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INVITED REVIEW

The Role of CD4$^+$ T Cells in the Immunotherapy of Brain Disease by Secreting Different Cytokines

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Abstract

Upon different stimulation, naïve CD4$^+$ T cells differentiate into various subsets of T helper (Th) cells, including Th1, Th2, Th17, and Tregs. They play both protective and pathogenic roles in the central nervous system (CNS) by secreting different cytokines. Failure of the homeostasis of the subgroups in the CNS can result in different brain diseases. Recently, immunotherapy has drawn more and more attention in the therapy of various brain diseases. Here, we describe the role of different CD4$^+$ T cell subsets and their secreted cytokines in various brain diseases, as well as the ways in which by affecting CD4$^+$ T cells in therapy of the CNS diseases. Understanding the role of CD4$^+$ T cells and their secreted cytokines in the immunotherapy of brain disease will provide new targets and therapeutics for the treatment of brain disease.

Keywords CD4$^+$ T cells · Brain disease · Immunotherapy · Cytokines

Introduction

The human immune system has evolved sophisticated mechanisms that allow rapid and destructive responses to protect its organisms from pathogenic infection, injury, or stress (Kim and Cantor 2019; Salvador et al. 2021). Adaptive immunity is a sign of the immune system of higher animals. This response is composed of antigen-specific responses of T lymphocytes and B lymphocytes. T cells develop from progenitor cells in bone marrow cells, migrate to the thymus, differentiate and mature in lymphoid tissue, such as lymph nodes, spleen, tonsils, and mucosa, then become T cells with immune activity. T cells combine with major histocompatibility complex II (MHC II) molecules and differentiate into CD4$^+$ T cells (Parkin and Cohen 2001). CD4$^+$ T cells continuously circulate in the body and enter all organs, including the brain (Pasciuto et al. 2020). The brain physiologically relies on CD4$^+$ T cells to support brain development and homeostasis, and abnormal cells and pathogens under pathological conditions are monitored by CD4$^+$ T cells (Mundt et al. 2019). After encountering antigen-presenting cells (APCs) carrying cognate antigens, naïve CD4$^+$ T cells differentiate into different Th subsets namely Th1, Th2, Th17, and regulatory T cells (Tregs) based on their cytokine profiles (Brummelman et al. 2018; Soskic et al. 2019). After antigen clearance, most of the effector cells were apoptotic, while a small number of them survived to produce long-term memory cells forming CD4$^+$ tissue-resident memory (TRM) cells. CD4$^+$ TRM cells can respond to the antigenic agents and perform immediate effector functions to prevent reinfection. However, in some cases, the long-term survival of CD4$^+$ TRM cells in inflammatory or autoimmune environments can lead to host immunopathology (Schreiner and King 2018). (Fig. 1).

By producing a series of unique cytokines, Th phenotypes play a key role in regulating the immune response to various infections and participate in the pathogenesis of many inflammatory diseases (Zhu 2018). The commitment of CD4$^+$ T cells to one of these lineages is influenced by signals received during initial interactions with APCs, including cytokines, costimulatory signals, and signals of

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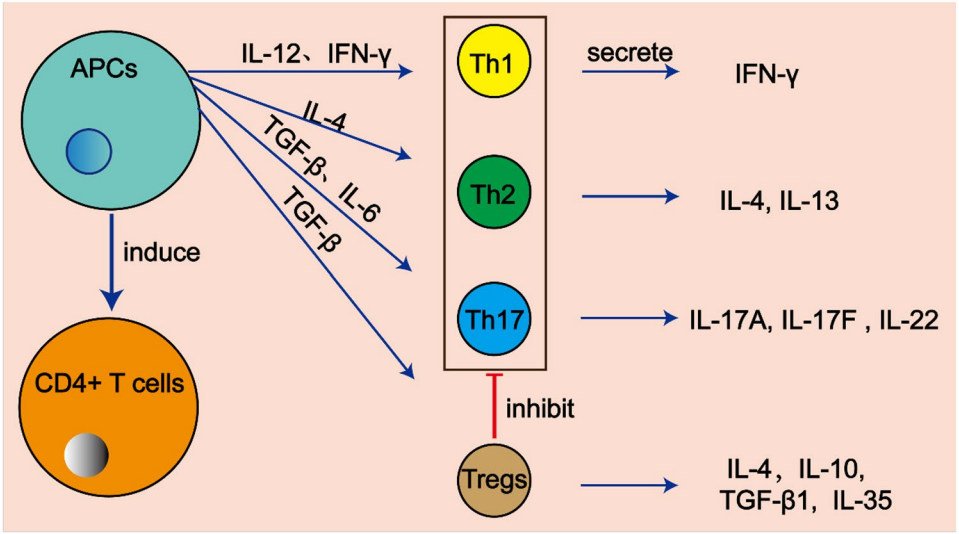

Fig. 1 The process by which $CD4^+$ T cells activate, differentiate into effector T cells, and secrete inflammatory cytokines. APCs secrete different inflammatory factors to induce different subtypes of $CD4.^+$ T cells, which play immunomodulatory roles by secreting different cytokines. Tregs inhibit the production of Th1, Th2, and Th17

the quality and duration of the T-cell receptor (TCR) binding MHC II: peptide complexes. Post-initiation signaling also affects the sustained differentiation of $CD4^+$ Th cell lines (Vella et al. 2017). Different Th-cell subsets exhibit different protective immune functions. Initial $CD4^+$ T cells differentiate into Th1 induced by IL-12 and interferon-gamma (IFN-γ). Th1 cells are mainly used for host defense against intracellular pathogens, including viruses, protozoa, and bacteria. They are also responsible for the development of certain forms of organ-specific autoimmunity. One of the main functions of Th1 cells is to activate macrophages by producing IFN-γ. $CD4^+$ T cells are differentiated into Th2 under the induction of IL-4. Th2 is key to mediating an immune response against extracellular parasites, including worms. Under the co-induction of TGF-β and IL-6, Th17 is differentiated. Th17 cells produce three main cytokines: IL-17A, IL-17F, and IL-22. The primary function of the first two cytokines is to recruit and activate neutrophils. They also stimulate different types of cells to produce inflammatory cytokines, including IL-6. IL-22 is an important cytokine that stimulates mucosal barrier cells to produce antimicrobial peptides, pro-inflammatory cytokines, and chemokines. $CD4^+$ T cells are induced by transforming growth factor-beta (TGF-β) alone to differentiate into Tregs (Lutz 2016; Sungnak et al. 2019; Zhu 2018). Tregs inhibits monocyte activity by secreting IL-4 and IL-10, and stimulates macrophages to polarize toward an anti-inflammatory phenotype. Tregs inhibit $CD4^+$ T cell-mediated inflammation by secreting IL-10, TGF-β1, and IL-35, to maintain peripheral tolerance and prevent autoimmune attacks on autoreactive T cells. In the CNS, Tregs is recruited by IL-33 and plays a repair role, promoting the re-myelination and differentiation of oligodendrocytes by stimulating the polarization of M2 macrophages (Li et al. 2018). Most long-term highly specific antibody responses require the help of $CD4^+$ T cells (Eisenbarth et al. 2021).

