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T-cell receptor signaling modulated by the co-receptors: Potential targets for stroke treatment

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ABSTRACT

Stroke is a severe and life-threatening disease, necessitating more research on new treatment strategies. Infiltrated T lymphocytes, an essential adaptive immune cell with extensive effector function, are crucially involved in post-stroke inflammation. Immediately after the initiation of the innate immune response triggered by microglia/macrophages, the adaptive immune response associated with T lymphocytes also participates in the complex pathophysiology of stroke and partially informs the outcome of stroke. Preclinical and clinical studies have revealed the conflicting roles of T cells in post-stroke inflammation and as potential therapeutic targets. Therefore, exploring the mechanisms that underlie the adaptive immune response associated with T lymphocytes in stroke is essential. The T-cell receptor (TCR) and its downstream signaling regulate T lymphocyte

Abbreviations: ICH, intracerebral hemorrhage; DC, dendritic cells; Th1 cells, helper T1 cells; Th2 cells, helper T2 cells; Treg cells, regulatory T cells; APC, antigen-presenting cells; TCR, T cell receptors; MHC, major histocompatibility complex; ITAMS, immunoreceptor tyrosine-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; ZAP-70, the tyrosine-protein kinase ZAP-70; Fyn, the tyrosine-protein kinase Fyn; LAT, linker for T cells; PLC-1, phospholipase C gamma1; Grb2, growth factor receptor bound protein 2; Grap, adapter protein associated with Grb2; Gads, Grb2-associated adapter downstream of Shc; NFAT, nuclear factor of activated T cells; PKCθ, protein kinase C-θ; IKK, inhibitor of NF-kappa B kinase; NF-κB, nuclear factor kappa-B; RASGRP1, RAS guanyl releasing protein 1; RASERK1/2, RAS-extracellular regulated protein kinases 1/2; TSC1/2-mTOR, mammalian target of rapamycin.; P38, p38 Mitogen-activated protein kinases; JNK, c-Jun N-terminal kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; DAG, diacylglycerol; IP3, inositol-3-phosphate; ICAM-1, intercellular adhesion molecule-1; LFA, lymphocyte function-associated antigen; TIM1, T cell immunoglobulin and mucin domain-containing protein 1; TIM-4, T cell immunoglobulin and mucin domain-containing protein 4; FasL, Fas ligand; 4–1BB CD137, TNFR superfamily member (TNFRSF9); 4–1BBL, the ligand of TNFR superfamily member (TNFRSF9, CD137); OX40, tumor necrosis factor receptor superfamily member 4; OX40L, OX40 ligand; GITR, glucocorticoid-induced tumor necrosis factor receptor; GITRL, GITR ligand; ICOS, inducible T-cell costimulatory; ICOSL, ICOS ligand; Gal9, galectin-9; TNF, tumor necrosis factor-alpha; TNFR2, tumor necrosis factor receptor 2; HVEM, herpesvirus entry mediator (TNFRSF14, CD270); BTLAs, B and T lymphocyte attenuators: TIGIT, T cell Ig and ITIM domain; FGL1, fibrinogen-like protein 1; LAG-3, lymphocyte activation gene 3; PD-1, programmed death-1; PD-L1/2, programmed death ligand 1/2; CTLA4, cytotoxic T-lymphocyte-associated protein 4; MDSCs, myeloid-derived suppressor cells; FoxO1, forkhead box O1; Tfh, follicular helper T cells; TRAF2, TNF receptor-associated factor 2; IL-17A, interleukin 17 A; JAK, the Janus kinases; TGF-β, transforming growth factor-β; IFN-γ, interferon-gamma; RORgt, retinoic acid receptor-associated orphan receptor gt; N/A, not available; TrkC, the tropomyosin receptor kinase C; WT mice, wild-type mice; SD rats, Sprague-Dawley rats; BBB, blood-brain barrier; HMGB1, high mobility group box 1 protein; TLRs, toll-like receptors; MOG, myelin oligodendrocyte glycoprotein; CD28SA, CD28 superagonistic monoclonal antibody; iNSPCs, ischemia-induced neural stem/progenitor cells; I/R, ischemia/reperfusion; mTOR, mammalian target of rapamycin; S6K, ribosomal protein S6 kinase; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; tMCAO, transient middle cerebral artery occlusion; MMP-9, matrix metalloproteinase-9; HIF-1α, hypoxia-inducible factor-1α; eGFR, estimated glomerular filtration rate.

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differentiation and activation. This review comprehensively summarizes the various molecules that regulate TCR signaling and the T-cell response. It covers both the co-stimulatory and co-inhibitory molecules and their roles in stroke. Because immunoregulatory therapies targeting TCR and its mediators have achieved great success in some proliferative diseases, this article also summarizes the advances in therapeutic strategies related to TCR signaling in lymphocytes after stroke, which can facilitate translation.

1. Introduction

Stroke is one of the leading causes of disability and death worldwide. Specifically, the stroke-induced burden is high in low- and middle-income countries [1,2]. Etiologically, stroke has two distinct pathologies. Ischemic stroke is due to the narrowing or blockage of a blood vessel supplying the specific region of the brain. Hemorrhagic stroke (spontaneous intracerebral hemorrhage, sICH) is caused by the spontaneous rupture of a small penetrating artery or arteriole in the brain parenchyma [3]. Due to limitations in the therapeutic time window or the low level of evidence on which most treatment methods are based [4,5], it is imperative to explore alternative strategies to treat stroke. The pathophysiological process of stroke is complex and is meaningfully modified by the origin being ischemic or hemorrhagic. However, the immune-inflammatory response plays a critical role in the onset of brain injury and in the following repair processes after ischemic or hemorrhagic stroke [6,7]. As immunoregulatory therapy regulating lymphocyte infiltration and activation can represent a promising strategy for treating stroke [7,8], a clear exigence exists to understand better the mechanisms related to lymphocyte infiltration, activation, or differentiation in the lesioned brain after stroke.

Immediately after a stroke, local microglia and astrocytes are activated and respond to the injury, promoting the influx of circulating immune cells, predominantly macrophages. Subsequently, the release of inflammatory cytokines, free radicals, and chemokines attracts and activates lymphocytes, which rapidly infiltrate the injured brain and can profoundly influence the severity of brain injury and neurologic outcomes [6,9,10]. Lymphocytes make up a large proportion of leucocytes, and their numbers also dominate infiltrated immunocytes in the brain of injured animals or patients with acute stroke [11,12]. T lymphocytes are involved in innate and adaptive immune responses to stroke [13]. Due to the pro-inflammatory or anti-inflammatory characteristics of its subpopulations, T lymphocytes play complex interdependent roles that synergize to help remove dead tissue but can also damage brain cells and generate maladaptive inflammation [6,12,14]. Mice lacking T cells or where T cell migration to the brain is inhibited have reduced lesion volumes or improved functional outcomes after stroke [15,16]. Therefore, immunomodulation therapies targeting T lymphocytes by alleviating their detrimental impact or increasing their beneficial roles may represent a promising strategy for treating stroke.

