheral $CD8^+$ T cells in patients with MG with and without treatment

The first report on peripheral $CD8^+$ T cells in patients with MG was published in 1988, although there were no reported significant differences in peripheral blood lymphocyte subsets (including $CD4^+$, $CD8^+$, and the ration of $CD4^+/CD8^+$) in patients with or without a thymus [39].

Activated $CD8^+$ and $CD4^+$ T cells co-exist in the peripheral blood of patients with MG, and the numbers of $CD8^+$ and $CD4^+$ T cells are related to the severity of the disease [40]. Furthermore, in both patients with MG and healthy controls, $CD8^+$ peripheral blood mononuclear cells (PBMCs) and $CD8^+$ lines responded vigorously to autologous antigen (Ag) (including AchR), which can activate $CD4^+$ cells. The $CD8^+$ cell lines responded equally well to the different Ag- and phytohemagglutinin-activated $CD4^+$ cells [41]. Moreover, one report showed that the amount or function of $CD8^+$ T cells was destroyed in patients with MG. The authors also confirmed that the inhibitory function of $CD8^+$ cells and exogenous interleukin (IL)-2 completely restored this suppression in vitro. The expression of $CD8^+$ was decreased in 71% of patients with MG [42]. However, another report showed that the percentages of $CD8^+$ T cells in peripheral blood were not significantly different among three groups: ocular MG (OMG), generalized MG, and healthy controls [43].

MG usually coexists with several diseases. In autoimmune thyroid diseases, compared with thyroid antibody (TAb)-negative patients, TAb-positive patients appeared to have a higher prevalence of OMG, higher percentages of $CD8^+$ $CD28^+$ cells, lower AChR-Ab titers, and percentages and absolute counts of total $CD8^+$ T cells [44]. In patients with Sjogren's syndrome, $CD8^+$ cells and their two subsets significantly increased in untreated patients with MG. In a female patient with MG and Good's syndrome that presented with paroxysmal nocturnal hemoglobinuria, $CD8^+$ T cells are directly responsible for inhibiting the growth of control PBMC. $CD8^+$ T cells from patients with MG showed a reduced number of Vβ-TCR families (Vβ2, Vβ5.3, Vβ14, and Vβ20). $CD8^+$ T cells are associated with damaging hematopoietic precursors as confirmed by co-culture experiments and spectratyping analyses [45].

In patients with MG, inflammatory cell infiltration was observed in the heart and skeletal muscles; however, the severity varied. The heart showed widespread inflammatory infiltrates containing multinucleated giant cells with massive myocardial degeneration. $CD8^+$ cells were observed in both necrotic and non-necrotic muscle fibers. A limited number of mononuclear cells infiltrating the perimysial or perivascular regions were $CD8^+$ cells. Muscle fibers, including normal-appearing ones, aberrantly express diffuse MHC class I on surface membranes (Table 1) [46].

There have been several reports on the cell culture of $CD8^+$ T cells in patients with MG. Out of all T-cell lines tested, $CD4^+$ cells were only present in seven AChR-specific T-cell lines obtained from three patients with MG. In addition, predominant $CD4^+CD8^-$ (15/38) and

Table 1 peripheral CD8 + T cells in patients of MG with and without treatment

Study ID	Sample	Treatment	CD8 percentage	CD4/CD8 ratio	CD8 subset	Significant findings of CD8 in MG
Machi 1988	MG	Total	39.9 ± 8.0	1.34 ± 0.43	N/A	None
	MG	Non-Tx	39.6 ± 7.4	1.41 ± 0.42	N/A	None
	MG	Tx	40.2 ± 9.3	1.24 ± 0.45	N/A	None
	HC	None	39.2 ± 5.5	1.40 ± 0.34	N/A	N/A
Kawanami 1990	MG	Total	N/A	N/A	N/A	N/A
	MG	None	29.7 ± 3.0	1.2 ± 0.16	N/A	N/A
	MG	Tx(−)PSL(+)	26.5 ± 2.1	1.3 ± 0.18	N/A	N/A
	MG	Tx(+) PSL(−)	25.8 ± 3.5	1.7 ± 0.31	N/A	N/A
	MG	Tx(+) PSL(+)	29.6 ± 1.1	0.94 ± 0.24	N/A	N/A
	HC Female	None	26.8 ± 1.7	1.5 ± 0.1	N/A	N/A
	HC male	None	28.4 ± 1.4	1.3 ± 0.1	N/A	N/A
Shimizu 1990	MG	Total	28.0 ± 10.5	1.8 ± 1.0	CD8 + CD11 +, CD8 + CD11−	CD8 + CD11 +, CD8 + CD11−
	MG	Tx(+) PSL(−)	22.8 ± 4.3	2.2 ± 0.8	CD8 + CD11 +, CD8 + CD11−	CD8 + CD11 +, CD8 + CD11-
	MG	Tx(−)PSL(+)	30.8 ± 12.6	1.5 ± 1.0	CD8 + CD11 +, CD8 + CD11−	CD8 + CD11 +, CD8 + CD11-
	MG	Tx(+) PSL(−)	25.2 ± 6.5	2.1 ± 0.9	CD8 + CD11 +, CD8 + CD11−	CD8 + CD11 +, CD8 + CD11-
	MG	Tx(+) PSL(+)	30.2 ± 12.1	1.7 ± 1.2	CD8 + CD11 +, CD8 + CD11−	CD8 + CD11 +, CD8 + CD11−
Fujii 1991	MG group A	Tx(+) PSL(+)	39.3 ± 9.2	1.23 ± 0.36	N/A	N/A
	MG group B	Tx(+) PSL(−)	33.3 ± 13.6	1.89 ± 0.70	N/A	N/A
	HC	None	39.2 ± 5.5	1.40 ± 0.34	N/A	N/A
Tanaka 2009	MG	Tx(+)	Mean 21	N/A	N/A	N/A
	MG	None	Mean 14	N/A	N/A	N/A

a few $CD4^{-}CD8^{+}$ cells (5/38) were observed in 38 AchR or recombinant mammalian AchR α chain peptide (X4) T-cell lines obtained from 11 healthy individuals. Similarly, out of seven human AchR β subunit-specific T-cell lines obtained from patients with MG (four lines) and healthy controls (three lines), only one $CD4^{+}$ and $CD8^{+}$ (ratio around 1:1) were observed.

$CD8^{+}$ T cells in patients with MG under different treatments

Thymoma is a non-malignant thymus tumor characterized by many non-malignant lymphocytes usually associated with MG. The percentage of mature single-positive T lymphocytes (including $CD4^{-}CD8^{+}$ cells) in thymomas with MG increased significantly compared with that without MG. In addition, compared with the proportion of $CD8^{+}$ cells in thymocytes of patients with MG without thymoma, those inpatients with MG with thymoma increased significantly during the incubation period with IL-2.

Thymus responses to T-cell differentiation and maturation. Thymectomy (Tx) improved the clinical outcomes in patients with MG with or without thymomas [47, 48]. After Tx and steroid therapy, $CD8^{+}$ T cells decreased immediately after Tx and returned to pre-treatment levels within three weeks. These results are similar to those of other studies [49–51]. Subsequently, the percentage of $CD8^{+}CD11^{-}$ cells decreased, whereas that of $CD8^{+}$ $CD11^{+}$ cells increased after Tx and prednisolone treatment. The absolute number of $CD45RA^{+}CD8^{+}$ $CD62L^{+}$ and $CD45RO^{+}CD8^{+}$T cells decreased significantly in the blood of patients with MG who underwent Tx [49]. $CD8^{+}$ T cells in patients with MG increased after Tx, whereas a decrease was observed in prealbumin and albumin levels [52]. Naïve cytotoxic T cells ($CD8^{+}CD27^{+}CD28^{+}$) were reduced in patients who underwent thymectomy [51]. $CD8^{+}$ T-cell counts were markedly higher in the conventional trans-sternal extended Tx (TS) group on postoperative days 1 and 3 but remained relatively stable in the video-assisted thoracoscopic surgery group. On postoperative day 7, $CD4^{+}$ counts were similar in the TS and video-assisted thoracoscopic surgery groups, whereas $CD8^{+}$ counts remained higher in the TS group [53].

$CD8^{+}$ T cells in patients with MG with and without thymoma

Immunosuppressive therapy, including steroids and tacrolimus, is a common treatment for MG. The percentage of DR^{+} and $CD8^{+}/DR^{+}$ T cells in the blood increased and the level of $CD4^{+}$ T cells decreased when patients with MG received immunosuppressive therapy (steroids alone or in combination with azathioprine). Tacrolimus (FK506) is an immunosuppressive agent similar to cyclosporin A that inhibits the action of calcineurin, a serine/threonine phosphatase, thereby suppressing IL-2

production. Tacrolimus treatment significantly attenuated T-cell receptor excision circle (TREC) levels in cultured $CD4^{-}CD8^{+}$ cells, but the total cell counts did not change significantly. In addition, compared with that in patients with MG without thymoma, levels of $CD8^{+}$ T cells in patients with MG with thymoma decreased significantly after tacrolimus therapy [54]. Additionally, P-glycoprotein (P-gp) actively transports glucocorticoids (GC) out of target cells, thereby reducing its efficacy. Compared with patients with MG without GC therapy, P-gp function in $CD8^{+}$ T cells was higher in patients with MG with long-term GC therapy (Table 2) [50].

In summary, these studies provide strong evidence of the critical role of $CD8^{+}$ T cells in the pathogenesis of patients with MG with or without treatment, including patients with MG with or without other diseases, with in situ $CD8^{+}$ T cells in the heart and skeletal muscle and $CD8^{+}$ T cells in the CSF, as well as those undergoing different treatments, such as Tx and immunosuppressive therapy. Although $CD8^{+}$ T cells are important in the pathogenesis of MG, existing studies on $CD8^{+}$ T cells are fewer than those for $CD4^{+}$ T cells in relation to MG. We have previously reported that the classical T-cell culture system was favorable for $CD4^{+}$ T cells rather than $CD8^{+}$ T cells in EAE and EAU. Possibly, the major subset of $CD8^{+}$ T cells is cytotoxic T-lymphocytes (CTL), which easily causes cell damage, even to themselves, and the expansion of $CD8^{+}$ T cells in vitro requires support from $CD4^{+}$ T cells and their secreted cytokines [31, 32, 34, 55]. Therefore, there is a similar condition in MG/EAMG, which is also a T cell-mediated autoimmune disease.