Due to the diversity of $CD4^+$ T cell subsets, $CD4^+$ T cells play various protective or pathogenic roles in the CNS (Zhao et al. 2009). Overreactions of Th1 and Th17 cells are the main contributors to chronic inflammation and autoimmune brain diseases (Chen et al. 2013), and they are a logical target of therapeutic strategies (Marusina et al. 2017). In neurodegenerative diseases, the loss of redox balance will lead to the change of differentiation and the number of $CD4^+$ T cell subsets, which will lead to the increase of Th1 and Th17 responses. Interestingly, Tregs and Th2 regulate the inflammatory response to maintain immune tolerance. In this regard, it has been found that the mobilization of Tregs and Th2 to the damaged regions of the CNS can provide neuroprotection and become a therapeutic strategy to control the process of neurodegenerative inflammation (Solleiro-Villavicencio and Rivas-Arancibia 2018). Recently immunotherapy has been applied in treating various brain diseases, including autoimmune diseases (eg. multiple sclerosis), brain tumor diseases (eg. glioma), neurodegenerative diseases (eg. Parkinson, Alzheimer's), and cerebrovascular diseases. Th1 and Th17 cells mediate the development of multiple sclerosis (MS) (Baecher-Allan et al. 2018). While Th1 cells have important antitumor effects. Tregs mediate the pro-tumor effect, which can inhibit the maturation of dendritic cells, the activation, proliferation, and function of effector cells, and provide an immune escape for glioma (Wu et al. 2019). In Parkinson's disease (PD), it is mainly the Th1 subtype that promotes α-SYN-mediated neuronal injury (Labrador-Garrido et al. 2014; Lindestam Arlehamn et al. 2019; Williams et al. 2021). In Alzheimer's disease (AD), proinflammatory subsets such as Th1 and Th17 are the main sources of proinflammatory cytokines, which can reduce endothelial cell integrity and stimulate astrocytes,

resulting in the generation of amyloid beta (Aβ)-peptide. Anti-inflammatory subsets such as Th2 and Tregs reduce inflammation and regulate the function of Th1 and Th17. Recently, pathogenic Th17 cells have been shown to have stronger invasive ability than other CD4$^+$ T cell subsets (Kubick et al. 2020). In cerebrovascular diseases, CD4$^+$ T cells are activated and differentiated into different cell subtypes (Baragetti et al. 2018). Th1 and Th17 have the characteristics of high pro-inflammatory function and aggravating brain injury. Th2 and Tregs seem to be endogenous protective subgroups, which can inhibit cerebral vascular inflammation, and realize self-tolerance and brain repair (Wang et al. 2019; Zhao et al. 2018). (Fig. 2).

In this review, we focus on the pathogenic and therapeutic role of CD4$^+$ T cells, as well as the affecting mechanisms and current drugs that affect CD4$^+$ T cells in brain diseases. Furthermore, we propose potential therapeutic methods and future development directions in treating brain diseases by adjusting CD4$^+$ T cells. Understanding the molecular details of these pathogenic CD4$^+$ T cells will provide new targets and methods for therapeutic development, which can be applied to a series of neurological diseases.

CD4$^+$ T Cells Enter the Brain in Normal and Disease Conditions

CD4$^+$ T cells are rarely found in healthy mice or human brains. It is closely related to the maturation of microglia. In the whole brain of healthy adult mice, the number of CD4$^+$ T cells is about 2000, and the density of CD4$^+$ T cells in healthy human brain tissue resected during temporal lobe surgery is similar to that in mice (Pasciuto et al. 2020). Non-CNS self-antigen (Ag) -specific CD4$^+$ T cells can also penetrate central nervous vessels and aggregate in meningeal and perivascular areas. However, these ignorant cells of the CNS are not reactivated there and therefore do not invade the nerve parenchyma. Even CD4$^+$ T cells that