To search for potential targets for the immunomodulation of T lymphocytes for stroke, we need to further elucidate the mechanism associated with the infiltration, activation, or differentiation of T lymphocytes in the lesioned brain. T-cell-associated responses, including Th1, Th2, Th17, and Treg responses, have been found in the pathophysiological process of stroke [6,17]. However, few systematic reviews have illustrated the possible checkpoints associated with the facilitation or inhibition of the above immune response in the ischemic or hemorrhagic brain. T lymphocytes have traditionally been thought to exert their function through T cell receptors (TCR) on their surface, which regulate T cell activation by recognizing antigens presented by antigen-presenting cells (APC) and then trigger a complex signaling cascade [18,19]. In addition, recent studies have investigated the regulatory effects of TCR and its downstream signaling pathways on T lymphocytes after stroke [20,21].

Furthermore, therapies targeting TCR or immune checkpoints in the downstream TCR signaling have achieved great success concerning proliferative diseases [22]. In this article, we summarize the roles of the TCR, including antigens, co-stimulatory or co-inhibitory molecular receptors, and their downstream signaling pathways in T lymphocytes under the pathological conditions of stroke. In addition, we emphasize the potential translational value of immunomodulation targeting TCR and its co-receptors in stroke treatment.

2. TCR and TCR signaling

2.1. Structure of the TCR complex

The TCR complex comprises two chains, six-cluster differentiation 3 (CD3) chains, and additional components, including coreceptors, kinases, and ligands [23]. There are four TCR genotypes known as TCRα, TCRβ, TCRγ, and TCRδ, which form two distinct heterodimers: TCRα/TCRβ or TCRγ/TCRδ [23]. The diversity of the TCR library comes from the somatic recombination of genes that encode the TCR, including gene fragments of variables (V), diversity (D), and junction (J) [24]. Structurally, the TCR chains consist of an extracellular region, a transmembrane region, and a shorter cytoplasmic tail. The extracellular region contains a variable immunoglobulin (V) domain, a constant immunoglobulin (C) domain, and a connecting peptide [25]. The recombinases RAG1 and RAG2 facilitate the assembly of the V domain from gene segments that serve as the antigen recognition site [26,27]. The C domains of TCRαβ or TCRγδ heterodimers are linked to the three dimers of CD3 chains, including δε, γε, and ζζ in human or δε (γγ), γε, and ζζ in murine, forming a complex TCR-CD3 [26,27]. The phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMS) in CD3 chains is vital for signal transduction mediated by the TCR-CD3 complex [27].

As co-receptors, both CD4 and CD8 molecules help the TCR complex select different ligands [28]. T cell ligands include major histocompatibility complex (MHC) class I molecules bound to antigen peptides (pMHC-I) and MHCII molecules bound to antigen peptides (pMHC-II) [18]. $CD8^+$ T cells recognize pMHC-I molecules present in any nucleated cell. In contrast, $CD4^+$ T cells recognize pMHC-II molecules in APC, such as B cells, macrophages, and dendritic cells (DC) [28]. After MHC molecules are recognized by the extracellular domains of CD4 and CD8, the lymphocyte-specific protein tyrosine kinase (Lck), a Src-related protein tyrosine kinase (PTK), binds to the intracellular tails of the CD4 and CD8 chains, accompanied by a reduction in CD45 expression [29]. The structure and components of the TCR complex are summarized in Fig. 1.

2.2. TCR signaling pathways

The binding of TCR to MHC molecules triggers multiple signaling changes. Several PTKs, including Lck, the noncatalytic region of tyrosine kinase (Nck), the tyrosine-protein kinase Fyn (Fyn), and the tyrosine-protein kinase ZAP-70 (ZAP-70), are involved in the proximal signaling of the TCR [26,30]. By connecting to the intracellular tails of the CD4 and CD8 chains, Lck and Nck, members of the Src family of kinases, phosphorylate ITAMs on CD3 [23,26]. Lck-induced phosphorylation of ITAMs is necessary for interactions with ZAP-70 [26,30]. Furthermore, phosphorylation of ZAP-70 tyrosine kinase also activates a transmembrane adapter protein named LAT (linker for T cells) [26,31]. Moreover, phosphorylation in Lck, Fyn, and ZAP-70 leads to a downstream signaling cascade by activating a second messenger, enzymes, and various adapter proteins such as PLC-1 (phospholipase C gamma1),

Grb2 (growth factor receptor bound protein 2), Grap (adapter protein associated with Grb2), Gads (Grb2-associated adapter downstream of Shc), etc. [26,30].

TCR-triggered distal signaling cascades include the Ca^{2+}-calcineurin-NFAT (nuclear factor of activated T cells), PKCθ (protein kinase C-θ)-IKK (inhibitor of NF-kappa B kinase)-NFκB (nuclear factor kappa-B), RASGRP1 (RAS guanyl releasing protein 1)-RASERK1/2 (RAS-extracellular regulated protein kinases 1/2), TSC1/2-mTOR (mammalian target of rapamycin), and P38 (p38 Mitogen-activated protein kinases) and JNK (c-Jun N-terminal kinase) pathways (Fig. 2) [26]. Signal transduction in these pathways also needs the help of secondary messengers, enzymes, and various adaptor proteins, including LAT, phosphatidylinositol 4,5-bisphosphate (PIP2), diacylglycerol (DAG), inositol-3-phosphate (IP3), etc. [26,31]. LAT is the first essential adapter to transmit TCR signals [32]. Together with ZAP-70, it can activate PLC-γ1, the primary molecule connecting the proximal to distal signaling cascades of the TCR [26]. The activated PLC-γ1 can hydrolyze membrane-bound PIP2 in DAG and IP3 [26]. DAG can then activate PKCθ, RASGRP1, and PDK1-mediated pathways. In contrast, IP3 triggers the activation of a Ca^{2+}-dependent calcineurin NFAT pathway.