Evidence of $CD8^{+}$ T cells in EAMG

Peripheral $CD8^{+}$ T cells in patients of MG with and without treatment

The first report on peripheral CD8 + T cells in EAMG was also published in 1988, although there were no reported significant differences in peripheral blood lymphocyte subsets (including CD4 +, CD8 +, and the ration of CD4 + /CD8 +) in MG with or without a thymus. Ten acetylcholine receptor (AChR)-specific T cell clones from Lewis rats were studied. These clones had various AChR subunit and peptide specificities and proliferated in response to the antigen on the appropriate APC. All T cell clones were CD4 + CD8- and OX22-, helped anti-AChR antibody production by AChR-primed lymph node B cells, and could secrete IL-2. However, several lines of evidence suggest that IL-2 was not the lymphokine that mediated T cell help. B cells primed with native AChR and exposed in culture to very low concentrations of native AChR effectively presented the Ag to T cell lines, presumably owing to an uptake via Ag receptors; however, primed B cells were no more effective than non-specific APC

Table 2 peripheral CD8 + T cells in patients of EAMG with and without treatment

Study ID	Sample	Treatment	CD8 percentage	CD4/CD8 ratio	CD8 subset	Significant findings of CD8 in MG
Fujii 1988	Lewis rats	Total	39.9 ± 8.0	1.34 ± 0.43	N/A	None
	MG	Non-Tx	39.6 ± 7.4	1.41 ± 0.42	N/A	none
	MG	Tx	40.2 ± 9.3	1.24 ± 0.45	N/A	none
	HC	None	39.2 ± 5.5	1.40 ± 0.34	N/A	N/A
Kawanami 1990	MG	Total	N/A	N/A	N/A	N/A
	MG	None	29.7 ± 3.0	1.2 ± 0.16	N/A	N/A
	MG	Tx(−)PSL(+)	26.5 ± 2.1	1.3 ± 0.18	N/A	N/A
	MG	Tx(+) PSL(−)	25.8 ± 3.5	1.7 ± 0.31	N/A	N/A
	MG	Tx(+) PSL(+)	29.6 ± 1.1	0.94 ± 0.24	N/A	N/A
	HC Female	None	26.8 ± 1.7	1.5 ± 0.1	N/A	N/A
	HC male	None	28.4 ± 1.4	1.3 ± 0.1	N/A	N/A
Shimizu 1990	MG	Total	28.0 ± 10.5	1.8 ± 1.0	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$
	MG	Tx(+) PSL(−)	22.8 ± 4.3	2.2 ± 0.8	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$
	MG	Tx(−)PSL(+)	30.8 ± 12.6	1.5 ± 1.0	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$
	MG	Tx(+) PSL(−)	25.2 ± 6.5	2.1 ± 0.9	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$
	MG	Tx(+) PSL(+)	30.2 ± 12.1	1.7 ± 1.2	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$	$CD8^{+}CD11^{+}$, $CD8^{+}CD11^{-}$
Fujii 1991	MG group A	Tx(+) PSL(+)	39.3 ± 9.2	1.23 ± 0.36	N/A	N/A
	MG group B	Tx(+) PSL(−)	33.3 ± 13.6	1.89 ± 0.70	N/A	N/A
	HC	None	39.2 ± 5.5	1.40 ± 0.34	N/A	N/A
Tanaka 2009	MG	Tx(+)	Mean 21	N/A	N/A	N/A
	MG	None	Mean 14	N/A	N/A	N/A

at presenting a synthetic AChR peptide that is recognized by AChR-specific T cells but not by AChR-specific B cells. Increasing AChR doses to a certain level produced an antibody production response that was bell shaped and only stimulated by low AChR concentrations; higher AChR concentrations suppressed the antibody production response. The evidence suggested that AChR exerted its inhibitory effect through T cells, but not via IL-2.

An EAMG model is a valuable tool for studying the pathogenesis of MG. There is evidence in rat and mouse models to support the role of $CD8^+$ T cells in the pathogenesis of MG. Ten AchR-specific T-cell clones from Lewis rats in an EAMG model were $CD4^+CD8^-$ and OX22 −. The EAMG model was generated by peritoneally injecting thymocytes from patients with MG into severe combined immunodeficiency mice, then found that in a total of 21 T-cell lines, 60% were $CD4^+$ and 13% were CD8 +.

These results showed that the generation of $CD8^+$ T-cell lines and clones was more difficult than that of $CD4^+$ T cells in MG/EAMG. However, no abovementioned reports described the reason; thus, we suggest that the method of EAMG induction or cultural condition of T-cell clone selection from patients with MG or EAMG might favor $CD4^+$ T cells, which is similar to our findings in EAE and EAU [31, 32, 34, 55].

Major TCR V gene usage of $CD8^+$ T cells in MG

In the thymus, human thymocytes rearrange V and J segments to create a functional heterodimeric α/β TCR, which is expressed as a disulfide-linked heterodimer on the mature T cell to be recognized as antigen peptides by self-MHC. TCR V gene usage is critical for the pathogenesis of autoimmune diseases, including MG. The autoreactive $CD8^+$ cells from patients with MG might have specific Vα and Vβ gene usage [56].

Compared with $CD8^+$ cells from HC, several reports showed different patterns in the Vβ gene usage of $CD8^+$ cells from patients with MG, such as (1) Vαl2.1, and Vβ6.7, 8, 12; (2) Vβ1, 13.2, 17, and 20 [56]; (3) Vβ10, 13, and 17; (4) vβ3 and Vβ19; (5) Vα2.3, 12.1, and β2, 3, 5.1, 5.2, 5.3, 6.7, 8, 13, and 17. For different subtypes of MG, remarkable $CD8^+$ TCR Vβ-subset expansion was found in 64% and 72% of late-onset MG or thymoma-associated MG (vs. 16% with early-onset MG) [57].

The real pattern of the Vβ gene usage of $CD8^+$ cells from patients with MG is difficult to determine because results were obtained from different groups, which might have used different standards of testing. Moreover, due to the lack of reports in the past and the last decade, this topic must be studied further.

Cytokine and chemokine secretion of $CD8^+$ T cells in MG/EAMG

Patients with MG

In patients with MG with MuSK, tacrolimus inhibited $CD8^+$ T-cell proliferation and interferon (IFN)-γ and IL-2 production; however, tacrolimus inhibition was lower in $CD4^+$ T cells [58, 59]. Nevertheless, these results had two shortcomings: [1] $CD8^+$ T cells were not highly purified using fluorescence-activated cell sorting or magnetic separation enrichment but $CD3^+CD8^+$ were only separated from whole PBMCs using flow cytometry. [2] These PBMCs were stimulated with either αCD3 and αCD28 or phorbol 12-myristate 13-acetate and ionomycin in the presence of brefeldin A but not with autoantigens such as AchR. As we have previously performed in EAE and EAU, these T cells should be dominated by non-Ag-specific T cells, which are not able to induce diseases [31, 34, 55, 60].

Intracellular staining showed that the ratio of Th2 decreased significantly, and Th1 and Th17 were significantly increased in patients with MG [24]. IL-17-producing $CD4^+$ T cells (Th17) increased significantly with disease severity in patients with MG [36, 59]. Similarly, $CD8^+$ T-cell subsets producing IL-17 and IL-17/IFN-γ increased in patients with MG, whereas the increased cell levels were inhibited by the retinoic acid receptor-related-orphan-receptor-C (RORγ) inhibitor. These findings provide a rationale for the exploration of targeted Th17 therapies, including ROR-γ inhibitors, to treat patients with MG [61].

EAMG

Compared with female C57BL/6 J wild-type (*wt*) mice, the clinical EAMG score, AChR-specific T and B cell responses, and AChR-reactive IFN-γ and IL-4-expressing cells in lymphoid organs were inhibited in $CD4^-8^-$, $CD4^{-/-}$, and $CD8^{-/-}$ mice. The results suggest that both $CD4^+$ and $CD8^+$ T cells are essential for EAMG development. Another report showed that there was earlier development of EMG and more serum anti-AChR Abs in IL-10 transgenic C57BL/6 mice and that $CD8^+$-depleted splenocytes secreted markedly more IL-10 and lesser IFN-γ in vitro when stimulated with AChR from AChR-immunized transgenic mice [62].

T-cell marker expression of $CD8^+$ T cells in MG

CD45RA

CD45, the tyrosine phosphatase receptor type C (PTPRC) protein, is an essential molecule involved in thymocyte maturation. $CD45RA^+$ usually stands for the "naive" subset of $CD4^+$ T cells, and $CD45RO^+$ is major for "memory" T cells. Compared with HC, $CD8^+$ but not $CD4^+$ subsets among $CD45RA^+$ T cells increased

in the blood of patients with thymoma. Interestingly, after thymoma resection, the $CD8^+$ but not $CD4^+$ subset of $CD45RA^+$ T cells in the blood decreased [63]. Furthermore, the ratio of $CD45RO^+$ to $CD45RA^+$ T cells was lower in $CD8^+$ T cells of patients with early onset MG than in those of patients with late-onset MG and thymoma [64]. $CD8^+CD45RA^+$ lymphocytes in the muscle of patients with MG may signify an underlying thymoma and should not be misdiagnosed as polymyositis (PM) because all T lymphocytes in PM cases were $CD45RA^-$ [65]. Furthermore, in late-onset MG, approximately 25% of the expanded cells initially exhibited a naïve $CD62L^{+hi}/CD45RA^+$ recent thymic emigrant-like phenotype. These expansions were significantly associated with IgG antibodies against cytomegalovirus, IL-12, and IFN-α2. The $CD8^+$ TCRVβ expansion was stable over five years; however, recent thymic emigrant markers declined [66]. A significantly lower number of naïve helper T cells ($CD4^+CD45RA^+$) with an increased proportion of memory helper T cells ($CD4^+CD45RO^+$) and a significantly lower number of naïve cytotoxic T cells ($CD8^+CD27^+CD28^+$) were observed in patients that had undergone thymectomy. Their findings indicated the premature aging of the immune system after Tx in juvenile MG; however, the associated clinical consequences could not be verified [51].

Costimulatory molecules

$CD8^+$ cells of patients with MG expressed lower CD28 and higher CD80 and CD86. Furthermore, there were lower percentages of $CD8^+CD86^+$ Tcells in patients with an early onset of MG (< 40 years) compared with those with a late onset of MG (> 40 years). These data indicate that the CD28/CD80–CD86 costimulatory pathway is involved in MG [67]. The percentages of $CD4^+$ and $CD8^+$ T lymphocytes expressing the CD28 antigen were significantly lower in patients that had undergone thymectomy than in healthy subjects [68].

Chemokine receptors

Before therapy, patients with MG showed a reduction in the frequency of chemokine receptor 3 $(CXCR3)^+$ $CD4^+$ T cells, especially in the thymoma group; however, $CXCR3^+$ $CD8^+$ T cells remained normal. Conversely, after therapy, in the hyperplasia group, the expression of chemokine receptor 1 (CCR1) in $CD4^+$ and $CD8^+$ cells significantly increased and then returned to control levels [69]. $CD4^+$ $CXCR5^+$ T cells were mainly found in patients with MG; however, $CD8^+$ T cells were predominant in HC [70]. In patients with MG, B and dendritic cells showed significantly higher levels of glycolysis and glycolytic capacity than $CD8^+$ T cells, $CD4^+$ T cells, and their subsets [24].

Others

Higher expression levels of estrogen receptors were observed in $CD4^+$ helper T cells than in $CD8^+$ cells obtained from the PBMCs of patients with MG [71]. The IFN-γ-inducible protein 10 (CXCL10) receptor and CXCR3 expression in EAMG rats increased markedly only in $CD4^+$ and not in $CD8^+$ T cells or $CD19^+$ B cells [72]. Fas expression in peripheral $CD8^+$ T cells was higher in patients with MG with a normal thymus than in patients with MG with thymoma and controls. Moreover, Fas expression in $CD8^+$ cells was significantly higher in patients with MG treated with corticosteroids than in controls [73].