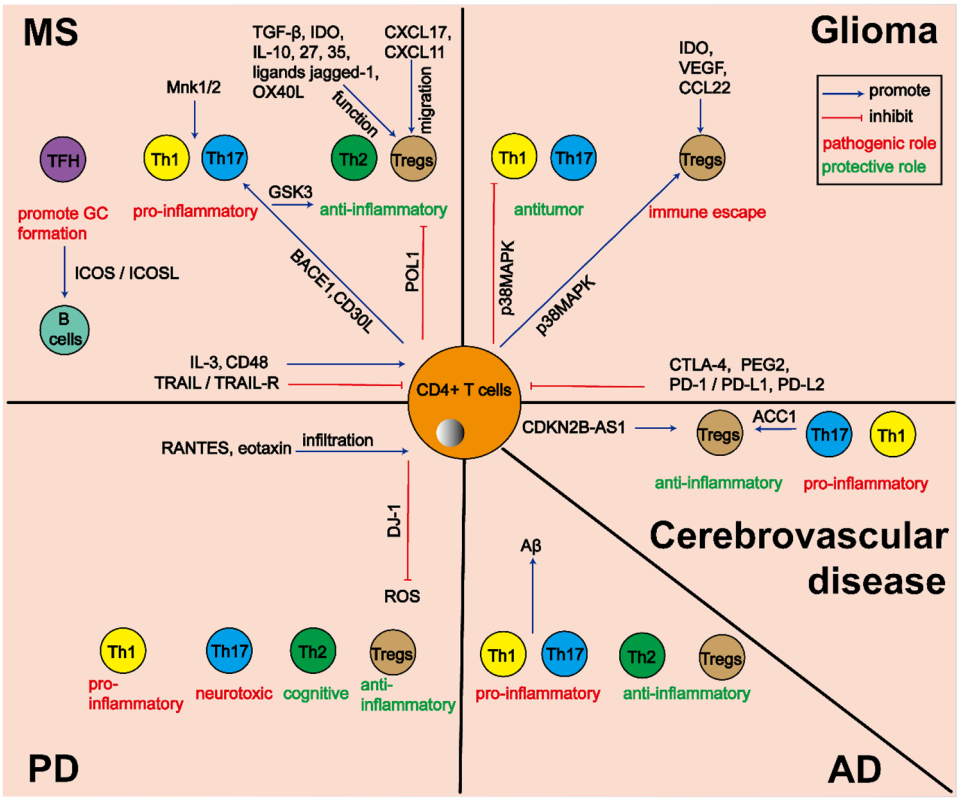

Fig. 2 The role of CD4$^+$ T cell subtypes in different diseases and their associated regulatory genes, proteins, and enzymes. CD4$^+$ T cell subtypes play both protective (green) and pathogenic (red) roles in different brain diseases. The immune regulatory effects of CD4.$^+$ T cells and their subtypes are promoted or inhibited by different genes, proteins, and enzymes. GC: germinal center; ICOS: inducible costimulatory; ICOSL: inducible costimulatory ligand; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; TRAIL-R: tumor necrosis factor-related apoptosis-inducing ligand-receptor; BACE1: β-site amyloid predictor protein-cleaving enzyme 1; CD30L: CD30 ligand; Mnk1/2: MAPK-interacting kinase 1 and 2; POL1: polymerase 1; GSK3: glycogen synthase kinase-3; PD-1: programmed cell death protein 1; PGE2: prostaglandin E2; IDO: indoleamine-2,3-dioxygenase; VEGF: vascular endothelial growth factor; ACC1: acetyl coenzyme A carboxylase 1

had been turned on were relatively harmless when they did not encounter homologous Ag again in their respective target tissues. Regardless of the molecular requirements for patrolling the CNS interface, if $CD4^+$ T cells do not find homologous Ag, they will be released to the surrounding via cerebrospinal fluid (CSF) and dual lymphatics. The entry of $CD4^+$ T cells into the bloodstream of a healthy CNS can, in principle, take three different blood vessel routes, namely blood vessels of the choroid plexus, the leptomeninges, or the nerve parenchyma. In immunosurveillance, $CD4^+$ T cells can patrol the boundary regions associated with the CNS, i.e., the meningeal layer (dura, arachnoid, and pia mater) adjacent to the CNS surrounds the subarachnoid space and Virchow-Robin space, sensing pathogenic changes. Although $CD4^+$ T cells entry into CNS parenchyma is restricted under stable conditions, various disease processes may initiate $CD4^+$ T cells entry into CNS parenchyma. Parenchymal microglia, marginally associated macrophages and CNS dendritic cells collect, process and present Ag. $CD4^+$ T cells can recognize small processed peptides that bind MHC II molecules and are present on the surface of APCs, which are reactivated in the meninges (Mundt et al. 2019).

At any time, there are 150,000–750,000 cells in the CSF of healthy individuals, 90% of which are T cells. The ratio of $CD4^+$ T cells to $CD8^+$ T cells is 3.5:1. $CD4^+$ T cells are likely to enter the CSF, thus entering subarachnoid space (SAS), mainly through choroid plexus, especially in healthy individuals and early neuroinflammatory diseases (Ransohoff and Engelhardt 2012). In a state of inflammation, APCs in CSF bind to $CD4^+$ T Cell receptors, and $CD4^+$ T Cells already in CSF secrete chemokines and inflammatory adhesion molecules to induce other $CD4^+$ T Cells to enter the brain parenchyma via the microvascular endothelium directly across the blood–brain barrier (BBB). Elevated expression of P-selectin and adhesion molecules in brain microvascular endothelial cells (BMECs) causes T cells to roll and slow down in the vascular system during inflammation. $CD4^+$ T Cells recognize IFN-γ-induced chemokines such as CXCL9 and CXCL10 secreted by pioneer $CD4^+$ T Cells and activate their integrins such as LFA-1 or VLA-4, which then bind to intercellular adhesion molecule-1 (ICAM-1) or vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells, respectively. As a result, $CD4^+$ T Cells stay on the ECs surface. In the perivascular space, $CD4^+$ T cells may be activated by interacting with perivascular APC. In MS and other pathogenic conditions, $CD4^+$ T cells can migrate to the parenchyma with the destruction of the astrocyte terminus and basement membrane. Any specific $CD4^+$ T cells, as long as they are recruited into CNS, can cause a hole in the BBB that allows antibodies to pass through. Regulation of BBB opening mediated by $CD4^+$ T cells in the perivascular space is essential for the delivery of antibodies and drugs to the CNS without causing immunopathology (Iwasaki 2017).

$CD4^+$ T Cells in MS

MS is a $CD4^+$ T cell-mediated autoimmune disease characterized by demyelination and neurodegeneration of the CNS (Baecher-Allan et al. 2018). In MS, myelin-specific $CD4^+$ T cells developed in peripheral lymphoid organs infiltrate CNS, where they encounter homologous antigens presented by local APCs. This interaction with APCs results in the reactivation of myelin-specific $CD4^+$ T cells (Rostami and Ciric 2013). Overactivation of the Th1 and Th17 subgroups is thought to be the direct cause of the disease (Zhang et al. 2013), while Th2 have beneficial effects on MS due to their antagonistic effect on Th1 cells (Lee et al. 2015). The loss of the number, function, and migration ability of Tregs leads to the limitation of the self-immune tolerance of MS (Danikowski et al. 2017). Follicular helper $CD4^+$ T (TFH) cells are considered to be a unique lineage of $CD4^+$ Th cells, which promote germinal center (GC) formation. It helps B cells to promote immunoglobulin affinity maturation, transformation-like recombination, and the production of memory B cells, thus aggravating the severity of the disease (Zhang et al. 2021).