Furthermore, after TCR participation, the DAG-RASGRP1-RAS-ERK1/2 and PI3K-AKT pathways can activate mTORC1 and mTORC2 [26]. However, P38 activity mediated by a nonclassical pathway downstream of proximal TCR signaling is likely independent of MAPK cascades in T cells [26]. In this case, the activation of TCR proximal signaling results in the phosphorylation of P38 at the Y323 residue by ZAP-70, which triggers autophosphorylation on regulatory residues (T180-X-Y182) followed by activation of p38 [26]. JNK activation is likely mediated by PKCθ and the CARMA3-BCL10-MALT1 (CBM) complex upon activation of TCR proximal signaling. The BCL10 oligomers in

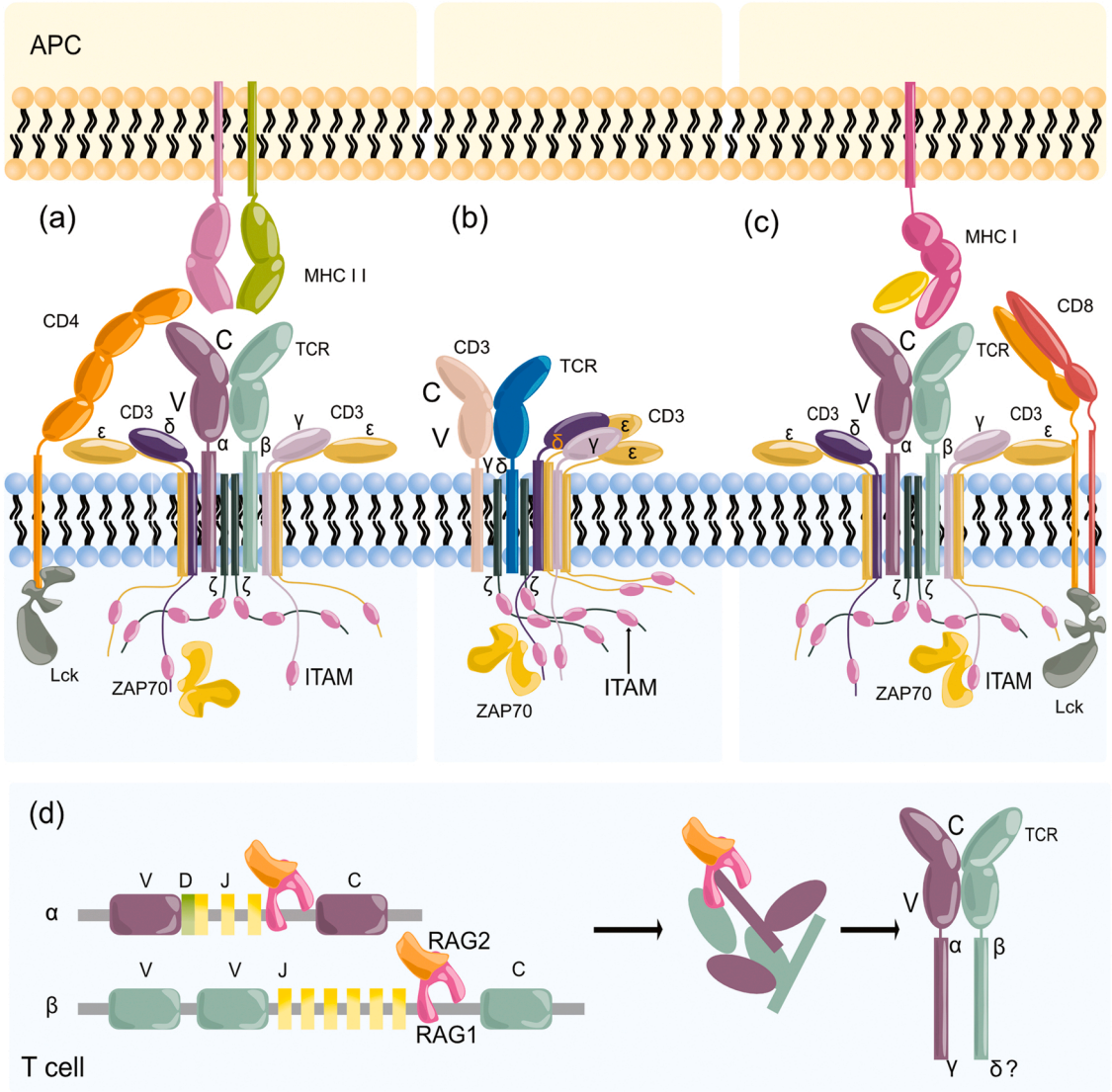

Fig. 1. Structure of the TCR complex. The TCR complex is composed of two TCR chains (αβ or γδ), six-cluster differentiation 3 (CD3) chains, and the coreceptors CD4 or CD8. The TCR in $CD4^+$ T cells recognizes MHC class II molecules expressed in antigen-presenting cells. In contrast, the TCR in $CD8^+$ T cells receives the stimulation of MHC I molecules expressed in nucleated cells. Lck-loaded CD4 or CD8 molecules phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMS) in CD3 chains, essential for signal transduction mediated by the TCR-CD3 complex. After ITMAS is phosphorylated, ZAP-70 interacts with ITMAS phosphotyrosine sites and mediates additional tyrosine phosphorylation. (a) The transmembrane structure of αβTCR complex in $CD4^+$ T cells. (b) The transmembrane structure of γδTCR complex. (c) The transmembrane structure of αβTCR complex in $CD8^+$ T cells. (d) Recombination-activating genes (RAGs) of T cells. *Rag1* and *Rag2* encode the RAG1 and RAG2 recombinases expressed in developing lymphocytes. With the help of *Rag2*, *Rag1* recognizes and cuts the TCR gene. The *RAG1/2* complex is also involved in polymerizing the TCR polypeptide chains. RAG1 and RAG2 facilitate the assembly of the V domain from the gene segments that serve as the antigen recognition site. Abbreviations: APC, antigen-presenting cells; TCR, T cell receptors; MHC, major histocompatibility complex; ITAMS, immunoreceptor tyrosine-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; ZAP-70, the tyrosine-protein kinase ZAP-70.