Effector $CD4^+$ T cells expressing $CD57^+$, $CD57^+$ killer cell lectin-like receptor $G1^+$, $CD57^+TIGIT^+$, CTLA-4, EOMES, FOXP3, and PD-1 increased after eculizumab treatment. However, HLA-DR expression on $CD8^+$ T cells decreased or remained at low levels, and a mild-to-moderate-level increase in PD-1 expression was observed in $CD8^+$ T cells after eculizumab treatment. Furthermore, C5aR was expressed on $CD4^+$ and $CD8^+$ T cells at low levels before and after eculizumab treatment. $CD8^+$, $CD4^+CD8^+$, and $CD4^+CD8^+CXCR5^+$ T-cell populations decreased after eculizumab treatment. $CD8^+$ T cells expressing $CD57^+TIGIT + CD27^{low}$ $CD28^{low}$ increased after eculizumab treatment [13]. In patients with MG, the expression of PI3KCA, AKT-1, mTORC1, HIF-1α, GLUT1, HK, PFK, and PK increased significantly in Th1, Th17, and $CD4^+$ $CD25^-$ cells, and the expression of AKT-1, HIF-1α, GLUT1, PK, and CPT1A increased significantly in $CD4^+$ $CD25^+$ Tregs. However, there were no significant changes in the above signaling pathways in any subset of $CD8^+$ T cells [24].

Regulatory $CD8^+$ T cells in MG

Tregs play a critical role in regulating immune tolerance and preventing autoimmunity, and $CD4^+$ $Foxp3^+$ Tregs have been well-studied [74, 75]. Recent studies on $CD8^+$ Tregs have shown good improvements [74]. Some CD8 + T cell subsets have been defined as $CD8^+$ Tregs from different reports in different experimental systems [74]. For example, $CD8^+$ $Foxp3^+$ Tregs are involved in tissue transplantation and alloantigen-induced immune responses [76–81]. $CD8^+$ $CD103^+$ cells were generated from naïve $CD8^+$ T cells cultured with TGF-β in vitro and showed inhibition in vivo, as well as in an aggressive tumor model, and expressed Foxp3 [82–84]; $CD8^+$ $CD28^-$ T cells were found in age-dependent accumulation and chronic antigen exposure [85–87]. $CD8^+$ $CD122^+$ $CD49d^+$ cells express both PD-1 and IL-10 and inhibit alloantigen-induced transplant rejection [88–91]. $CD8^+$ $CD122^{hi}$ $Ly49^+$ cells were discovered in young naïve mice [92, 93], EAE models [92, 94, 95], colitis [96,

97], hepatitis [98], arthritis [99], diabetes [100, 101], viral infection [102], tumor immunity [103], atherogenesis [104], and organ transplantation [105].

$CD4^+CD25^{high}Foxp3^+$ Tregs decreased in patients with MG; however, $CD8^+CD28^-$ and $CD8^+CD122^+$ Tregs do not change significantly [106]. Tacrolimus suppressed $CD4^+$ regulatory and helper T cells in MG, such as Tregs ($CD4^+CD25^+FOXP3^+$), peripheral blood Tfh (Tfh-like cells: $CD4^+CXCR5^+$), and follicular Tregs ($CD4^+CXCR5^+FOXP3^+$) [59]. The percentage of $CD4^+CD25^+CD127^-$ Tregs in the peripheral blood of patients with generalized MG was significantly lower than that in patients with OMG and HCs [43]. The populations of $CD8^+CD28^-$ and $CD8^+CD122^+$ Tregs did not differ between patients with MG and healthy controls; patients with MG exhibited a decrease in $CD4^+CD25^{high}Foxp3^+$ Tregs and an increase in $CD19^+$BAFF-R^+ B cells, revealing that patients with MG should display the dysfunction of T-cell balance and the activation of B-cell maturation [106]. The dual APL unregulated Foxp3 expression in $CD8^+CD28^-$ cells and the secretion of TGF-β and IL-10 are independent of CD8 cells. In TAChR-immunized $CD8^{-/-}$ knockout mice, the inhibitory effect of dual APL failed, the expression of caspase 3 and 8 was unregulated, the expression of Bcl-xL was downregulated, and $CD4^+CD25^+$ Tregs were induced by dual APL. This suggests that $CD8^+CD28^-$ regulatory cells play a partial role in inhibiting EAMG via dual APL [107].

CD20-expressing T cells (or $CD20^+$ T cells) in autoimmune diseases

Anti-CD20 mAbs is a potential therapy for both antibody-mediated and T cell-mediated autoimmune diseases [108], such as MS [109–112], rheumatoid arthritis (RA) [113–115], systemic lupus erythematosus [115–117], antineutrophil cytoplasmic antibody-associated vasculitis [117, 118], polymyositis/dermatomyositis [119, 120], primary Sjögren's syndrome [121, 122], idiopathic autoimmune thrombocytopenia and neutropenia [123], and MG [119, 124, 125]. Two mechanisms might explain the effect of rituximab on T cells: one is the indirect effect on B cell depletion that could influence T cell function, while the other, which might be more important, is the direct depletion of CD20 + T cells [126].

Typically, CD20 is expressed by mature B cells [127, 128]. However, there are some reports of CD20 being expressed by some T cells, which are called CD20-expressing T cells ($CD3^+$ $CD20^+$ T cells). CD20-expressing T cells were first reported in T cell lymphoma [129], RA [130] and animal-model experimental arthritis (EA) [131], MS [126, 132–136], EAE [136], and neuromyelitis optical spectrum disorder (NMOSD) [132], as well as in healthy individuals (3–5% of all $CD3^+$ cells) [137]. Furthermore, $CD3^+$ B cells have been reported [138].

MS and EAE

In MS patients, CD20-expressing T cells have specific characteristics [132, 134, 135, 139]: located at the thymus, bone marrow, and secondary lymphatic organs, as well as CSF, even without inflammation [132, 135]; expressed CD8-related cytotoxic program (granzyme-B, Perforin, Runx3, IRF4, CD28, CD56, CD57, CD94, CD150, CD215) [139]; enriched in CD8 + and CD45RO + memory cells and in CCR7- cells [132]; high secretion of IL-4–, IL-17–, IFN-γ, and TNF-α [132]; reduced by rituximab [126], fingolimod [132], alemtuzumab [132], dimethyl fumarate [132] [135], and ocrelizumab [134], but increased by natalizumab [132]. Another study provided more evidence of CD20-expressing T cells in MS patients. At the pretreatment stage, higher frequencies of CD20dimCD8 + T cells were related to a higher concentration of myelin basic protein in CSF, higher gadolinium-lesion counts, higher T2-weighted lesion volume, and lower normal appearing white matter and thalamus volume in MRI; this might predict outcomes of anti-CD20 treatment [135]. Depletion of CD20dimCD8 + T cells could improve outcomes of anti-CD20 treatment. Furthermore, anti-CD20 treatment was not able to reconstitute CD20dimCD8 + T cells [140].

CD20 + T cells were also found in active EAE mice, and the adoptive transfer of CD20 + T cells into EAE mice enhanced the disease without the assistance of B cells [136].

RA and EA or murine collagen-induced arthritis (CIA)

In peripheral blood T cells, frequencies of CD20-expressing T cells were 0.1–6.8% in healthy individuals and 0.4–2.6% in RA patients [130]. These CD20 + T cells co-expressed CD8 (45%) and CD4 (55%), as well as differentiation/activation associated markers (CD29, CD38, CD45RO, CD49a, CD56, CD69, CD154, CD161, and CD166), but did not express other B cell markers (CD19, CD21, CD24, or soluble IgM). These CD20 + T cells secreted IFN-γ, IL-1, IL-2, IL-4, IL-8, IL-10, IL-17, MCP-1, TGF-β, and TNF-α; increased calcium flux; and easily entered apoptosis under stimulation, compared to CD20- T cells [130].

$CXCR5^+$ $CD8^+$ T cells in autoimmune diseases

Recently, a novel subset of CD8 T cells, CXCR5 + $CD8^+$ T cells, were identified [141–143]. CXCR5 + $CD8^+$ T cells have been found to infiltrate the B cell follicle in response to several diseases, including viral infection (simian immunodeficiency virus (SIV) or human immunodeficiency virus (HIV) [144–170], lymphocytic

choriomeningitis virus (LCMV) [149, 171, 172], hepatitis B virus (HBV) [173–180], polycythemia-inducing FV [180], FluA [181, 182], HSV [183], DENV2 [184, 185], and SARS CoV-2 [186–190], EBV [191]); cancer (colorectal cancer [192–194], NCLC [195], hepatocellular carcinoma [175, 196], hematologic malignancies [197], pancreatic tumors [198], gastric cancer [199], breast cancer [200], thyroid cancer [201], melanoma [202], and lymphoma [203]); bacterial infection (*Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* [204]); parasitic infection (*Leishmania mexicana* [205]); immunodeficiency disease (CVID [206]); autoimmune diseases [4, 131, 207–210] (rheumatoid arthritis (RA) [131, 207] [211], primary Sjögren syndrome (pSS) [208] [212], and multiple sclerosis (MS) [210, 213]).

$CXCR5^+$ CD8 T cells have special phenotypes: for example, 1) cell markers including CD11a, CD11b, CD20, CD25, CD27, CD28, CD38, CD39, CD40, CD43, CD44hi, CD45RA, CD45RO, CD57, CD62L, CD69, CD83, CD94, CD95, CD101, CD103, CXCR5,CD107, CD127, CD137, CD161, CD200, CD244, HLA-DR, 41BBL, Slamf6, and TCRVa7.2 [13, 131, 145, 146, 149, 151–155, 157–160, 163–165, 167, 168, 171, 174, 176–178, 180–182, 184–190, 193–195, 197, 199, 201, 204, 205, 207, 211, 212, 214]; 2) cytokines, chemokines and receptors (CSF-1, IL-2, IL-4, IL-6, IL-7, IL-7R, IL-10, IL-17, IL-18Ra, IL-21, IL-21R, IL-22, IL-23, IL-27, IL-27R, IL-35, IFN-I, IFNAR1, IFN-γ, TGF-β, TNF-α, IL-4R (CD124), CCR2, CCR4, CCR5, CCR6, CCR7, CCR9, CCL5, CXCL1, CXCL5, CXCL10, CXCL12 (SDF-1α), CXCL13, CXCR3, CXCR4, CXCR5, CX3CR1, MIP-1β) [144–146, 149, 151, 153, 154, 157, 159–162, 165, 167, 168, 170, 172–174, 176, 177, 179, 181–186, 188, 190, 191, 193–197, 199, 200, 205, 206, 209, 211, 212]; 3) transcription factors (Bcl-6, CDCA7, CTLA-4, CULT1, E2A, pERK1/2, granulysin, granzyme B, Helios, ICOS, Id2, ISGs, interferon pathway associated molecules (MX1, MX2, GBP1, and ISG15), Ki-67, KLRG1, LAG-3, MAMU-DRA, MEF2C, NFATC1, NFATC2, PD-1, PD-L1, PD-L2, perforin, PRDM1, RANTES, SOX4, SPRY2, STAT2, STAT6, TCF4, TCF24, and Tim-3) [145, 146, 148, 149, 151–158, 162–166, 168, 172, 174, 175, 178, 211].