In experimental autoimmune encephalomyelitis (EAE), which is a typical model for MS, the influx of $CD4^+$ T cells is closely related to the expression of IL-3 in the CNS (Renner et al. 2016). The activation of $CD4^+$ T cells can be inhibited by the interaction between tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and its receptor (TRAIL-R) (Chyuan et al. 2018). $CD4^+$ T cells lacking β-site amyloid predictor protein-cleaving enzyme 1 (BACE1) and the CD30 ligand (CD30L) can weaken the ability of Th17 to induce disease, which results in impaired pathogenicity of $CD4^+$ T cells in EAE mice (Hernandez-Mir et al. 2019). Th1 and Th17 differentiation are diminished in MAPK-interacting kinase 1 and 2 (Mnk1/2) KO mice in the EAE model, which is associated with lighter clinical scores (Gorentla et al. 2013). When the expression of polymerase 1 (POL1) is silenced, Th2 cytokines and Tregs are increased resulting in ameliorating EAE (Zilkha-Falb et al. 2017). Inhibiting serine/threonine kinase glycogen synthase kinase-3 (GSK3) leads to pathogenic Th1 and Th17 secreting more IL-10 to play a therapeutic role in MS (Hill et al. 2015). IL-10 produced by Tregs plays an important role in the regulation of Th1 and Th17, leading to the inhibition of immune responses in EAE disease (Tian et al. 2018). TGF-β, indoleamine-2,3-dioxygenase (IDO), IL-10, IL-27, IL-35, and the ligands jagged-1 and OX40L enhance Tregs function. Chemokines CCL17 and CXCL11 can affect Treg migration (Danikowski et al. 2017). Inducible costimulator (ICOS) on TFH cells connecting with ICOS ligand (ICOSL)

on B cells to promote the disease. Therefore, TFH and ICOS involved in the MS pathogenesis may be potential therapeutic targets (Zhang et al. 2021). These strategies have been shown to improve the disease and are therefore promising for the treatment of MS patients. (Fig. 2).

Immunotherapy drugs are reported to treat MS or its pre-clinical animal model EAE include small molecule drugs (Prazosin, Gemcitabine, Tofacitinib, Dimethyl fumarate, et al.), large molecule drugs (Glatiramer acetate, S-nitrosoglutathione, et al.) and nano drugs (multiwalled carbon nanotube). These drugs ameliorate disease by affecting $CD4^+$ T cells polarization subtypes and inhibiting the production of inflammatory factors. Tysabri (Biogen Idec) antibody targets the α4/β1 integrin receptor and is clinically used to reduce the adhesion of $CD4^+$ T cells to endothelial cells and their migration to target tissues in the treatment of MS (Manocha et al. 2018). Gemcitabine can reduce clinical scores of EAE and promote myelin repair by inhibiting Th17 and inflammatory cytokines (IL-17A and IL-1 β) in lymphocytes and the spinal cord (Yi et al. 2012). Tofacitinib alleviates EAE by modifying dendritic cells (DCs) to reduce Th1 and Th17 and increase Tregs (Zhou et al. 2016). Dimethyl fumarate (DMF) inhibits brain-derived Th17/Th1 and induces Th2 to reduce the severity of EAE (Brück et al. 2018). Prazosin, an α_1-adrenoceptor antagonist, attenuated the proliferation of Th17 but increased the frequency of Tregs in an EAE rat model (Pilipović et al. 2019). Glatiramer acetate (GA) is an immunomodulatory therapy approved by the FDA for MS. Th2 induced by GA accumulates in the CNS through the BBB, where they can be stimulated in situ by myelin basic protein, to play a role in the treatment of diseased organs (Aharoni et al. 2000). It also increases the number of Tregs through the raised expression level of Foxp3, thereby inhibiting the activation and proliferation of autoimmune $CD4^+$ T cells in EAE mice (Hong et al. 2005). The antimicrobial peptide murine β-defensin-14 (mBD14) can induce Tregs. It caused amelioration of the disease with less CNS inflammation in EAE mice, which indicates it may be beneficial for MS (Bruhs et al. 2016). S-nitrosoglutathione (GSNO) promotes $CD4^+$ T cells to express more IL-10 and less IL-17, resulting in the increase of Tregs and decrease of Th17 to ameliorate EAE disease (Singh et al. 2018). Intravenous immunoglobulin (IVIG) therapy significantly increased the percentage of Tregs in EAE (Chong et al. 2013). Erythropoietin (EPO) can reduce the ratio of Th1 and Th17 lymphocyte subsets isolated from the CNS of EAE (Chen et al. 2010). Nonprotein amino acid γ-aminobutyric acid (GABA) treatment inhibits the development of Th1 response, but increases Tregs, ameliorating disease in EAE. Homotaurine acts as a $GABA_A$-R agonist to inhibit the development of Th1 and Th17 response but increases the Tregs reaction in both monophasic and a relapsing–remitting mouse model of EAE (Tian et al. 2018). Anti-NKG2A $F(ab')_2$ Ab ameliorates EAE by skewing the proportion of Th1 and Th17 toward Th2 subsets (Leavenworth et al. 2010). Adriel S Moraes et al. co-incubation of multi-walled carbon nanotube with APCs produces high levels of IL-27 and inhibits the development of Th17, resulting in less serious EAE (Moraes et al. 2013). (Table 1).