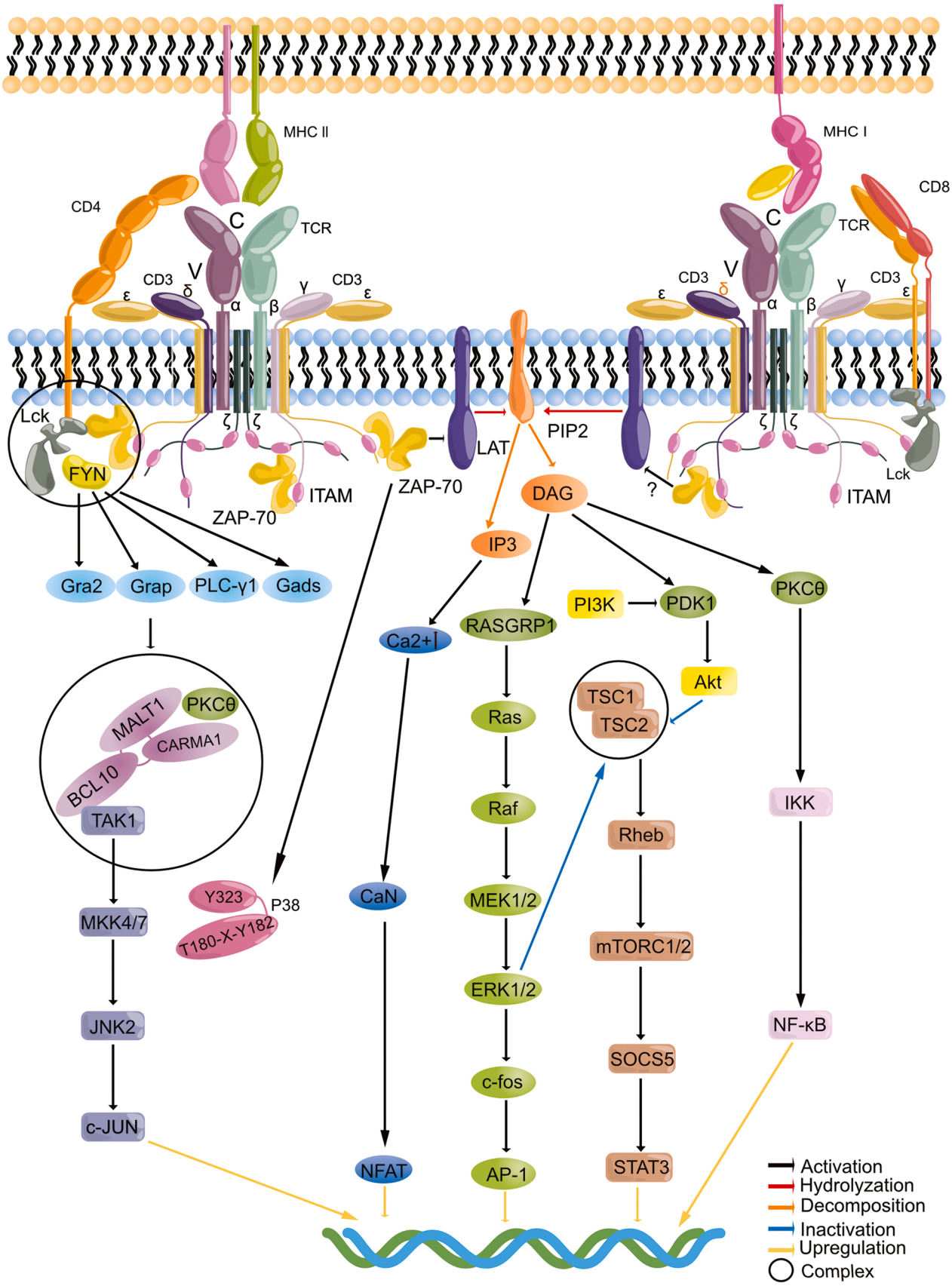

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Fig. 2. TCR signal transduction. The binding of TCR to MHC molecules triggers multiple signaling cascades. Several PTKs, including Lck, Nck, Fyn, ZAP-70, ITAMs, etc., are involved in the proximal signaling of TCR. Phosphorylation in Lck, Fyn, and ZAP-70 leads to a downstream signaling cascade by activating PLC-γ1, Grb2, Grap, Gads, etc. TCR-triggered distal signaling cascades include the Ca^{2+}-calcineurin-NFAT, PKCθ-IKK-NFκβ, RASGRP1-RASERK1/2, TSC1/2-mTOR, and P38 and JNK pathways. After being phosphorylated by ZAP-70, LAT will activate PLC-γ1 and activated PLC-γ1 will hydrolyze membrane-bound PIP2 into DAG and IP3. The membrane-bound DAG activates PKCθ, RASGRP1, and PDK1-mediated pathways. In contrast, IP3 triggers the activation of a $Ca2^{+}$-dependent calcineurin NFAT pathway. Furthermore, after participation in TCR, both the DAG-RASGRP1-RAS-ERK1/2 and PI3K-AKT pathways can activate mTORC1 and mTORC2. P38 activity is activated in a nonclassical pathway, probably independent of MAPK cascades. JNK is likely activated through PKCθ and the CARMA3-BCL10-MALT1 (CBM) complex after the proximal TCR signaling is activated. These signaling pathways are critical for T cell activation, differentiation, or migration. This knowledge was obtained primarily from αβ T cells. It is prudent to apply these theories to other T subsets (the meaning of the symbol '?' in this figure). Abbreviations: TCR, T cell receptors; MHC, major histocompatibility complex; ITAMS, immunoreceptor tyrosine-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; ZAP-70, the tyrosine-protein kinase ZAP-70; Fyn, the tyrosine-protein kinase Fyn; LAT, linker for T cells; PLC-1, phospholipase C gamma1; Grb2, growth factor receptor bound protein 2; Grap, adapter protein associated with Grb2; Gads, Grb2-associated adapter downstream of Shc; NFAT, nuclear factor of activated T cells; PKCθ, protein kinase C-θ; IKK, inhibitor of NF-kappa B kinase; NF-κB, nuclear factor kappa-B; RASGRP1, RAS guanyl releasing protein 1; RASERK1/2, RAS-extracellular regulated protein kinases 1/2; TSC1/2-mTOR, mammalian target of rapamycin; P38, p38 Mitogen-activated protein kinases; JNK, c-Jun N-terminal kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; DAG, diacylglycerol; IP3, inositol-3-phosphate.

the CBM complex can recruit TAK1 (MAP3K7), MKK7 (MAP2K7), and JNK2, which leads to the activation of JNK [26].

2.3. The co-signaling molecules of the TCR

T cell activation (survival), proliferation, differentiation, or migration is determined by the interaction of TCR with antigen-binding MHC and by combining co-stimulatory or co-inhibitory signals, which can amplify or weaken the initial signal triggered by TCR [18]. Positive co-stimulating molecules provide a second signal to induce the full activation of T cells. In contrast, co-inhibitory molecules negatively regulate or terminate the immune response, prevent overreaction-induced tissue damage, and maintain the stability of the internal environment [18]. According to the structural characteristics of the co-stimulatory or co-inhibitory molecules, the co-signaling molecules of TCRs are classified into the following four families: immunoglobulin (Ig) superfamily, tumor necrosis factor-tumor necrosis factor receptor (TNF-TNFR) superfamily, T cell immunoglobulin and mucin (TIM) superfamily, and integrin family [33,34]. They are also receptors on the surface of activated T lymphocytes.