Conclusion

In this review, we focused on the updated information on $CD8^+$ T cells in MG/EAMG, as well as on the relevant evidence (peripheral, in situ, CSF, and under different conditions), in vitro culture, TCR usage, cytokine and chemokine expression, cell marker expression, Tregs, and Tc17. However, the mechanism underlying the regulatory role of $CD8^+$ T cells in MG/EAMG remains unclear. In addition, the following questions should be addressed in future studies: (1) Why are fewer studies available on $CD8^+$ T cells in MG than those on $CD4^+$ T cells in MG?; (2) Is the classical T-cell culture system favorable to $CD4^+$ T cells compared to $CD8^+$ T cells, and is it similar to our experience with studies on $CD8^+$ T cells in EAE and EAU [31, 32, 34, 55]?; (3) What is the real pattern of the Vβ gene usage of autoantigen-specific $CD8^+$ cells from patients with MG?; (4) As $CD8^+$ T cells were not highly purified and were not stimulated by autoantigens, what are the real images of the physiology and function of autoantigen-specific $CD8^+$ cells from MG/EAMG available?; (5) Which subset of autoantigen-specific $CD8^+$ cells (Tc1, Tc17, IL-17^+IFN-γ^+CD8^+ T cells, or IL-17^+IFN-γ^+TNF-α^+CD8^+ T cells) plays the most critical role in the pathogenesis of MG/EAMG? Did they like the similar studies that have been performed on EAE, diabetes, and systemic lupus erythematous disease [32]; (6) Which subsets of autoantigen-specific $CD8^+$ Tregs play a regulatory role in MG/EAMG among $CD8^+$CD28, $CD8^+CD122^+$ [106], $CD8^+$ $CD122^+$ $CD49d^+$ cells [88–91], or $CD8^+$ $CD122^{hi}$ $Ly49^+$ cells [92–105], which have been well studied in other diseases. Hence, it is necessary to perform further studies on $CD8^+$ T cells in MG/EAMG, especially on autoantigen-specific $CD8^+$ Tregs.

In additional, there are many reports of CD20-expressing T cells (or CD20 + T cells) and $CXCR5^+$ CD8 T cells on autoimmune diseases, especially on MS and RA. Unfortunately, up to now, there has been no report on these T cells on MG, which may be a good direction for future studies on MG.

Abbreviations

Ab	Autoantibody
AChR	Muscle nicotinic acetylcholine receptor
Ag	Antigen
CSF	Cerebrospinal fluid
CTL	Cytotoxic T-lymphocytes
EAE	Experimental autoimmune encephalomyelitis
EAMG	Experimental autoimmune myasthenia gravis
EAU	Experimental autoimmune uveitis
HC	Healthy control
IFN	Interferon
IL	Interleukin
MG	Myasthenia gravis
MHC	Major histocompatibility complex
MuSK	Muscle-specific tyrosine kinase
OMG	Ocular MG
PBMCs	Peripheral blood mononuclear cells
RORγ	Retinoic acid receptor-related-orphan-receptor-C
TCR	T-cell receptors
Tfh	Follicular Th
Th	T helper
Th17	IL-17-producing $CD4^+$ T cells
Tregs	Regulatory T cells
Tx	Thymectomy

Acknowledgements

Not applicable.

Author contributions
Y.P. received funding support and developed the research hypothesis. YP, HY, QC, YHX, and HJ MQD SL SYY wrote the main manuscript. The final manuscript is the product of the joint writing efforts of all authors.

Funding
This work was supported by the Scientific Research Project of Hunan Provincial Health Commission, PR China (No. C2023030765 to YP), Key Plans of Hunan Administration Traditional Chinese Medicine (No. A2023039 to YP), University-Hospital Joint-Fund of Hunan University of Chinese Medicine (No. 2022XYLH198 to YP), Fund for Creative Research Group of Affiliated First Hospital of Hunan Traditional Chinese Medical College, PR China (No. 2021B-003 to YP), and Technology Plan Project of Zhuzhou City, Hunan Province, China (No. 2021-009 to YP).

Availability of data and materials
All data generated or analyzed during this study are included in this published article. The data supporting this article are listed within the article. For additional information, please contact the corresponding author.

Declarations

Ethics approval and consent to participate
This is a review, hence, not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interests.

Received: 13 December 2023 Accepted: 7 February 2024
Published online: 20 February 2024