Moreover, some immunotherapies currently investigated are promising for clinical trials. The use of autoantigen-specific Tregs is attractive as cell therapy for autoimmune diseases. Shimpei Kasagi et.al achieved specific immunotherapy for EAE successfully by producing autoantigen-specific Tregs, which have clinical significance for the development of new effective therapies for MS (Kasagi et al. 2019). Immune cell adoptive therapy has also been explored for the treatment of MS. Claire-Maelle Fovet et.al implemented a preclinical program in a cynomolgus monkey model of EAE using a recombinant antibody against the dendritic cell sialic acid-free glycoprotein receptor that allowed antigen-specific adaptive immune modulation, induced MoG-specific Tregs, which alleviate the disease (Fovet et al. 2019). CD70 is an immune marker and an important co-stimulator of highly pathogenic pro-inflammatory Th1/Th17. Adoptive transfer of CD70-/-CD4 + T lymphocytes induced milder EAE disease than the transfer of WT $CD4^+$ T cells (Dhaeze et al. 2019). There are also various other targets tested in clinical trials for better MS therapy. NLRC3 attenuates the antigen presentation function of DCs and its ability to activate and polarize $CD4^+$ T cells into Th1 and Th17 subsets, making it a potential therapeutic target for the adaptive immune response that drives MS and other autoimmune diseases (Fu et al. 2019). In a mouse model of MS, overexpression of Smad7 favored the expansion of intestinal $CD4^+$ T cells into an inflammatory phenotype and migration of intestinal $CD4^+$ T cells into CNS. Smad7 in intestinal T cells may be a valuable therapeutic target for MS to achieve intestinal immune tolerance and suppress CNS inflammation (Haupeltshofer et al. 2019). NKG2D promotes higher proinflammatory cytokine production by Th1 and Th17 cells which suggested NKG2D is an important target for ameliorating Th1- and Th17-mediated chronic inflammatory diseases (Babic et al. 2020).

$CD4^+$ T Cells in Glioma

Glioma is the most common primary tumor in the brain (Chen et al. 2017). $CD4^+$ T cells are indispensable in the immunotherapy of gliomas, but the accumulation of Tregs is related to poor prognosis (Sayour et al. 2015; Wu et al. 2019). Tregs not only play an important role in promoting immunosuppression but also promote angiogenesis (Mu et al. 2017). Glioma cells secrete many chemokines,

Table 1 Drugs for the therapy of brain diseases and their mechanism of regulating $CD4^+$ T cells

Disease	Drugs	Mechanisms on $CD4^+$ T cells	Reference
MS	Tysabri	$CD4^+$ T cells↓	(Manocha et al. 2018)
	Gemcitabine	Th17↓	(Yi et al. 2012)
	Tofacitinib	Th1↓, Th17↓; Tregs↑	(Zhou et al. 2016)
	DMF	Th1↓, Th17↓; Th2↑	(Brück et al. 2018)
	Prazosin	Th17↓; Tregs↑	(Pilipović et al. 2019)
	GA	Th2↑; Tregs↑	(Aharoni et al. 2000; Hong et al. 2005)
	mBD14	Tregs↑	(Bruhs et al. 2016)
	GSNO	Th17↓; Tregs↑	(Singh et al. 2018)
	IVIG	Tregs↑	(Chong et al. 2013)
	EPO	Th1↓, Th17↓	(Chen et al. 2010)
	GABA	Th1↓; Tregs↑	(Tian et al. 2018)
	Homotaurine	Th1↓, Th17↓; Tregs↑	(Tian et al. 2018)
	Anti-NKG2A $F(ab')_2$ Ab	Th1↓, Th17↓; Th2↑	(Leavenworth et al. 2010)
	multiwalled carbon nanotube	Th17↓	(Moraes et al. 2013)
Glioma	TMZ	$CD4^+$ T cells↑; Tregs↓	(Thomas et al. 2017)
	Bev	$CD4^+$ T cells↑; Tregs↓	(Thomas et al. 2017)
	TMZ chemotherapy combined with tumor antigen-pulsed DCs	Tregs↓	(Kim et al. 2010)
	Vaccination of DCs transfected with il13ra2 mRNA	$CD4^+$ T cells↑	(Saka et al. 2010)
	pTOP constructed by inserting an OVA-MHC class II-restricted epitope	$CD4^+$ T cells↑	(Lopes et al. 2021)
	human L19-TNF fusion protein	$CD4^+$ T cells↑	(Weiss et al. 2020)
	α-Galcer	$CD4^+$ T cells↑	(Hunn et al. 2012)
	tumor lysate vaccine and Fc-OX40L costimulatory molecule	$CD4^+$ T cells↑	(Murphy et al. 2012)
	PCC0208009	Tregs↓; $CD4^+$ T cells↑	(Sun et al. 2018)
	combining immunotherapy with GM-CSF and IFN-γ	$CD4^+$ T cells↑	(Smith et al. 2009)
	IDH1 vaccine	Th1↑	(Schumacher et al. 2014)
	AdCMVdelta24	Tregs↓	(Qiao et al. 2015)
	IL-12	Th1↑	(Chen et al. 2015)
	combination immunotherapy with GVAX and systemic agonist anti-OX40 monoclonal antibody OX40	Th1↑, Th2↓	(Jahan et al. 2018)
PD	Gdnfv	$CD4^+$ T cells↓	(Smith et al. 2015)
	human exfoliated deciduous teeth stem cells- derived conditioned medium	$CD4^+$ T cells↓	(Chen et al. 2020)
	Ginsenoside Rg1	Th protein↓	(Zhou et al. 2015b)
	antigen-presenting cell-targeting glucan microparticle vaccine delivery system combined delivery of α-syn plus rapamycin	Tregs↑	(Rockenstein et al. 2018)
	VIP2	Tregs↑	(Olson et al. 2015)
	$bvPLA_2$	Tregs↑	(Chung et al. 2015)
	α-Syn vaccine	Tregs↑	(Christiansen et al. 2016; Sanchez-Guajardo et al. 2013)
	calpain inhibition	Th1↓; Tregs↑	(Samantaray et al. 2015)
	Azd1480	$CD4^+$ T cells↓	(Samantaray et al. 2015)

Table 1 (continued)

Disease	Drugs	Mechanisms on $CD4^+$ T cells	Reference
AD	donepezil	Th1↓	(Jiang et al. 2013; Nizri et al. 2008)
	rivastigmine	Th1↓, Th17↓	(Jiang et al. 2013; Nizri et al. 2008)
	Memantine	Th1↓	(Manocha et al. 2018)
	Anti-CD49d antibodies	$CD4^+$ T cells↓	(Manocha et al. 2018)
	XPro1595	$CD4^+$ T cells↓	(MacPherson et al. 2017)
	$bvPLA_2$	$CD4^+$ T cells↓; Tregs↑	(Baek et al. 2020)
	IL-2	Tregs↑	(Dansokho et al. 2016)
Cerebrovascular disease	Tofacitinib	$CD4^+$ T cells↓	(Dansokho et al. 2016)
	immunoglobulin-fused form of PD-L therapy	Th1↓, Th17↓; Th2↑, Tregs↑	(Han et al. 2017)
	pMHC	$CD4^+$ T cells↓	(Yang et al. 2017)

cytokines, and growth factors to promote the infiltration of $CD4^+$ T cells and Tregs. The population of $CD4^+$ T cells increased with tumor grade, beginning with 39% in WHO grade II to 73% in WHO grade III, and 98% in grade IV (Gieryng et al. 2017). It should be pointed out that glioma has developed a series of strategies to evade and inhibit the antitumor immune response (Dai et al. 2018).