The Ig superfamily, including CD28, inducible co-stimulatory T cells (ICOS), CD2, and CD84, and the members of the TNF-TNFR superfamily, including the glucocorticoid-induced tumor necrosis factor receptor (GITR), CD27, the ligand of tumor necrosis factor receptor superfamily member 4 (OX40), member of the TNFR superfamily (TNFRSF9, 4–1BB, CD137), CD40 Ligand (CD40L), and Fas (CD95), are all co-stimulatory molecules [18,35–41]. In addition, lymphocyte function-associated antigen (LFA), attributed to the integrin family, and T cell immunoglobulin and mucin domain-containing protein 1 (TIM-1), belonging to the TIM family, are also co-stimulatory molecules of TCR [35,41–44]. However, Ig superfamily members, including cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed death-1 (PD-1), lymphocyte activation gene 3 (LAG-3), T cell Ig and ITIM domain (TIGIT), and B and T lymphocyte attenuators (BTLAs), are co-inhibitory molecules [18,33,45]. Furthermore, T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), belonging to the TIM family, and tumor necrosis factor receptor 2 (TNFR2), belonging to the TNF-TNFR superfamily, are also co-inhibitory molecules [26,46]. Recent reviews have well summarized the characteristics of the ligands, downstream signals, and biological properties of these co-signaling molecules expressed on T cells [26,45]. Here, we briefly summarize their ligands and their synergistic effects with TCR in Fig. 3.

3. TCR signaling and Th response

The TCR signaling pathways are critical for differentiating functional T cell subsets [47,48]. After TCR stimulation, naive $CD8^{+}$ T lymphocytes can differentiate into CTL and memory T cells, which are an essential source of IFN-γ [49]. Furthermore, with stimulation of TCR and its co-stimulatory receptors, $CD4^{+}$ T cells also differentiate into subtypes, including Th1, Th2, Th9, Th17, Th40, Treg, etc. These lymphocytes can produce specific cytokines and perform their biological functions [47]. Factors that can influence the TCR signal's intensity include the TCR's affinity, the antigen dose, and the duration of TCR-pMHC interactions [50].

Furthermore, co-signaling molecules may also influence the intensity of the TCR signal [51]. Although TCR signaling may not affect the end-stage cell lysis capacity of $CD8^{+}$ T cells in *vitro* [52], the strength and duration of the TCR signal profoundly influence the development fate of $CD4^{+}$ T cells in vivo [53]. Powerful and persistent TCR signaling induced by a higher dose of antigens drives FOXP3 Treg cell development [54,55]. Higher affinity TCR promotes Th1 differentiation, whereas lower affinity TCR leads to polarization toward Th2 differentiation [51]. Similarly, low doses of antigens promote Th2 differentiation, while high amounts of antigens favor Th1 differentiation [56]. The differentiation or polarization of $CD4^{+}$ lymphocytes also depends on stimulating some cytokines and the increased expression of specific transcription factors [51,57]. In the following, we will discuss how TCR and its co-stimulatory or co-inhibitory factors influence the differentiation or polarization of $CD4^{+}$ lymphocytes by regulating the expression of the corresponding cytokines and transcription factors (Table 1).

Th1: Th1 cells enhance and promote the elimination of specific intracellular pathogens [58]. Th1 differentiation requires the stimulation of interferons (IFN-γ) and interleukin (IL)− 12. IFN-γ and IL-12 can promote *T-bet* transcription by increasing STAT1 expression, leading to differentiated $CD4^{+}$ cells in the Th1 direction [13]. In this process, IFN-γ can initiate communication coordination between STAT1 and TCR [47]. By strengthening the intensity of the TCR signal, the co-stimulatory molecule promotes Th1 differentiation by activating the mTOR1 pathway through the PI3K-Akt axis [34]. In addition, CD28 may also favor Th1 differentiation by increasing the activity of other co-stimulatory receptors, such as ICOS [34]. In the absence of CD28, another co-stimulatory molecule, LFA-1, has been shown to promote Th1 differentiation by inducing *T-bet* while downregulating GATA-3 and CD226 signaling [34]. In addition, CD266 also promotes the Th1 response, as it is always expressed in Th1 cells, while TIGIT and TIM-3 can inhibit Th1 differentiation [34].

Th2: STAT6 mediated by the interaction of TCR signals and IL-4 receptor signals promotes Th2 differentiation. It upregulates the expression of the transcription factor *GATA-3*, thus inducing Th2 differentiation and improving parasite clearance [58]. Sustained CD28 co-stimulation plays a vital role in Th2 differentiation by enhancing IL-4 reactivity [34]. In addition, CD28 also promotes Th2 development by increasing the activity of ICOS. Studies have indicated that Th2 cells express significantly higher levels of ICOS than Th1 cells and that blocking ICOS reduces the production of IL-4 and IL-10 and inhibits Th2 cell differentiation [34]. Furthermore, OX40 is essential for producing IL-4 in T cells and favors Th2 differentiation [58]. TIM-1 is constitutively expressed in $CD4^{+}$ T cells and DCs [34]. Among them, the TIM-1 signal in DCs can upregulate co-stimulating molecules and pro-inflammatory