References

1. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14(10):1023–36.
2. Jin W, Luo Z, Yang H. Peripheral B cell subsets in autoimmune diseases: clinical implications and effects of B cell-targeted therapies. J Immunol Res. 2020;2020:9518137.
3. Song J, Zhao R, Yan C, Luo S, Xi J, Ding P, et al. A targeted complement inhibitor CRIg/FH protects against experimental autoimmune myasthenia gravis in rats via immune modulation. Front Immunol. 2022;13: 746068.
4. Fan R, Que W, Liu Z, Zheng W, Guo X, Liu L, et al. Single-cell mapping reveals dysregulation of immune cell populations and VISTA+ monocytes in myasthenia gravis. Clin Immunol. 2022;245: 109184.
5. Zhong H, Jiao K, Huan X, Zhao R, Su M, Goh LY, et al. Herpesvirus entry mediator on T cells as a protective factor for myasthenia gravis: a mendelian randomization study. Front Immunol. 2022;13: 931821.
6. Cutter G, Xin H, Aban I, Burns TM, Allman PH, Farzaneh-Far R, et al. Cross-sectional analysis of the Myasthenia Gravis patient registry: disability and treatment. Muscle Nerve. 2019;60(6):707–15.
7. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren J. Myasthenia gravis. Nat Rev Dis Primers. 2019;5(1):30.
8. Dalakas MC. Immunotherapy in myasthenia gravis in the era of biologics. Nat Rev Neurol. 2019;15(2):113–24.
9. Uzawa A, Kuwabara S, Suzuki S, Imai T, Murai H, Ozawa Y, et al. Roles of cytokines and T cells in the pathogenesis of myasthenia gravis. Clin Exp Immunol. 2021;203(3):366–74.
10. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. BMC Neurol. 2010;10:46.
11. Howard JF Jr, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16(12):976–86.
12. Mantegazza R, Wolfe GI, Muppidi S, Wiendl H, Fujita KP, O'Brien FL, et al. Post-intervention status in patients with refractory myasthenia gravis treated with eculizumab during REGAIN and Its open-label extension. Neurology. 2021;96(4):e610–8.
13. Li Y, Yi JS, Howard JF Jr, Chopra M, Russo MA, Guptill JT. Cellular changes in eculizumab early responders with generalized myasthenia gravis. Clin Immunol. 2021;231: 108830.
14. Howard JF Jr, Nowak RJ, Wolfe GI, Freimer ML, Vu TH, Hinton JL, et al. Clinical effects of the self-administered subcutaneous complement inhibitor zilucoplan in patients with moderate to severe generalized myasthenia gravis: results of a phase 2 randomized, double-blind, placebo-controlled. Multicenter Clin Trial JAMA Neurol. 2020;77(5):582–92.
15. Howard JF Jr, Bril V, Vu T, Karam C, Peric S, Margania T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021;20(7):526–36.
16. Koseoglu E, Sungur N, Muhtaroglu S, Zararsiz G, Eken A. The beneficial clinical effects of teriflunomide in experimental autoimmune myasthenia gravis and the investigation of the possible immunological mechanisms. Cell Mol Neurobiol. 2022;43(5):2071.
17. Yilmaz V, Ulusoy C, Hajtovic S, Turkoglu R, Kurtuncu M, Tzartos J, et al. Effects of teriflunomide on B cell subsets in MuSK-induced experimental autoimmune myasthenia gravis and multiple sclerosis. Immunol Invest. 2021;50(6):671–84.
18. Uzawa A, Kawaguchi N, Kanai T, Himuro K, Kuwabara S. Serum high mobility group box 1 is upregulated in myasthenia gravis. J Neurol Neurosurg Psychiatry. 2015;86(6):695–7.
19. Uzawa A, Kawaguchi N, Kanai T, Himuro K, Oda F, Kuwabara S. Increased serum peroxiredoxin 5 levels in myasthenia gravis. J Neuroimmunol. 2015;287:16–8.
20. Xie Y, Li HF, Jiang B, Li Y, Kaminski HJ, Kusner LL. Elevated plasma interleukin-17A in a subgroup of myasthenia Gravis patients. Cytokine. 2016;78:44–6.
21. Zhang CJ, Gong Y, Zhu W, Qi Y, Yang CS, Fu Y, et al. Augmentation of circulating follicular helper T cells and their impact on autoreactive B cells in myasthenia gravis. J Immunol. 2016;197(7):2610–7.
22. Zhang X, Liu S, Chang T, Xu J, Zhang C, Tian F, et al. Intrathymic Tfh/B cells interaction leads to ectopic GCs formation and anti-AChR antibody production: central role in triggering MG occurrence. Mol Neurobiol. 2016;53(1):120–31.
23. Kohler S, Keil TOP, Hoffmann S, Swierzy M, Ismail M, Rückert JC, et al. CD4(+) FoxP3(+) T regulatory cell subsets in myasthenia gravis patients. Clin Immunol. 2017;179:40–6.
24. Li Z, Peng Y, Li Y, Zhou R, Chen D, Jin W, et al. Glucose metabolism pattern of peripheral blood immune cells in myasthenia gravis patients. Ann Transl Med. 2020;8(9):577.
25. Li Y, Yang S, Li Z, Meng H, Jin W, Yang H, et al. Soluble glucocorticoid-induced tumor necrosis factor receptor regulates Helios expression in myasthenia gravis. J Transl Med. 2019;17(1):168.
26. Wen Y, Yang B, Lu J, Zhang J, Yang H, Li J. Imbalance of circulating CD4(+)CXCR5(+)FOXP3(+) Tfr-like cells and CD4(+)CXCR5(+)FOXP3(-) Tfh-like cells in myasthenia gravis. Neurosci Lett. 2016;630:176–82.
27. Zhang J, Chen Y, Jia G, Chen X, Lu J, Yang H, et al. FOXP3 -3279 and IVS9+459 polymorphisms are associated with genetic susceptibility to myasthenia gravis. Neurosci Lett. 2013;534:274–8.
28. Yang G, Yang X, Zhang J, Li G, Zheng D, Peng A, et al. Transcriptional repressor Blimp1 regulates follicular regulatory T-cell homeostasis and function. Immunology. 2018;153(1):105–17.
29. Huan X, Luo S, Zhong H, Zheng X, Song J, Zhou L, et al. In-depth peripheral CD4(+) T profile correlates with myasthenic crisis. Ann Clin Transl Neurol. 2021;8(4):749–62.
30. Wang Z, Yan Y. Immunopathogenesis in myasthenia gravis and neuromyelitis optica. Front Immunol. 2017;8:1785.
31. 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(24):2934–40.
32. Peng Y, Deng X, Zeng Q, Tang Y. Tc17 cells in autoimmune diseases. Chin Med J. 2022;135(18):2167–77.
33. Peng YZF, Deng X, Zhou JX, Gao S, Chen ZX, et al. Experimental autoimmune encephalomyelitis inhibited by Huangqi guizhi wuwu decoction via Th2 cytokine enhancement. World J Tradit Chin Med. 2021;7:467–76.
34. Peng Y, Shao H, Ke Y, Zhang P, Han G, Kaplan HJ. Minimally activated CD8 autoreactive T cells specific for IRBP express a high level of Foxp3 and are functionally suppressive. Invest Ophthalmol Vis Sci. 2007;48(5):2178–84.
35. Robat-Jazi B, Hosseini M, Shaygannejad V, Nafissi S, Rezaei A, Mansourain M, et al. High frequency of Tc22 and Th22 cells in myasthenia gravis patients and their significant reduction after thymectomy. NeuroImmunoModulation. 2018;25(2):80–8.
36. Hosseini M, Robat-Jazi B, Shaygannejad V, Naffisi S, Mirmossayeb O, Rezaei A, et al. Increased proportion of Tc17 and Th17 cells and their significant reduction after thymectomy may be related to disease progression in Myasthenia Gravis. NeuroImmuno Modulation. 2017;24(4–5):264–70.
37. Qin HBLH, Jia CY, Zhang XF, Zhang XL, Cheng M. The regulation of interleukin-7/CD127 signaling pathway on CD8+ T cells in patients with myasthenia gravis. Chin J Neurol. 2022;55(6):597–604.
38. Zhong H, Zhao C, Luo S. HLA in myasthenia gravis: from superficial correlation to underlying mechanism. Autoimmun Rev. 2019;18(9): 102349.
39. Machi M, Itoyama Y, Goto I, Kuroiwa Y. Surface phenotypes of lymphoid cells altered in the human myasthenic thymus. Neurology. 1988;38(4):592–6.
40. Protti MP, Manfredi AA, Straub C, Howard JF Jr, Conti-Tronconi BM. CD4+ T cell response to the human acetylcholine receptor alpha subunit in myasthenia gravis a study with synthetic peptides. J Immunol. 1990;144(4):1276–81.
41. Protti MP, Manfredi AA, Wu XD, Moiola L, Howard JF Jr, Conti-Tronconi BM. Myasthenia gravis T epitopes on the delta subunit of human muscle acetylcholine receptor. J Immunol. 1991;146(7):2253–61.
42. Yang ZX, Xu KL, Xiong H. Clinical characteristics and therapeutic evaluation of childhood myasthenia gravis. Exp Ther Med. 2015;9(4):1363–8.
43. Hu Y, Wang J, Rao J, Xu X, Cheng Y, Yan L, et al. Comparison of peripheral blood B cell subset ratios and B cell-related cytokine levels between ocular and generalized myasthenia gravis. Int Immunopharmacol. 2020;80: 106130.
44. Zhang Q, Bi Z, Yang M, Gui M, Bu B. Differences in immunophenotypes between myasthenia gravis patients with and without thyroid antibodies. Muscle Nerve. 2022;65(5):553–9.
45. Palmieri G, Selleri C, Montella L, Bulgarelli G, Vitiello L, Merkabaoui G, et al. Thymoma followed by paroxysmal nocturnal hemoglobinuria: a unique clinical association in the context of multiorgan autoimmunity with a potential role for CD8+ T lymphocytes. Am J Hematol. 2006;81(10):774–8.
46. Suzuki S, Utsugisawa K, Yoshikawa H, Motomura M, Matsubara S, Yokoyama K, et al. Autoimmune targets of heart and skeletal muscles in myasthenia gravis. Arch Neurol. 2009;66(11):1334–8.
47. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in Myasthenia Gravis. N Engl J Med. 2016;375(6):511–22.
48. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. Lancet Neurol. 2019;18(3):259–68.
49. Sempowski G, Thomasch J, Gooding M, Hale L, Edwards L, Ciafaloni E, et al. Effect of thymectomy on human peripheral blood T cell pools in myasthenia gravis. J Immunol. 2001;166(4):2808–17.
50. Tanaka S, Masuda M, Nakajima K, Ido N, Ohtsuka T, Nishida M, et al. P-glycoprotein function in peripheral T lymphocyte subsets of myasthenia gravis patients: clinical implications and influence of glucocorticoid administration. Int Immunopharmacol. 2009;9(3):284–90.
51. Popperud TH, Gul KA, Brunborg C, Olaussen RW, Abrahamsen TG, Osnes LT, et al. Thymectomy in juvenile myasthenia gravis is safe regarding long term immunological effects. Front Neurol. 2021;12: 596859.
52. Xin Y, Cai H, Wu L, Cui Y. The Effect of immunonutrition on the postoperative complications in thymoma with myasthenia gravis. Mediators Inflamm. 2016;2016:8781740.
53. Chen B, Wang Y, Geng Y, Huang Y, Guo S, Mao X. Marked improvement of anti-N-methyl-D-aspartate receptor encephalitis by large-dose methylprednisolone and plasmapheresis therapy combined with (18) F-fluorodeoxyglucose positron emission tomography imaging: a case report. Exp Ther Med. 2014;8(4):1167–9.
54. Mitsui T, Kuroda Y, Ueno S, Matsui N, Kaji R. FK506 attenuates thymic output in patients with myasthenia gravis. Arch Med Sci. 2013;9(6):1090–6.
55. Peng Y, Zhu F-Z, Deng X, Zhou J-X, Gao S, Chen Z-X, et al. Experimental autoimmune encephalomyelitis inhibited by huangqi guizhi wuwu decoction via th2 cytokine enhancement. World J Tradit Chin Med. 2021;7(4):467–76.
56. Infante AJ, Baillargeon J, Kraig E, Lott L, Jackson C, Hämmerling GJ, et al. Evidence of a diverse T cell receptor repertoire for acetylcholine receptor, the autoantigen of myasthenia gravis. J Autoimmun. 2003;21(2):167–74.
57. Tackenberg B, Kruth J, Bartholomaeus JE, Schlegel K, Oertel WH, Willcox N, et al. Clonal expansions of CD4+ B helper T cells in autoimmune myasthenia gravis. Eur J Immunol. 2007;37(3):849–63.
58. Yi JS, Guidon A, Sparks S, Osborne R, Juel VC, Massey JM, et al. Characterization of CD4 and CD8 T cell responses in MuSK myasthenia gravis. J Autoimmun. 2014;52:130–8.
59. Li Y, Guptill JT, Russo MA, Massey JM, Juel VC, Hobson-Webb LD, et al. Tacrolimus inhibits Th1 and Th17 responses in MuSK-antibody positive myasthenia gravis patients. Exp Neurol. 2019;312:43–50.
60. Peng Y, Han G, Shao H, Wang Y, Kaplan HJ, Sun D. Characterization of IL-17(+) interphotoreceptor retinoid-binding protein-specific T cells in experimental autoimmune uveitis. Invest Ophthalmol Vis Sci. 2007;48(9):4153–61.
61. Yi JS, Russo MA, Raja S, Massey JM, Juel VC, Shin J, et al. Inhibition of the transcription factor ROR-γ reduces pathogenic Th17 cells in acetylcholine receptor antibody positive myasthenia gravis. Exp Neurol. 2020;325: 113146.
62. Ostlie NS, Karachunski PI, Wang W, Monfardini C, Kronenberg M, Conti-Fine BM. Transgenic expression of IL-10 in T cells facilitates development of experimental myasthenia gravis. J Immunol. 2001;166(8):4853–62.
63. Hoffacker V, Schultz A, Tiesinga JJ, Gold R, Schalke B, Nix W, et al. Thymomas alter the T-cell subset composition in the blood: a potential mechanism for thymoma-associated autoimmune disease. Blood. 2000;96(12):3872–9.
64. Tackenberg B, Nitschke M, Willcox N, Ziegler A, Nessler S, Schumm F, et al. CD45 isoform expression in autoimmune myasthenia gravis. Autoimmunity. 2003;36(2):117–21.
65. Zamecnik J, Vesely D, Jakubicka B, Simkova L, Pitha J, Schutzner J, et al. Muscle lymphocytic infiltrates in thymoma-associated myasthenia gravis are phenotypically different from those in polymyositis. Neuromuscular Disorders NMD. 2007;17(11–12):935–42.
66. Tackenberg B, Schlegel K, Happel M, Eienbröker C, Gellert K, Oertel WH, et al. Expanded TCR Vbeta subsets of CD8(+) T-cells in late-onset myasthenia gravis: novel parallels with thymoma patients. J Neuroimmunol. 2009;216(1–2):85–91.
67. Teleshova N, Matusevicius D, Kivisäkk P, Mustafa M, Pirskanen R, Link H. Altered expression of costimulatory molecules in myasthenia gravis. Muscle Nerve. 2000;23(6):946–53.
68. Krawczyk P, Adamczyk-Korbel M, Kieszko R, Korobowicz E, Milanowski J. Immunological system status and the appearance of respiratory system disturbances in thymectomized patients. Arch Immunol Ther Exp. 2007;55(1):49–56.
69. Suzuki Y, Onodera H, Tago H, Saito R, Ohuchi M, Shimizu M, et al. Altered expression of Th1-type chemokine receptor CXCR3 on CD4+ T cells in myasthenia gravis patients. J Neuroimmunol. 2006;172(1–2):166–74.
70. Matsumoto Y, Matsuo H, Sakuma H, Park IK, Tsukada Y, Kohyama K, et al. CDR3 spectratyping analysis of the TCR repertoire in myasthenia gravis. J Immunol. 2006;176(8):5100–7.
71. Nancy P, Berrih-Aknin S. Differential estrogen receptor expression in autoimmune myasthenia gravis. Endocrinology. 2005;146(5):2345–53.