One of the important markers of T cell depletion is programmed cell death protein 1 (PD-1) (Vidyarthi et al. 2019). PD-1 on $CD4^+$ T cells binds to PD-L1 overexpressed by tumor cells, thus attenuating the activation and effector function of $CD4^+$ T cells, resulting in $CD4^+$ T cells anergy, apoptosis, or Tregs development. The activation of naïve $CD4^+$ T cells was blocked by CTLA-4 (Filley et al. 2018; Zhang and Braun 2014). The proliferation of $CD4^+$ T cells can be reduced by prostaglandin E2 (PGE2) through IL-2 and IL-2 receptors (Authier et al. 2015). Th2 and Tregs are chemotactic by CCL22 expressed by monocytes and DCs (Zhou et al. 2015a). Tregs can induce by IDO and vascular endothelial growth factor (VEGF). Tregs can induce via its metabolite kynurenine, which acts on the aryl hydrocarbon receptor and induces the synthesis of the Treg-recruiting chemokine CCL22 (Hanihara et al. 2016; Thomas et al. 2017). Tregs are inhibited by the p38MAPK inhibitor. On the other hand, Th1 is positively affected by the p38MAPK inhibitor (Kühnöl et al. 2013). (Fig. 2).

The current standard drug treatment is limited to temozolomide (TMZ) and bevacizumab (Bev) (Banissi et al. 2009), and all of them can treat disease by affecting $CD4^+$ T cells. These drugs prolong survival mainly by promoting the number and infiltration of $CD4^+$ T cells into CNS and inhibiting Tregs. Radiation, TMZ, and Bev can reduce the number of peripheral Tregs in patients with newly diagnosed glioblastoma (Thomas et al. 2017). Adjuvant treatment of glioma patients with the DC vaccine can reduce the number of Tregs (Fong et al. 2012). TMZ chemotherapy combined with tumor antigen-pulsed DCs can enhance antitumor immunity partly by inhibition of Tregs (Kim et al. 2010). There are also some potential therapeutic approaches to ameliorate the disease by inducing the production of $CD4^+$ T cells, infiltrating into tumor tissues, or influencing their differentiation subtypes, such as large molecule drugs (vaccine, inhibitor). Vaccination of DCs transfected with il13ra2 mRNA can induce $CD4^+$ T lymphocyte proliferation, and then induce specific immune responses to the tumor and anti-tumor effects in a mouse glioma model (Saka et al. 2010). Alessandra Lopes et al. found that the pTOP constructed by inserting an OVA-MHC class II-restricted epitope effectively activated the proliferation of specific CD4 T cells by appropriate treatment of MHC-II epitopes in the GL261 mouse model (Lopes et al. 2021). Immune cytokines are a promising immunotherapy for glioma. Systemic administration of human L19-TNF fusion protein can increase tumor infiltration of $CD4^+$ T cells in orthotopic immunocompetent mouse glioma models (Weiss et al. 2020). In the implantable GL261 murine glioma model, the immune-adjuvant α-galactosylceramide (α-Galcer) supports the development of $CD4^+$ T-cell-mediated adaptive immune response. It is possible that $CD4^+$ T cells directly target tumor cells via MHC II (Hunn et al. 2012). The combination of tumor lysate vaccine and Fc-OX40L costimulatory molecule can significantly increase the proliferation of glioma-bearing mice brain infiltrating $CD4^+$ T cells (Murphy et al. 2012). IDO highly expressed in glioma correlates with poor clinical outcomes for it can increase the recruitment of Tregs. PCC0208009 is an efficient IDO inhibitor, by inhibiting Tregs and increasing the percentages of $CD4^+$ T cells, PCC0208009 can significantly enhance the antitumor effect of TMZ in GL261 and C6 models (Sun et al. 2018). Combining immunotherapy with GM-CSF produced by GL261 cells and recombinant IFN-γ of preestablished GL261 mouse gliomas could increase the number of activated tumoricidal $CD4^+$ T cells, thus eradicating the established brain tumors (Smith et al. 2009). Monoallelic point mutations of isocitrate dehydrogenase type 1 (IDH1) are an early and decisive event in the development of glioma. IDH1 (R132H) vaccine induces Th1 to produce a specific antitumor immune response against IDH1 (R132H) mutant glioma mice (Schumacher et al. 2014).

Intratumoral administration of adenovirus AdCMVdelta24 into glioblastoma multiforme mouse model can reduce tumor infiltrative Tregs and IDO in glioma cells as well as reprogram Tregs from an immunosuppressive state to a stimulated state (Qiao et al. 2015). IL-12 promotes IFN-γ to promote Th1-mediated antitumor cytotoxic immunity of C6 glioma rats (Chen et al. 2015). In glioma-bearing mice, combination immunotherapy with GVAX and systemic agonist anti-OX40 monoclonal antibody OX40 increased the percentage of Th1 and reduced the Th2 fraction in their brain (Jahan et al. 2018). (Table 1).

There is some potential immunotherapy promising in clinical trials for glioma therapy. IDH1 vaccine shows therapy effects in glioma mice by inducing Th1 cells, which is in clinical development in early phase trials (Schumacher et al. 2014). Treatment of chimeric antigen receptor (CAR) T-cell with genetically modified T cells showed significant responses in an individual case, and targeting activity may be associated with increased $CD4^+$ T-cell infiltration. Further data are needed to understand the potential benefits (Tan et al. 2020). Adjuvant treatment of glioma patients with the DC vaccine results in a reduced number of Tregs, which indicates that DC immunotherapy has good clinical application prospects (Fong et al. 2012).