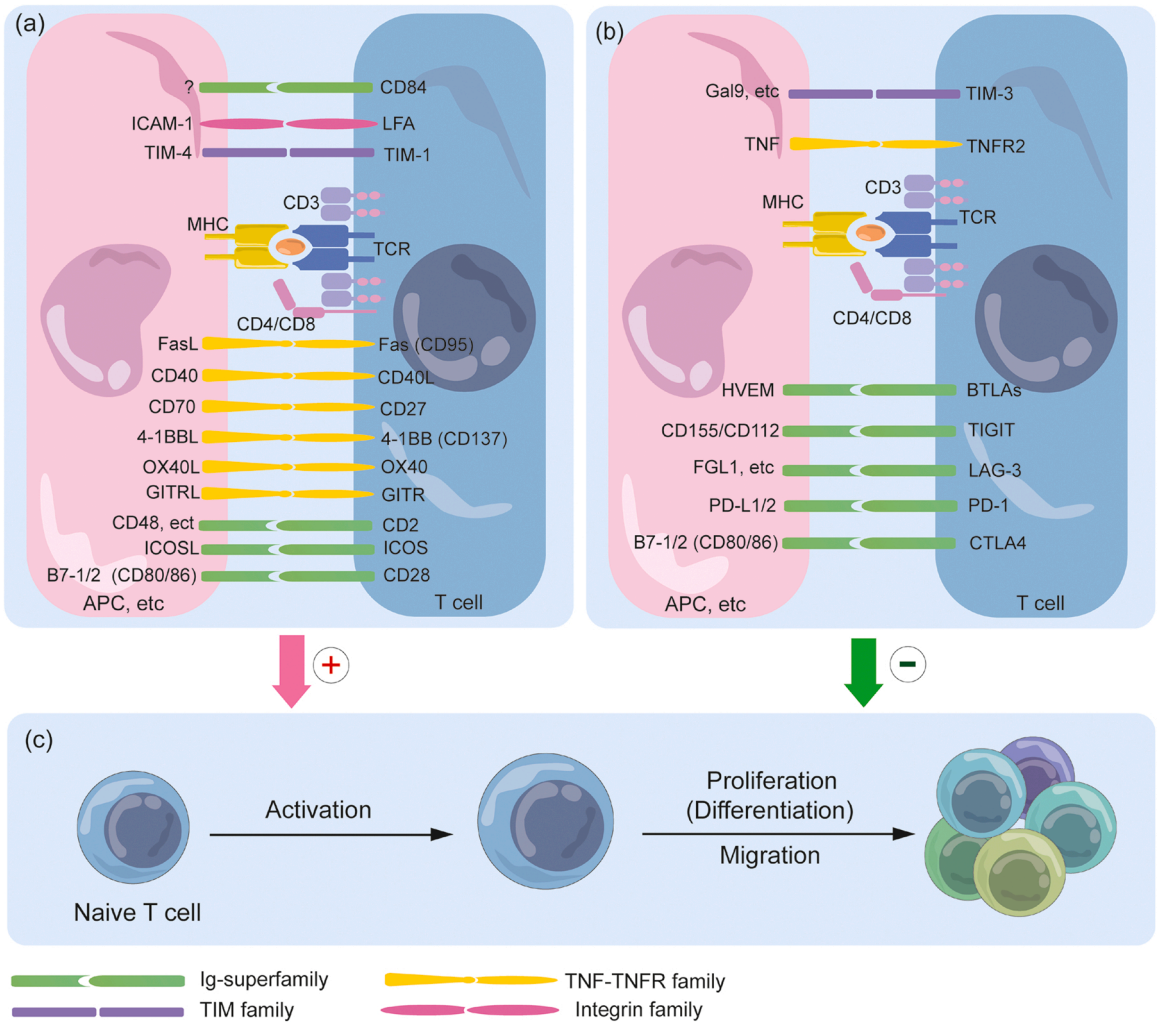

Fig. 3. The co-signaling molecules of TCR and their ligands in T cells. Co-stimulatory molecules (a) and co-inhibitory molecules (b) attributed to the Ig superfamily, the TNF-TNFR superfamily, the TIM family, and the integrin family are expressed in T cells. When communicating with the ligands expressed by APCs, endothelial cells, etc., they can amplify (+) or weaken (-) the initial signal triggered by the TCR (c). Positive co-stimulating molecules, including CD28, ICOS, GITR, etc., provide a second signal to induce the full activation of T cells. On the contrary, co-inhibitory molecules, including CTLA4, PD-1, LAG-3, etc., negatively regulate or terminate the immune response, prevent overreaction-induced tissue damage, and maintain the stability of the internal environment. They are crucial for T cell activation (survival), proliferation, differentiation, or migration. Without these co-stimulations, T cells will die or become anergic. As critical immune checkpoints, these molecules have gained considerable attention as targets of immunomodulatory therapy. Abbreviations: APC, antigen-presenting cells; TCR: T cell receptors; MHC, major histocompatibility complex; ICAM-1, intercellular adhesion molecule-1; LFA, lymphocyte function-associated antigen; TIM1, T cell immunoglobulin and mucin domain-containing protein 1; TIM-4, T cell immunoglobulin and mucin domain-containing protein 4; FasL, Fas ligand; 4–1BB (CD137), TNFR superfamily member (TNFRSF9); 4–1BBL, the ligand of TNFR superfamily member (TNFRSF9, CD137); OX40, tumor necrosis factor receptor superfamily member 4; OX40L, OX40 ligand; GITR, glucocorticoid-induced tumor necrosis factor receptor; GITRL, GITR ligand; ICOS, inducible T-cell costimulatory; ICOSL, ICOS ligand; Gal9, galectin-9; TNF, tumor necrosis factor-alpha; TNFR2, tumor necrosis factor receptor 2; HVEM, herpesvirus entry mediator (TNFRSF14, CD270); BTLAs, B and T lymphocyte attenuators: TIGIT, T cell Ig and ITIM domain; FGL1, fibrinogen-like protein 1; LAG-3, lymphocyte activation gene 3; PD-1, programmed death-1; PD-L1/2, programmed death ligand 1/2; CTLA4, cytotoxic T-lymphocyte-associated protein 4; Ig superfamily, immunoglobulin superfamily; TNF-TNFR superfamily, tumor necrosis factor-tumor necrosis factor receptor superfamily; TIM family receptors, T cell immunoglobulin and mucin superfamily.

cytokines, thus promoting effector T-cell responses while inhibiting FOXP3$^+$ Treg reactions [35].

Th9: The Th9 immune response occurs in various immune-related diseases [59]. By increasing the expression of STAT6, stimulatory cytokines (TGF-β and IL-4) are essential for differentiating the Th9 immune response. In this process, the transcription of *Pu.1* and *IRF4* will increase. In mice, TGF-β and IL-4, in the presence of TCR and CD28 signals (APCs, plate-bound anti-CD3 plus anti-CD28 or anti-CD3/CD28 coated microbeads), are necessary and sufficient to induce the differentiation of naïve CD4$^+$ CD25$^-$T cells into Th9 cells [60]. Furthermore, the OX40 ligand (OX40L) and TNF-like factor 1 A (TL1A) may also modulate the potential for in *vitro* differentiation to Th9 in both mouse and human CD4$^+$ T cells [60].

Th17: The combined effects of IL-6 and TGF-β are responsible for inducing naïve CD4$^+$ T cell differentiation into Th17 cells [61]. In the presence of TGF-β, STAT3 is activated, stimulating the expression of the nuclear receptor *RORgt* (retinoic acid receptor-associated orphan receptor gt) and leading to Th17 differentiation [61]. Th17 cells activated by TGF-β and IL-6 can produce IL-17 and IL-21. Like Th1 differentiation, Th17 cells develop after weak or intense antigenic stimulation in TCR, and CD28 favors their differentiation [50,62]. Perhaps the primary function of CD28 in Th17 differentiation is its ability to induce ICOS [63]. ICOS strongly enhances Th17 differentiation in human CD4$^+$ T cells in *vitro* [47]. However, there is also evidence that Th17 cell differentiation is independent of ICOS. At the same time, ICOS promotes the activation of c-Maf, increasing IL-23R expression and IL-21

Table 1
TCR signaling and $CD4^+$ T cell response.