72. Feferman T, Maiti PK, Berrih-Aknin S, Bismuth J, Bidault J, Fuchs S, et al. Overexpression of IFN-induced protein 10 and its receptor CXCR3 in myasthenia gravis. J Immunol. 2005;174(9):5324–31.
73. Mai W, Liu X, Fan Y, Liu H, Hong HY, Han R, et al. Up-regulated expression of Fas antigen in peripheral T cell subsets in patients with myasthenia gravis. Clin Invest Med. 2012;35(5):E294.
74. Mishra S, Srinivasan S, Ma C, Zhang N. CD8(+) regulatory T cell—a mystery to be revealed. Front Immunol. 2021;12: 708874.
75. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Annu Rev Immunol. 2012;30:531–64.
76. Agle K, Vincent BG, Piper C, Belle L, Zhou V, Shlomchik W, et al. Bim regulates the survival and suppressive capability of CD8(+) FOXP3(+) regulatory T cells during murine GVHD. Blood. 2018;132(4):435–47.
77. Beres AJ, Haribhai D, Chadwick AC, Gonyo PJ, Williams CB, Drobyski WR. CD8+ Foxp3+ regulatory T cells are induced during graft-versus-host disease and mitigate disease severity. J Immunol. 2012;189(1):464–74.
78. Robb RJ, Lineburg KE, Kuns RD, Wilson YA, Raffelt NC, Olver SD, et al. Identification and expansion of highly suppressive CD8(+)FoxP3(+) regulatory T cells after experimental allogeneic bone marrow transplantation. Blood. 2012;119(24):5898–908.
79. Sawamukai N, Satake A, Schmidt AM, Lamborn IT, Ojha P, Tanaka Y, et al. Cell-autonomous role of TGFβ and IL-2 receptors in CD4+ and CD8+ inducible regulatory T-cell generation during GVHD. Blood. 2012;119(23):5575–83.
80. Lerret NM, Houlihan JL, Kheradmand T, Pothoven KL, Zhang ZJ, Luo X. Donor-specific CD8+ Foxp3+ T cells protect skin allografts and facilitate induction of conventional CD4+ Foxp3+ regulatory T cells. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2012;12(9):2335–47.
81. Churlaud G, Pitoiset F, Jebbawi F, Lorenzon R, Bellier B, Rosenzwajg M, et al. Human and Mouse CD8(+)CD25(+)FOXP3(+) regulatory T cells at steady state and during interleukin-2 therapy. Front Immunol. 2015;6:171.
82. Zhong H, Liu Y, Xu Z, Liang P, Yang H, Zhang X, et al. TGF-β-induced CD8(+)CD103(+) regulatory T cells show potent therapeutic effect on chronic graft-versus-host disease lupus by suppressing B cells. Front Immunol. 2018;9:35.
83. Liu Y, Lan Q, Lu L, Chen M, Xia Z, Ma J, et al. Phenotypic and functional characteristic of a newly identified CD8+ Foxp3- CD103+ regulatory T cells. J Mol Cell Biol. 2014;6(1):81–92.
84. Gabriely G, da Cunha AP, Rezende RM, Kenyon B, Madi A, Vandeventer T, et al. Targeting latency-associated peptide promotes antitumor immunity. Sci Immunol. 2017. https://doi.org/10.1126/sciimmunol.aaj1738.
85. Arosa FA, Esgalhado AJ, Padrão CA, Cardoso EM. Divide, conquer, and sense: CD8(+)CD28(-) T cells in perspective. Front Immunol. 2016;7:665.
86. Strioga M, Pasukoniene V, Characiejus D. CD8+ CD28- and CD8+ CD57+ T cells and their role in health and disease. Immunology. 2011;134(1):17–32.
87. Vuddamalay Y, van Meerwijk JP. CD28(-) and CD28(low)CD8(+) regulatory T cells: of mice and men. Front Immunol. 2017;8:31.
88. Dai H, Wan N, Zhang S, Moore Y, Wan F, Dai Z. Cutting edge: programmed death-1 defines CD8+CD122+ T cells as regulatory versus memory T cells. J Immunol. 2010;185(2):803–7.
89. Okuno Y, Murakoshi A, Negita M, Akane K, Kojima S, Suzuki H. CD8+ CD122+ regulatory T cells contain clonally expanded cells with identical CDR3 sequences of the T-cell receptor β-chain. Immunology. 2013;139(3):309–17.
90. Dai Z, Zhang S, Xie Q, Wu S, Su J, Li S, et al. Natural CD8+CD122+ T cells are more potent in suppression of allograft rejection than CD4+CD25+ regulatory T cells. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2014;14(1):39–48.
91. Liu H, Qiu F, Wang Y, Zeng Q, Liu C, Chen Y, et al. CD8+CD122+PD-1+ tregs synergize with costimulatory blockade of CD40/CD154, but Not B7/CD28, to prolong murine allograft survival. Front Immunol. 2019;10:306.
92. Hu D, Ikizawa K, Lu L, Sanchirico ME, Shinohara ML, Cantor H. Analysis of regulatory CD8 T cells in Qa-1-deficient mice. Nat Immunol. 2004;5:516.
93. Mishra S, Liao W, Liu Y, Yang M, Ma C, Wu H, et al. TGF-β and eomes control the homeostasis of CD8+ regulatory T cells. J Experim Med. 2021. https://doi.org/10.1084/jem.20200030.
94. Lee YHIY, Rifa M, Shi Z, Isobe K, Suzuki H. Essential role of CD8+CD122+ regulatory T cells in the recovery from experimental autoimmune encephalomyelitis. J Immunol. 2008;180:825–32.
95. Yu PBR, Waldmann TA. IL-15-dependent CD8+ CD122+ T cells ameliorate experimental autoimmune encephalomyelitis by modulating IL-17 production by CD4+ T cells. Eur J Immunol. 2014;44:3330–41.
96. Endharti ATOY, Shi Z, Misawa N, Toyokuni S, Ito M, et al. CD8+CD122+ regulatory T cells (Tregs) and CD4+ Tregs cooperatively prevent and cure CD4+ cell-induced colitis. J Immunol. 2011;186:41–52.
97. Shimokawa C, Kato T, Takeuchi T, Ohshima N, Furuki T, Ohtsu Y, et al. CD8(+) regulatory T cells are critical in prevention of autoimmune-mediated diabetes. Nat Commun. 2020;11(1):1922.
98. Varthaman A, Khallou-Laschet J, Clement M, Fornasa G, Kim HJ, Gaston AT, et al. Control of T cell reactivation by regulatory Qa-1-restricted CD8+ T cells. J Immunol. 2010;184(12):6585–91.
99. Leavenworth JW, Tang X, Kim HJ, Wang X, Cantor H. Amelioration of arthritis through mobilization of peptide-specific CD8+ regulatory T cells. J Clin Investig. 2013;123(3):1382–9.
100. Stocks BT, Wilson CS, Marshall AF, Hoopes EM, Moore DJ. Regulation of diabetogenic immunity by IL-15-activated regulatory CD8 T cells in type 1 diabetes. J Immunol. 2019;203(1):158–66.
101. Jiang H, Canfield SM, Gallagher MP, Jiang HH, Jiang Y, Zheng Z, et al. HLA-E-restricted regulatory CD8(+) T cells are involved in development and control of human autoimmune type 1 diabetes. J Clin Investig. 2010;120(10):3641–50.
102. Holderried TA, Lang PA, Kim HJ, Cantor H. Genetic disruption of CD8+ Treg activity enhances the immune response to viral infection. Proc Natl Acad Sci USA. 2013;110(52):21089–94.
103. Alvarez Arias DA, Kim HJ, Zhou P, Holderried TA, Wang X, Dranoff G, et al. Disruption of CD8+ Treg activity results in expansion of T follicular helper cells and enhanced antitumor immunity. Cancer Immunol Res. 2014;2(3):207–16.
104. Taghavie-Moghadam PL, Waseem TC, Hattler J, Glenn LM, Dobrian AD, Kaplan MH, et al. STAT4 regulates the CD8(+) regulatory T Cell/T follicular helper cell axis and promotes atherogenesis in insulin-resistant Ldlr(-/-) mice. J Immunol. 2017;199(10):3453–65.
105. Choi JY, Eskandari SK, Cai S, Sulkaj I, Assaker JP, Allos H, et al. Regulatory CD8 T cells that recognize Qa-1 expressed by CD4 T-helper cells inhibit rejection of heart allografts. Proc Natl Acad Sci USA. 2020;117(11):6042–6.
106. Li X, Xiao BG, Xi JY, Lu CZ, Lu JH. Decrease of CD4(+)CD25(high) Foxp3(+) regulatory T cells and elevation of CD19(+)BAFF-R(+) B cells and soluble ICAM-1 in myasthenia gravis. Clin Immunol. 2008;126(2):180–8.
107. Ben-David H, Sharabi A, Dayan M, Sela M, Mozes E. The role of CD8+CD28 regulatory cells in suppressing myasthenia gravis-associated responses by a dual altered peptide ligand. Proc Natl Acad Sci USA. 2007;104(44):17459–64.
108. Faurschou M, Jayne DR. Anti-B cell antibody therapies for inflammatory rheumatic diseases. Annu Rev Med. 2014;65:263–78.
109. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676–88.
110. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011;378(9805):1779–87.
111. Fernández O, Aladro Y, Arroyo R, Brieva L, Calles-Hernández MC, Carrascal P, et al. 12th Post-ECTRIMS meeting: review of the novelties from the 2019 ECTRIMS congress (II). Rev Neurol. 2020;70(11):417–29.
112. Sorensen PS, Lisby S, Grove R, Derosier F, Shackelford S, Havrdova E, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology. 2014;82(7):573–81.
113. Novikova DS, Popkova TV, Nasonov EL. The effect of anti-B-cell therapy on the development of atherosclerosis in patients with rheumatoid arthritis. Curr Pharm Des. 2012;18(11):1512–8.
114. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572–81.
115. Reddy V, Klein C, Isenberg DA, Glennie MJ, Cambridge G, Cragg MS, et al. Obinutuzumab induces superior B-cell cytotoxicity to rituximab