$CD4^+$ T Cells in PD

PD affects about 7 million to 10 million people around the world. The activation of resident infiltration of $CD4^+$ T lymphocytes results in neurodegeneration (Thakur et al. 2017). In PD, Th1 and Th17 show harmful functions because of their pro-inflammatory properties, but Th2 and Tregs have beneficial effects because of their anti-inflammatory properties. Microglial play a central role in neuroinflammation, these different $CD4^+$ T cell subsets polarize microglia toward a pro-inflammatory or anti-inflammatory state. The cross-talk between $CD4^+$ T cells and microglial has the potential to be a therapeutic strategy (González et al. 2015). Th2 cytokines, IL-4 and IL-13, participate in cognitive function by stimulating astrocytes in the meninges and hippocampus (Brombacher et al. 2017). Th17 plays a neurotoxic role by promoting the activation of glial cells (Liu et al. 2017). Reactive oxygen species (ROS) formation in $CD4^+$ T cells of DJ-1 deficient mice was higher than that of wild-type mice (Zhou et al. 2017). The expression of $CD4^+$ T cell subsets increased in MPTP mice, which is an animal model of Parkinson's disease. One month after MPTP administration, $CD4^+$ T lymphocytes entered the substantia nigra of the non-human primate model induced by MPTP (Seo et al. 2020).

It has been reported that the activation and migration of $CD4^+$ T cells to CNS are under the control of calpain (Samantaray et al. 2015). The infiltration of $CD4^+$ T cells into substantia nigra can be reduced by the functional blocking antibodies against recombinant human C–C Motif Chemokine 5 (RANTES) and eotaxin (Chandra et al. 2016). The proliferation of $CD4^+$ T cells is affected by leucine-rich repeat kinase 2 (LRRK2), which plays an important role in signal transduction and antigen presentation of DCS (Kubo et al. 2020). Daniela Elgueta et. al found that the selective changes of DRD3 signal in $CD4^+$ T cells of PD patients have a therapeutic effect on the inhibition of motor injury in PD animals (Elgueta et al. 2019). (Fig. 2).

Drugs used to treat PD include small molecule drugs (such as Ginsenoside Rg1), large molecule drugs (α-Syn vaccine, Gdnfv, et al.), nanoparticles (antigen and rapamycin nanoparticles), and other treatments. These drugs ameliorate disease by inhibiting $CD4^+$ T cell activation and proliferation, affecting $CD4^+$ T cell polarization subtypes, and inhibiting the production of inflammatory factors. GDNF is a neurotrophic factor of dopaminergic neurons. Gdnfv is an engineering form of wild-type Gdnf, which is expressed and purified from mammalian cells. It can reduce $CD4^+$ T cell proliferation in PBMCs collected from volunteers representing the world's MHC haplotypes (Smith et al. 2015). Intravenous administration of human exfoliated deciduous teeth stem cells- derived conditioned medium produced by the standardized procedure can significantly reduce the levels of $CD4^+$ T cells in substantia nigra and striatum in rotenone-induced PD rat (Chen et al. 2020). Ginsenoside Rg1 can decrease the expression of Th protein in the substantia nigra of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) -induced mouse model of PD (Zhou et al. 2015b). Using the antigen-presenting cell-targeting glucan microparticle vaccine delivery system combined delivery of α-syn plus rapamycin, can induce antigen-specific Tregs in PDGF-α-syn transgenic male and female mice (Rockenstein et al. 2018). Olson et al. developed a vasoactive intestinal peptide2 (VIP2) receptor selective agonist that can transfer $CD4^+$ T cells from effector cells to Tregs in MPTP-intoxicated mice (Olson et al. 2015). Bee venom phospholipase A_2 ($bvPLA_2$) is a major bee venom compound, which binds directly to CD206 on DCs, thus promoting the secretion of PGE_2, inducing Tregs differentiation through PGE_2 receptor signal, and promoting the survival of dopaminergic neurons in PD mice model (Chung et al. 2015). The subcutaneous route of bvPLA2 may be helpful for the treatment of PD (Baek et al. 2018). The α-Syn vaccine can enlarge the original Tregs population and long-lasting infiltration of Tregs in the whole nigrostriatal system, which induces immune tolerance to α-Syn in animal models of PD (Christiansen et al. 2016; Sanchez-Guajardo et al. 2013). In the MPTP model, calpain inhibition reduces the number of Th1 and increases the number of Tregs population, thus reducing the severity of the disease (Samantaray et al.

2015). Azd1480, a Jak1 / 2 inhibitor, inhibits neuroinflammation induced by α-Syn by inhibiting $CD4^+$ T cells infiltration and proinflammatory cytokines/chemokines production in a rat model of PD overexpression α-SYN (Qin et al. 2016). These drugs reduce inflammation in the brain and inhibit the development of disease by reducing Th1 and Th17 subtypes and increasing Tregs. (Table 1).

$CD4^+$ T Cells in AD

AD is associated with age-related degeneration and dementia. This decline in function is related to plaque deposition with Aβ-peptide and the inflammatory phenotype of microglia (Rosset et al. 2015). Proinflammatory subsets such as Th1 and Th17 are the main source of proinflammatory cytokines, which can reduce endothelial integrity and stimulate astrocytes to produce amyloid β (Kubick et al. 2020). The frequency of Th17 and Th1 in the brain of AD double transgenic APΔE9 mouse is higher, which suggests that T cells have a stronger ability for infiltration and activation (Ahuja et al. 2017). Dysfunctional BBB, which is related to vascular inflammation and leukocyte migration to the brain, is involved in the pathogenesis of AD. $CD4^+$ T cells adhere to the cerebral vascular endothelial cells and migrate to the brain parenchyma of AD patients (Pietronigro et al. 2019). Tregs can strictly control Aβ-specific $CD4^+$ T cell response in both physiological and pathological environments (Dansokho et al. 2016).