T cell response	Differentiation cytokines	Signal transducers and transcription activators	Transcription factors	TCR signaling involved	Co-stimulatory molecules involved	Co-inhibitory molecules involved	References
Th1	IFN-γ, IL-12	STAT 1	*T-bet*	Strong TCR stimulation	CD28, ICOS, LFA-1, and CD266	TIGIT and TIM-3	[13,34,47,58]
Th2	IL-4	STAT6	*GATA-3*	Weak TCR signals	CD28, ICOS and OX40	TIM-1	[34,35,58]
Th9	TGF-β, IL-4	STAT6	*Pu.1 and IRF4*	N/A	CD28	N/A	[51,57]
Th17	IL-6, TGF-β	STAT3	*RORgt*	TCR signal strength required remains unclear, the TCR may only play a secondary, context-dependent role in directing Th17 differentiation	CD28, ICOS	PD-1	[47,50,61–63]
Treg	IL-6 and TNF	STAT5	*Foxp3*	Strong TCR stimulation promotes the development of Treg cells	CD28, GITR	CTLA-4, TIM-3, PD-1	[7,35,47,64]

Abbreviations: N/A, not available; IL-12, interleukin-12; IL-4, interleukin-4; IL-6, interleukin-6; TGF-β, transforming growth factor-β; IFN-γ, interferon-gamma; Treg cells, regulatory T cells; Th1 cells, helper T1 cells; Th2 cells, helper T2 cells; Th9 cells, helper T9 cells; Th17 cells, helper T17 cells; TCR, T cell receptors; RORgt, retinoic acid receptor-associated orphan receptor gt; ICOS, inducible T-cell costimulatory; TIGIT, T cell Ig and ITIM domain; GITR, glucocorticoid-induced tumor necrosis factor receptor; LFA-1, lymphocyte function-associated antigen-1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed death-1; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; TNF, tumor necrosis factor alpha; FOXP3, forkhead box protein P3; Tim-1, T cell immunoglobulin and mucin domain-containing protein 1.

production, allowing paracrine and autocrine expansion of the Th17 response [61]. In addition to co-stimulatory molecules, co-inhibitory molecules such as PD-1 also regulate Th17 differentiation [61]. However, CD28 and ICOS contradict this effect [47].

Treg: Treg cells are essential for lymphocyte homeostasis and immune tolerance. In the presence of IL-6 and TNF, its differentiation depends on STAT5 activation and *Foxp3* transcription [47,64]. Furthermore, Treg cell differentiation also requires TCR and TGF-β receptor (TGF-βR) signaling. Combined with the effects of the TGF-β-induced smad-dependent signaling pathway, *Foxp3* transcription is triggered by TCR-induced transcription factors, including NFAT, AP-1, and NF-κB [47]. Furthermore, some co-stimulatory or co-inhibitory molecules, such as CD28, CTLA-4, PD-1, TIM-3, GITR, etc., can positively or negatively regulate Treg cell differentiation [7,35].

4. T-cell remolding and invasion in stroke

4.1. TCR gene transcripts after stroke

TCR repertoire analysis may help predict the therapeutic efficacy of some interventions and the prognosis of infectious diseases, autoimmune diseases, cancers, etc. [65–67]. Additional evidence also indicates that analysis in the broader Epstein-Barr virus-specific TCR repertoire could help identify the specific etiology of patients with multiple sclerosis [68]. Although previous research has illustrated that the TCRβ locus is present in the murine CNS and its expression is dynamically regulated during development [69], only a few studies have detected changes in gene expression of different TCR chains after stroke.

In a study on subarachnoid hemorrhage (SAH), investigators evaluated and compared the immune repertoire of TCR in patients with good and poor grades to elucidate T cell immunology. The TCR β chain (TRB) CDR3 repertoire in the peripheral blood was dynamic after SAH. Poor-grade SAH patients showed reduced clonality and increased diversity and CDR3 length. Furthermore, TRBV19–01/TRBJ02–04 and TRBV28–01/TRBJ02–04 were the V-J pairs that raised the most and decreased the most, respectively, at follow-up 7 days after onset compared to admission and compared to good-grade SAH. The VJ pairs with the highest increase and decrease in patients with poor-grade SAH were TRBV28–01/TRBJ02–06 and TRBV30–01/TRBJ02–04, respectively. It suggests that monitoring the TRB CDR3 repertoires helps better understand the adaptive immune response and identify therapeutic targets in patients with SAH [70].

Another study in SAH evaluated the compositions and variations of the repertoire between admission and the delayed period of cerebral ischemia for patients with severe delayed cerebral ischemia and patients without severe delayed cerebral ischemia. Among 728 pairs of annotated VJ genes, the relative frequencies of two pairs of VJ were different at the beginning of delayed cerebral ischemia than at admission, with T cells increasing by more than 15%. These findings suggest that changes in the repertoires of TRB CDR3 can facilitate T cell proliferation and serve as biomarkers to identify severe delayed cerebral ischemia in patients with SAH [71].

In peripheral blood from patients with acute intracerebral hemorrhage (ICH), a large number of T cell-specific genes were highly enriched, including 54 TCR genes that are involved in T cell activation and co-stimulation, CD28 signaling in Th cells, ICOS-ICOS ligand (ICOSL) signaling in Th cells, CTLA4 signaling in CTLs, CTL-mediated apoptosis of target cells, Th1 and Th2 pathways [72].

Another study detected and compared the differences in the architecture of the TCR transcriptome in peripheral blood between patients with ischemic stroke, patients with hemorrhagic stroke, and healthy controls. TCR gene transcripts were only differentially expressed in ICH but not in ischemic stroke, compared to healthy controls. Specifically, compared to healthy controls, the 33 differentially expressed TCR gene transcripts encode the alpha chain (TRA) decreased in patients with ICH. Furthermore, the expression of many TCR transcripts was time-dependent, with 55 differentially expressed TCR gene transcripts negatively regulated within 24 h after ICH [73].

Additional research also showed that several overrepresented T cell pathways were suppressed in the periphery, including PKCθ signaling in T lymphocytes, CD28 signaling in Th cells, ICOS-ICOSL signaling in Th cells, calcium-induced apoptosis of T lymphocytes, and Th1 pathway [74]. Furthermore, an animal study has illustrated that the TCR repertoire of brain Treg cells was much less diverse than that of splenic Treg cells after ischemic stroke [75]. In addition, TCR in Treg cells may be necessary to regulate the Treg response [75].

The TCR repertoire is flexible and adapted to different circumstances. Older people have a lower diversity of TRA and TRB than younger people [76]. The TCR immune repertoire, such as clonality, diversity, and rearrangement, provides a research approach to understanding T cell immunology under different pathologic conditions. Exploring changes in TCR gene transcripts in peripheral blood and damaged brain tissue and evaluating its clinical implications should be a priority in stroke research.