in rheumatoid arthritis and systemic lupus erythematosus patient samples. Rheumatology. 2017;56(7):1227–37.
116. Jung SM, Kim WU. Targeted immunotherapy for autoimmune disease. Immune network. 2022;22(1): e9.
117. Kaegi C, Wuest B, Crowley C, Boyman O. systematic review of safety and efficacy of second- and third-generation CD20-targeting biologics in treating immune-mediated disorders. Front Immunol. 2021;12: 788830.
118. Reddy YN, Siedlecki AM, Francis JM. Breaking down the complement system: a review and update on novel therapies. Curr Opin Nephrol Hypertens. 2017;26(2):123–8.
119. Klotz L, Wiendl H. Monoclonal antibodies in neuroinflammatory diseases. Expert Opin Biol Ther. 2013;13(6):831–46.
120. Meyer A, Lefevre G, Bierry G, Duval A, Ottaviani S, Meyer O, et al. In antisynthetase syndrome, ACPA are associated with severe and erosive arthritis: an overlapping rheumatoid arthritis and antisynthetase syndrome. Medicine. 2015;94(20): e523.
121. Letaief H, Lukas C, Barnetche T, Gaujoux-Viala C, Combe B, Morel J. Efficacy and safety of biological DMARDs modulating B cells in primary Sjögren's syndrome: Systematic review and meta-analysis. Joint Bone Spine. 2018;85(1):15–22.
122. Chen S, Liu Y, Shi G. Anti-CD20 antibody in primary Sjögren's syndrome management. Curr Pharm Biotechnol. 2014;15(6):535–41.
123. Faurschou M, Hasselbalch HC, Nielsen OJ. Sustained remission of platelet counts following monoclonal anti-CD20 antibody therapy in two cases of idiopathic autoimmune thrombocytopenia and neutropenia. Eur J Haematol. 2001;66(6):408–11.
124. Chen TX, Fan YT, Peng BW. Distinct mechanisms underlying therapeutic potentials of CD20 in neurological and neuromuscular disease. Pharmacol Ther. 2022;238: 108180.
125. Ingelfinger F, Kramer M, Lutz M, Widmer CC, Piccoli L, Kreutmair S, et al. Antibodies produced by cll phenotype B cells in patients with myasthenia gravis are not directed against neuromuscular endplates. Neurol Neuroimmunol Neuroinflam. 2023. https://doi.org/10.1212/NXI.0000000000200087.
126. Palanichamy A, Jahn S, Nickles D, Derstine M, Abounasr A, Hauser SL, et al. Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients. J Immunol. 2014;193(2):580–6.
127. Meinl E, Krumbholz M, Hohlfeld R. B lineage cells in the inflammatory central nervous system environment: migration, maintenance, local antibody production, and therapeutic modulation. Ann Neurol. 2006;59(6):880–92.
128. von Büdingen HC, Bar-Or A, Zamvil SS. B cells in multiple sclerosis: connecting the dots. Curr Opin Immunol. 2011;23(6):713–20.
129. Mohrmann RL, Arber DA. CD20-Positive peripheral T-cell lymphoma: report of a case after nodular sclerosis Hodgkin's disease and review of the literature. Modern Pathol Off J United States Can Acad Pathol. 2000;13(11):1244–52.
130. Wilk E, Witte T, Marquardt N, Horvath T, Kalippke K, Scholz K, et al. Depletion of functionally active CD20+ T cells by rituximab treatment. Arthritis Rheum. 2009;60(12):3563–71.
131. Pan P, Pineda MA, Wang Y, Khan A, Nyirenda MH. Aberrant pro-inflammatory responses of CD20(+) T cells in experimental arthritis. Cell Immunol. 2023;387: 104717.
132. Schuh E, Berer K, Mulazzani M, Feil K, Meinl I, Lahm H, et al. Features of human CD3+CD20+ T cells. J Immunol. 2016;197(4):1111–7.
133. Shinoda K, Li R, Rezk A, Mexhitaj I, Patterson KR, Kakara M, et al. Differential effects of anti-CD20 therapy on CD4 and CD8 T cells and implication of CD20-expressing CD8 T cells in MS disease activity. Proc Natl Acad Sci USA. 2023;120(3): e2207291120.
134. Gingele S, Jacobus TL, Konen FF, Hümmert MW, Sühs KW, Schwenkenbecher P, et al. Ocrelizumab depletes CD20$^+$ T cells in multiple sclerosis patients. Cells. 2018;8(1):12.
135. von Essen MR, Talbot J, Hansen RHH, Chow HH, Lundell H, Siebner HR, et al. Intrathecal CD8(+)CD20(+) T cells in primary progressive multiple sclerosis. Neurol Neuroimmunol Neuroinflam. 2023;10(5):200140.
136. Ochs J, Nissimov N, Torke S, Freier M, Grondey K, Koch J, et al. Proinflammatory CD20(+) T cells contribute to CNS-directed autoimmunity. Sci Transl Med. 2022;14(638):eabi4632.
137. Marino M, Bartoccioni E, Alboini PE, Evoli A. Rituximab in myasthenia gravis: a "to be or not to be" inhibitor of T cell function. Ann N Y Acad Sci. 2018;1413(1):41–8.
138. Nagel A, Möbs C, Raifer H, Wiendl H, Hertl M, Eming R. CD3-positive B cells: a storage-dependent phenomenon. PLoS ONE. 2014;9(10): e110138.
139. Boldrini VO, Quintiliano RPS, Silva LS, Damasceno A, Santos LMB, Farias AS. Cytotoxic profile of CD3+CD20+ T cells in progressive multiple sclerosis. Multiple Sclerosis Related Dis. 2021;52: 103013.
140. Shinoda K, Matsushita T, Nakamura Y, Masaki K, Sakai S, Nomiyama H, et al. Contribution of cortical lesions to cognitive impairment in Japanese patients with multiple sclerosis. Sci Rep. 2020;10(1):5228.
141. Valentine KM, Hoyer KK. CXCR5+ CD8 T cells: protective or pathogenic? Front Immunol. 2019;10:1322.
142. Turner CN, Mullins GN, Hoyer KK. CXCR5(+)CD8 T cells: potential immunotherapy targets or drivers of immune-mediated adverse events? Front Med. 2022;9:1034764.
143. Valentine KM, Mullins GN, Davalos OA, Seow LW, Hoyer KK. CD8 follicular T cells localize throughout the follicle during germinal center reactions and maintain cytolytic and helper properties. J Autoimmun. 2021;123: 102690.
144. Haran KP, Hajduczki A, Pampusch MS, Mwakalundwa G, Vargas-Inchaustegui DA, Rakasz EG, et al. Simian immunodeficiency virus (SIV)-specific chimeric antigen receptor-T cells engineered to target B cell follicles and suppress SIV replication. Front Immunol. 2018;9:492.
145. Mylvaganam GH, Rios D, Abdelaal HM, Iyer S, Tharp G, Mavigner M, et al. Dynamics of SIV-specific CXCR5+ CD8 T cells during chronic SIV infection. Proc Natl Acad Sci USA. 2017;114(8):1976–81.
146. Cartwright EK, Pampusch MS, Rendahl AK, Berger EA, Coleman-Fuller N, Skinner PJ. HIV-specific CAR T cells with CD28 or 4–1BB signaling domains are phenotypically and functionally distinct and effective at suppressing HIV and simian immunodeficiency virus. ImmunoHorizons. 2022;6(10):693–704.
147. Huot N, Rascle P, Tchitchek N, Wimmer B, Passaes C, Contreras V, et al. Role of NKG2a/c+CD8+ T cells in pathogenic versus non-pathogenic SIV infections. iScience. 2021;24(4):102314.
148. Mylvaganam GH, Chea LS, Tharp GK, Hicks S, Velu V, Iyer SS, et al. Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV. JCI Insight. 2018. https://doi.org/10.1172/jci.insight.122940.
149. He R, Hou S, Liu C, Zhang A, Bai Q, Han M, et al. Follicular CXCR5-expressing CD8(+) T cells curtail chronic viral infection. Nature. 2016;537(7620):412–28.
150. Mylvaganam GH, Velu V, Hong JJ, Sadagopal S, Kwa S, Basu R, et al. Diminished viral control during simian immunodeficiency virus infection is associated with aberrant PD-1hi CD4 T cell enrichment in the lymphoid follicles of the rectal mucosa. J Immunol. 2014;193(9):4527–36.
151. Perdomo-Celis F, Medina-Moreno S, Davis H, Bryant J, Taborda NA, Rugeles MT, et al. Characterization of CXCR5(+) CD8(+) T-cells in humanized NSG mice. Immunobiology. 2020;225(2): 151885.
152. Perdomo-Celis F, Taborda NA, Rugeles MT. Circulating CXCR5-expressing CD8+ T-cells are major producers of IL-21 and associate with limited HIV replication. J Acquired Immune Deficien Syndrome. 2018;78(4):473–82.
153. Perdomo-Celis F, Feria MG, Taborda NA, Rugeles MT. Induction of follicular-like CXCR5(+) CD8(+) T cells by TGF-β1/IL-23 Is limited during HIV infection. Viral Immunol. 2019;32(7):278–88.
154. Starke CE, Vinton CL, Ladell K, McLaren JE, Ortiz AM, Mudd JC, et al. SIV-specific CD8+ T cells are clonotypically distinct across lymphoid and mucosal tissues. J Clin Investig. 2020;130(2):789–98.
155. Martínez LE, Ibarrondo J, Guo Y, Penichet ML, Epeldegui M. Follicular CD8+ T cells are elevated in HIV infection and induce PD-L1 on B cells. J Immunol. 2023;210(1):33–9.
156. Olivo A, Lécuroux C, Bitu M, Avettand-Fenoel V, Boufassa F, Essat A, et al. CXCR3 and CXCR5 are highly expressed in HIV-1-specific CD8 central memory T cells from infected patients. Eur J Immunol. 2021;51(8):2040–50.
157. Adams P, Iserentant G, Servais JY, Vandekerckhove L, Vanham G, Seguin-Devaux C. Cytotoxic CD8+ T cells expressing CXCR5 are detectable in HIV-1 elite controllers after prolonged in vitro peptide stimulation. Front Immunol. 2020;11: 622343.
158. Ayala VI, Deleage C, Trivett MT, Jain S, Coren LV, Breed MW, et al. CXCR5-dependent entry of CD8 T cells into rhesus macaque B-cell follicles