Some drugs (donepezil, rivastigmine, memantine, XPro1595, IL-2) can ameliorate AD by affecting the infiltration and activation of $CD4^+$ T cells and increasing Tregs. Donepezil reduces the numbers of Th1 in EAE mice, and rivastigmine inhibits Th1 and Th17, both of which have no influence on Th2 (Jiang et al. 2013; Nizri et al. 2008). Memantine reduces Th1, while don't affect Tregs in mice. Anti-CD49d antibodies targeting the α4/β1 integrin α4 subunit modify AD by altering pro-inflammatory microglia and reducing the immunoreactivity of CD4 + T cells in the brain of a mouse model (Manocha et al. 2018). Soluble Tumor Necrosis Factor (sTNF) can regulate the permeability of BBB. XPro1595, a new biological preparation, can separate sTNF into inactive heterotrimers and reduces the total number of $CD4^+$ T cells in the brain of the 5xFAD mice model (MacPherson et al. 2017). $bvPLA_2$ can significantly reduce the Aβ deposition in the hippocampus of 3xTg-AD mice. This neuroprotective effect of $bvPLA_2$ is related to the inactivation of microglia and the decrease of $CD4^+$ T cell infiltration, which may be due to the increasing number of Tregs (Baek et al. 2020). IL-2 has therapeutic potential in innovative immunotherapy based on the amplification of Tregs in a murine model of AD (Dansokho et al. 2016). (Table 1).

$CD4^+$ T Cells in Cerebrovascular Disease

Cerebrovascular disease is a group of diseases that occur in cerebral blood vessels and cause brain tissue damage due to intracranial blood circulation disorder, including cerebral atherosclerosis (Baragetti et al. 2018), cerebral arteritis (He et al. 2017; Xie et al. 2019), cerebral artery injury (Fernandez et al. 2019), ischemic stroke disease, intracranial aneurysms (IA), intracerebral hemorrhage (ICH), giant cell arteritis (GCA), etc. Cerebrovascular disease is triggered by unknown environmental factors, which may activate and lead to the maturation of DCs located in the normal adventitia. These activated DCs then produce chemokines, which trigger the recruitment of $CD4^+$ T cells, then activate, proliferate and polarize into different subsets (Samson et al. 2017). Subsets of $CD4^+$ T cells in cerebrovascular disease have double effects, Th1 and Th17 are harmful, which produce IFN-γ and IL-17. While Tregs seem to be an endogenous protective subset, which can inhibit brain inflammation (Wang et al. 2019). Th1 is involved in granulomatous inflammatory damage in GCA (Watanabe et al. 2017a, b). The DCs in the vascular wall failed to express the immunosuppressive ligand PD-L1, which made the injured $CD4^+$ T cells not inhibited. Therefore, $PD\text{-}1^+$ $CD4^+$ T cells can enter the immune-specific vascular wall, where they produce a wide range of inflammatory cytokines, and play a direct role in driving intimal hyperplasia and intramural neoangiogenesis (Watanabe et al. 2017b; Zhang et al. 2017).

The balance of Tregs and Th17 can be regulated by acetyl coenzyme A carboxylase 1 (ACC1) to reduce neuroinflammation after stroke (Wang et al. 2019). T cells recognize antigens need a "second signal", which usually comes from the interaction of CD28 with CD80 and CD86 on antigen-presenting cells. The proliferation and cytokine production of $CD4^+$ T cells is inhibited by blocking CD28 (Zhang et al. 2019). The increased expression of CD74 on $CD4^+$ T cells may be a useful biomarker for predicting stroke severity and prognosis in patients with ischemic stroke (Yang et al. 2017). Tregs and endothelial progenitor cells (EPC) can reduce dyskinesia, reduce the infiltration of $CD4^+$ T cells into the brain and reduce the activation of microglia (McDonald et al. 2018). Th1 response is positively regulated by IL-15 (Lee et al. 2018). It is reported that the proliferation of Tregs is inhibited by the down-regulation of CDKN2B-AS1 (Lei et al. 2019). (Fig. 2).

Some macromolecular drugs are used to inhibit $CD4^+$ T cell proliferation and differentiation subtypes. The JAK inhibitor, tofacitinib, can effectively reduce the proliferation of proliferative intima, and minimized the resident memory T cells of $CD4^+$ T cells in mice carrying inflamed human arteries (Zhang et al. 2018). An immunoglobulin-fused form of PD-L therapy can specifically reduce the number of $CD4^+$ T cell infiltration and the percentage of Th1 and Th17 while it increasing the percentage of Th2 and Tregs in

a murine ICH model (Han et al. 2017). Some MHC class II/peptide structures (pMHC) can effectively treat experimental stroke mice, partly because they can competitively inhibit MIF/CD74 interaction and downstream signal transduction, thereby inhibiting $CD4^+$ T cells (Yang et al. 2017). These drugs reduce the severity of the disease by reducing the number of $CD4^+$ T cells, reducing Th1 and Th17 subtypes, and increasing Tregs. (Table 1).

Conclusion

In general, no specific $CD4^+$ T cell subsets are completely beneficial or completely harmful in all of the described neurological diseases. $CD4^+$ T cell subsets are essential for initiating responses to pathogen challenges, preventing inappropriate activation, maintaining tolerance, and participating in the anti-tumor immune response. Autoimmune and anti-tumor immune responses are regulated by the balance between Tregs and Th17. Immunopathology occurs when the homeostasis of the subgroup is not maintained. We can exploit the similar roles of immune cells in different diseases to find broader applications for immunomodulatory drugs.

Neuroimmune dysfunction is a common phenomenon in different forms of CNS diseases. The cross-link between central and peripheral immune mechanisms seems to be destroyed by a series of immune markers (such as CD4, HLA-DR, CD25, and CD28). These markers show the variability of brain diseases such as AD and PD, cerebrovascular encephalopathy, MS, glioma, etc. At present, immunotherapy enables us to treat a large number of nervous system diseases in a more precise and personalized way. In clinical practice, products designed for specific therapeutic targets and evaluated in clinical trials are becoming more and more frequent. However, due to the complexity of the immune system, various cytokines, transcription pathways, and signal axes interact and play an integrated role in various stages of different diseases. Further study of these effects may help to develop better and more specific therapeutic targets and avoid the overall regulation of the immune system, which will damage the immune function of patients and be vulnerable to a series of pathogenic threats.

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Declarations

Declaration of Interests None.

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