achieved through T-cell engineering. J Virol. 2017. https://doi.org/10.1128/JVI.02507-16.
159. Yang HG, Jiao YM, Huang HH, Zhang C, Zhang JY, Xu RN, et al. Transforming growth factor-β promotes the function of HIV-specific CXCR5(+) CD8 T cells. Microbiol Immunol. 2020;64(6):458–68.
160. Jiao YM, Yang HG, Huang HH, Tu B, Xing SJ, Mao L, et al. Dichotomous Roles of programmed cell death 1 on HIV-specific CXCR5(+) and CXCR5(-) CD8(+) T cells during chronic HIV infection. Front Immunol. 2017;8:1786.
161. Roider J, Maehara T, Ngoepe A, Ramsuran D, Muenchhoff M, Adland E, et al. High-frequency, functional HIV-specific T-follicular helper and regulatory cells are present within germinal centers in children but not adults. Front Immunol. 2018;9:1975.
162. Munusamy Ponnan S, Thiruvengadam K, Kathirvel S, Shankar J, Rajaraman A, Mathaiyan M, et al. Elevated numbers of HIV-specific poly-functional CD8(+) T cells with stem cell-like and follicular homing phenotypes in HIV-exposed seronegative individuals. Front Immunol. 2021;12: 638144.
163. McCarty B, Mwamzuka M, Marshed F, Generoso M, Alvarez P, Ilmet T, et al. Low peripheral T follicular helper cells in perinatally HIV-infected children correlate with advancing HIV disease. Front Immunol. 2018;9:1901.
164. Fardoos R, Nyquist SK, Asowata OE, Kazer SW, Singh A, Ngoepe A, et al. HIV specific CD8(+) T(RM)-like cells in tonsils express exhaustive signatures in the absence of natural HIV control. Front Immunol. 2022;13: 912038.
165. Collins DR, Hitschfel J, Urbach JM, Mylvaganam GH, Ly NL, Arshad U, et al. Cytolytic CD8(+) T cells infiltrate germinal centers to limit ongoing HIV replication in spontaneous controller lymph nodes. Sci Immunol. 2023;8(83):eade5872.
166. Ponnan SM, Vidyavijayan KK, Thiruvengadam K, Hilda JN, Mathayan M, Murugavel KG, et al. Role of circulating T follicular helper cells and stem-like memory CD4(+) T cells in the pathogenesis of HIV-2 infection and disease progression. Front Immunol. 2021;12: 666388.
167. Dias J, Fabozzi G, March K, Asokan M, Almasri CG, Fintzi J, et al. Concordance of immunological events between intrarectal and intravenous SHIVAD8-EO infection when assessed by Fiebig-equivalent staging. J Clin Investig. 2021. https://doi.org/10.1172/JCI151632.
168. Munusamy Ponnan S, Thiruvengadam K, Tellapragada C, Ambikan AT, Narayanan A, Kathirvel S, et al. Deciphering the role of mucosal immune responses and the cervicovaginal microbiome in resistance to HIV infection in HIV-exposed seronegative (HESN) women. Microbiol Spectr. 2021;9(2): e0047021.
169. George AF, Luo X, Neidleman J, Hoh R, Vohra P, Thomas R, et al. Deep phenotypic analysis of blood and lymphoid T and NK cells from HIV+ controllers and ART-suppressed individuals. Front Immunol. 2022;13: 803417.
170. Yue FY, Lo C, Sakhdari A, Lee EY, Kovacs CM, Benko E, et al. HIV-specific IL-21 producing CD4+ T cells are induced in acute and chronic progressive HIV infection and are associated with relative viral control. J Immunol. 2010;185(1):498–506.
171. Im SJ, Konieczny BT, Hudson WH, Masopust D, Ahmed R. PD-1+ stem-like CD8 T cells are resident in lymphoid tissues during persistent LCMV infection. Proc Natl Acad Sci USA. 2020;117(8):4292–9.
172. Huang Z, Zak J, Pratumchai I, Shaabani N, Vartabedian VF, Nguyen N, et al. IL-27 promotes the expansion of self-renewing CD8(+) T cells in persistent viral infection. J Exp Med. 2019;216(8):1791–808.
173. Jiang H, Li L, Han J, Sun Z, Rong Y, Jin Y. CXCR5(+) CD8(+) T cells indirectly offer B cell help and are inversely correlated with viral load in chronic hepatitis B infection. DNA Cell Biol. 2017;36(4):321–7.
174. Li Y, Tang L, Guo L, Chen C, Gu S, Zhou Y, et al. CXCL13-mediated recruitment of intrahepatic CXCR5(+)CD8(+) T cells favors viral control in chronic HBV infection. J Hepatol. 2020;72(3):420–30.
175. Jin Y, Lang C, Tang J, Geng J, Song HK, Sun Z, et al. CXCR5(+)CD8(+) T cells could induce the death of tumor cells in HBV-related hepatocellular carcinoma. Int Immunopharmacol. 2017;53:42–8.
176. Kumashie KG, Cebula M, Hagedorn C, Kreppel F, Pils MC, Koch-Nolte F, et al. Improved functionality of exhausted intrahepatic CXCR5+ CD8+ T cells contributes to chronic antigen clearance upon immunomodulation. Front Immunol. 2020;11: 592328.
177. Khanam A, Tang LSY, Kottilil S. Programmed death 1 expressing CD8(+) CXCR5(+) follicular T cells constitute effector rather than exhaustive phenotype in patients with chronic hepatitis B. Hepatology. 2022;75(3):690–708.
178. Zhao H, Han Q, Yang A, Wang Y, Wang G, Lin A, et al. CpG-C ODN M362 as an immunoadjuvant for HBV therapeutic vaccine reverses the systemic tolerance against HBV. Int J Biol Sci. 2022;18(1):154–65.
179. Li X, Zhang Q, Zhang W, Ye G, Ma Y, Wen C, et al. Expanded circulating follicular dendritic cells facilitate immune responses in chronic HBV infection. J Transl Med. 2020;18(1):417.
180. Knuschke T, Kollenda S, Wenzek C, Zelinskyy G, Steinbach P, Dittmer U, et al. A combination of anti-PD-L1 treatment and therapeutic vaccination facilitates improved retroviral clearance via reactivation of highly exhausted T cells. mbio. 2021. https://doi.org/10.1128/mBio.02121-20.
181. Tyllis TS, Fenix KA, Norton TS, Kara EE, McKenzie DR, David SC, et al. CXCR5(+)CD8(+) T cells shape antibody responses in vivo following protein immunisation and peripheral viral infection. Front Immunol. 2021;12: 626199.
182. Hoji A, Rinaldo CR Jr. Human CD8+ T cells specific for influenza A virus M1 display broad expression of maturation-associated phenotypic markers and chemokine receptors. Immunology. 2005;115(2):239–45.
183. Stanfield BA, Pahar B, Chouljenko VN, Veazey R, Kousoulas KG. Vaccination of rhesus macaques with the live-attenuated HSV-1 vaccine VC2 stimulates the proliferation of mucosal T cells and germinal center responses resulting in sustained production of highly neutralizing antibodies. Vaccine. 2017;35(4):536–43.
184. Qiu L, Wang H, Yu Q, Liu J, Chen S, Zhao Z. Protective role of follicular CXCR5(+)CD8(+) T cells against dengue virus 2 infection. Int J Infect Dis Off Publ Int Soc Infect Dis. 2019;83:12–9.
185. Rivino L, Kumaran EA, Jovanovic V, Nadua K, Teo EW, Pang SW, et al. Differential targeting of viral components by CD4+ versus CD8+ T lymphocytes in dengue virus infection. J Virol. 2013;87(5):2693–706.
186. Zhou P, Gong F, Ji T, Cao C, Zheng T. Enriched CXCR3(+) CXCR5(+) CD8(+) T cells in SARS-CoV-2 infected and vaccinated individuals effectively respond to the antigen in recall. J Infect. 2023;86(5):497–9.
187. Kudryavtsev IV, Arsentieva NA, Korobova ZR, Isakov DV, Rubinstein AA, Batsunov OK, et al. Heterogenous CD8+ T cell maturation and "polarization" in acute and convalescent COVID-19 patients. Viruses. 2022. https://doi.org/10.3390/v14091906.
188. Adam L, Rosenbaum P, Quentric P, Parizot C, Bonduelle O, Guillou N, et al. CD8+PD-L1+CXCR3+ polyfunctional T cell abundances are associated with survival in critical SARS-CoV-2-infected patients. JCI Insight. 2021. https://doi.org/10.1172/jci.insight.151571.
189. Esparcia-Pinedo L, Yarci-Carrión A, Mateo-Jiménez G, Ropero N, Gómez-Cabañas L, Lancho-Sánchez Á, et al. Development of an effective immune response in adults with down syndrome after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. Clin infect Dis Off Publ Infect Dis Soc Am. 2023;76(3):e155–62.
190. Yang J, Zhong M, Zhang E, Hong K, Yang Q, Zhou D, et al. Broad phenotypic alterations and potential dysfunction of lymphocytes in individuals clinically recovered from COVID-19. J Mol Cell Biol. 2021;13(3):197–209.
191. Chatterjee B, Deng Y, Holler A, Nunez N, Azzi T, Vanoaica LD, et al. CD8+ T cells retain protective functions despite sustained inhibitory receptor expression during Epstein-Barr virus infection in vivo. PLoS Pathog. 2019;15(5): e1007748.
192. Jifu E, Yan F, Kang Z, Zhu L, Xing J, Enda Y. CD8(+)CXCR5(+) T cells in tumor-draining lymph nodes are highly activated and predict better prognosis in colorectal cancer. Human Immunol. 2018;79(6):446–52.
193. Shen J, Luo X, Wu Q, Huang J, Xiao G, Wang L, et al. A subset of CXCR5(+)CD8(+) T cells in the germinal centers from human tonsils and lymph nodes help B cells produce immunoglobulins. Front Immunol. 2018;9:2287.
194. Xing J, Zhang C, Yang X, Wang S, Wang Z, Li X, et al. CXCR5(+)CD8(+) T cells infiltrate the colorectal tumors and nearby lymph nodes, and are associated with enhanced IgG response in B cells. Exp Cell Res. 2017;356(1):57–63.
195. Brummelman J, Mazza EMC, Alvisi G, Colombo FS, Grilli A, Mikulak J, et al. High-dimensional single cell analysis identifies stem-like cytotoxic CD8(+) T cells infiltrating human tumors. J Exp Med. 2018;215(10):2520–35.

196. Ye L, Li Y, Tang H, Liu W, Chen Y, Dai T, et al. CD8+CXCR5+T cells infiltrating hepatocellular carcinomas are activated and predictive of a better prognosis. Aging. 2019;11(20):8879–91.
197. Hofland T, Martens AWJ, van Bruggen JAC, de Boer R, Schetters S, Remmerswaal EBM, et al. Human CXCR5(+) PD-1(+) CD8 T cells in healthy individuals and patients with hematologic malignancies. Eur J Immunol. 2021;51(3):703–13.
198. Bai M, Zheng Y, Liu H, Su B, Zhan Y, He H. CXCR5(+) CD8(+) T cells potently infiltrate pancreatic tumors and present high functionality. Exp Cell Res. 2017;361(1):39–45.
199. Wang J, Li R, Cao Y, Gu Y, Fang H, Fei Y, et al. Intratumoral CXCR5(+) CD8(+)T associates with favorable clinical outcomes and immunogenic contexture in gastric cancer. Nat Commun. 2021;12(1):3080.
200. Bassez A, Vos H, Van Dyck L, Floris G, Arijs I, Desmedt C, et al. A single-cell map of intratumoral changes during anti-PD1 treatment of patients with breast cancer. Nat Med. 2021;27(5):820–32.
201. Zhou Y, Guo L, Sun H, Xu J, Ba T. CXCR5(+) CD8 T cells displayed higher activation potential despite high PD-1 expression, in tumor-involved lymph nodes from patients with thyroid cancer. Int Immunopharmacol. 2018;62:114–9.
202. Gangaev A, Rozeman EA, Rohaan MW, Isaeva OI, Philips D, Patiwael S, et al. Differential effects of PD-1 and CTLA-4 blockade on the melanoma-reactive CD8 T cell response. Proc Natl Acad of Sci United States Am. 2021. https://doi.org/10.1073/pnas.2102849118.
203. Tang J, Zha J, Guo X, Shi P, Xu B. CXCR5(+)CD8(+) T cells present elevated capacity in mediating cytotoxicity toward autologous tumor cells through interleukin 10 in diffuse large B-cell lymphoma. Int Immunopharmacol. 2017;50:146–51.
204. Shen Y, Qu QX, Jin MN, Chen C. Investigating the role of circulating CXCR5-expressing CD8+ T-cells as a biomarker for bacterial infection in subjects with pneumonia. Respir Res. 2019;20(1):54.
205. Diupotex M, Zamora-Chimal J, Gajón JA, Bonifaz LC, Becker I. CXCR5 and TIM-3 expressions define distinct exhausted T cell subsets in experimental cutaneous infection with *Leishmania mexicana*. Front Immunol. 2023;14:1231836.
206. de Lollo C, de Moraes VD, da Silva Oliveira LM, de Oliveira TT, Carneiro-Sampaio M, Jacob CM, et al. Impaired CD8(+) T cell responses upon Toll-like receptor activation in common variable immunodeficiency. J Transl Med. 2016;14(1):138.
207. Higashioka K, Yoshimura M, Sakuragi T, Ayano M, Kimoto Y, Mitoma H, et al. Human PD-1(hi)CD8(+) T cells are a cellular source of IL-21 in rheumatoid arthritis. Front Immunol. 2021;12: 654623.
208. Zhai X, Wang Y, Guo H, Liang Z, Feng M, Wu Y, et al. Altered levels of circulating CD8(+)CXCR5(+)PD-1(+)T follicular cytotoxic cells in primary Sjögren's syndrome. Clin Rheumatol. 2022;41(6):1697–708.
209. Valentine KM, Davini D, Lawrence TJ, Mullins GN, Manansala M, Al-Kuhlani M, et al. CD8 follicular T cells promote B cell antibody class switch in autoimmune disease. J Immunol. 2018;201(1):31–40.
210. Huber JE, Chang Y, Meinl I, Kümpfel T, Meinl E, Baumjohann D. Fingolimod profoundly reduces frequencies and alters subset composition of circulating T follicular helper cells in multiple sclerosis patients. J Immunol. 2020;204(5):1101–10.
211. Anang DC, Ramwadhdoebe TH, Hähnlein JS, van Kuijk B, Smits N, van Lienden KP, et al. Increased frequency of CD4(+) follicular helper T and CD8(+) follicular T cells in human lymph node biopsies during the earliest stages of rheumatoid arthritis. Cells. 2022;11(7):104.
212. Hinrichs AC, Kruize AA, Leavis HL, van Roon JAG. In patients with primary Sjögren's syndrome innate-like MAIT cells display upregulated IL-7R, IFN-γ, and IL-21 expression and have increased proportions of CCR9 and CXCR5-expressing cells. Front Immunol. 2022;13:1017157.
213. Longbrake EE, Cantoni C, Chahin S, Cignarella F, Cross AH, Piccio L. Dimethyl fumarate induces changes in B- and T-lymphocyte function independent of the effects on absolute lymphocyte count. Multiple Sclerosis. 2018;24(6):728–38.
214. Beura LK, Scott MC, Pierson MJ, Joag V, Wijeyesinghe S, Semler MR, et al. Novel lymphocytic choriomeningitis virus strain sustains abundant exhausted progenitor CD8 T cells without systemic viremia. J immunol. 2022;209(9):1691–702.

Publisher's Note