4.2. T cell frequency changes in Stroke

Acute stroke can lead to a decrease in the number of T lymphocytes and an increase in the number of Treg cells in the periphery. Different T lymphocyte subsets, including Th cells, Treg cells, etc., rapidly infiltrate the lesioned brain after stroke [6]. They may enter the ischemic or hemorrhagic brain through three pathways: the altered blood-brain barrier (BBB), the choroidal plexus, and the meninges [19,77,78].

Evidence has indicated that the number of infiltrating T lymphocytes increases between days 2–4, which stays the same until day 7 in ischemic tissue and peaks at day 4 in the infarct core after ischemic stroke in animals [6,10,79]. However, contrary to the dynamic changes in the total number of T lymphocytes illustrated above, some studies reported that the number of Th cells and CTL in the ischemic brain increased gradually and peaked at 1–2 weeks in animals [79,80]. On the other hand, $FOXP3^{+}$ Tregs recruited in and around the infarct area persistently increased from days 3–14 and remained high for 2 months [81]. Furthermore, Th17 cells also increased gradually from day 1 to day 3 in the ischemic brain [82]. Although there is a study that observed the infiltration of γδT cells in the ischemic brain of rats, some evidence obtained from ischemic stroke suggests that TCRγδ T cells do not enter the brain but are restricted instead to the pia mater in mice [83,84]. The dynamic changes of αβT cells and iNKT cells in the ischemic brain are unknown.

Regarding ICH, T lymphocyte infiltration peaked in the brain parenchyma around the hematoma on day 5 after ICH [85]. The number of infiltrated Th1 cells peaked on days 4–5, while Treg cells peaked on days 5–7 in the ICH brain of animals [85–87]. Furthermore, the number of γδT cells increases significantly in peripheral blood or the hemorrhagic brain on day 3 after ICH in rats [88]. Although our previous research showed that Th17 cells but not αβT cells or CTL counts increased remarkably in the peripheral blood of ICH patients within 30 h after symptom onset [11], few studies have detected dynamic changes of αβT cells, CTL, iNKT cells, and Th17 cells in the hemorrhagic brain of ICH animals or patients.

5. TCR function in stroke

5.1. T-cell activation manners in stroke

The innate immune response mediated by microglia recruits T lymphocytes from the circulation to the ischemic or hemorrhagic brain [13,89]. After being activated, T lymphocytes exert bidirectional modulation of stroke pathophysiology, as they have multiple subpopulations illustrated above [90]. Evidence suggests that Th, CTL, TCR αβT, TCR γδT, and iNKT cells exert detrimental roles, while Treg cells show a neuroprotective effect in the pathophysiology of acute stroke [6]. Further exploration of the mechanisms in the activation of T lymphocytes and their subpopulations may help to find novel immunomodulatory strategies to treat stroke [78].

T-cell activation in the post-stroke inflammatory response is antigen-independent or antigen-dependent (innate or adaptive) (Fig. 3). Using mice lacking the *RAG1* gene or the accessory molecules for TCR stimulation ($CD28^{-/-}$, $PD1^{-/-}$, $B7\text{-}H1^{-/-}$ mice), a study showed that T cells play a detrimental role within 24 h after ischemic stroke, suggesting that T lymphocyte activation is not specific to antigens at this stage [91]. Additionally, although HMGB1 (high mobility group box 1 protein) can act as a potential TIM-3 ligand, pro-inflammatory mediators, including cytokines, HMGB1, or TLR ligands (toll-like receptors), can also result in TCR-independent activation of lymphocytes in human stroke and experimental stroke models [18,20,78,92].

However, there is evidence for antigen dependence. By detecting the pMOG35–55-specific T-cell response with Elispot assay, additional research has observed the antigen-specific T-cell response in the ischemic brain 14 days after acute stroke [92,93]. Additionally, indirect evidence also suggests that antigen-specific T lymphocytes are critical for CNS damage. Neuronal and myelin antigens are present in the lymph nodes and palatine tonsils of stroke patients [94]. Specifically, a potent T lymphocyte response to MBP is associated with a worse outcome, while the induction of tolerance against MBP decreases the infarct volume in animals [20].

Besides, research on the repertoire of TCR after ischemic stroke in mice further validated the relationship between functional changes of TCR and Treg response after ischemic stroke. The four TCRα CDR3 sequences covered more than 5% of the entire sequence of next-generation TCR sequencing analyses of 42 combined mice, suggesting that there is recognition of a specific antigen-TCR in brain Treg cells [75]. Furthermore, Treg cells isolated from ischemic mice accumulate in the brain more efficiently than Treg cells from sham mice, suggesting that antigen recognition is vital for expanding Treg cells in the brain [75].

In particular, in a mouse model of focal cerebral ischemia, the number of myelin oligodendrocyte glycoprotein (MOG)-specific T cells increases in the spleen, with increased flow of MOG-specific T cells into the brain [95]. In mice expressing Nur77 under a GFP promotor, an early and immediate gene is expressed after TCR activation. The antigen-specific T-cell response in the spleen of these mice starts at 16 h, decreases on day 2, then gradually increases and peaks on day 4 after experimental ischemic stroke. Furthermore, the antigen-specific T-cell response increases on days 2–7 in peripheral blood and ischemic brain tissues [20]. Therefore, the investigators speculated that antigens in the periphery might stimulate T lymphocytes and then return to the brain after ischemic stroke [20]. As peripheral blood lymphopenia links with systemic immunosuppression and infectious complications [6], the antigen-specific T cell response may also profoundly influence the frequency and activation of T lymphocytes in the peripheral blood or CNS, which then affects the prognosis of ischemic stroke.

Currently, few studies have explored the antigen-specific T-cell response after ICH. Furthermore, no studies have identified antigens involved in T lymphocyte activation in the periphery and the CNS after stroke. Therefore, it is critical to explore further the antigens presented by APCs that can trigger or inhibit T lymphocyte activation through TCR and its downstream signals in the periphery and CNS after an ischemic and hemorrhagic stroke. Furthermore, as mentioned above, to further explore the reasons for reducing the frequency or function of circulating lymphocytes in stroke [6], it is also crucial to investigate whether antigens leaked from the lesioned brain to the periphery favor systemic immunosuppression by communicating with TCR in stroke. Additional research on this may benefit the development of potential targets for immunoregulatory therapy after stroke.

5.2. The roles of the TCR complex in stroke

The recombinant TCR ligand (RTL) targeting brain-reactive T cells can inhibit T cell-mediated inflammation in the CNS without inducing general immunosuppression [96]. Previous animal studies have examined its role in ischemic but not hemorrhagic stroke (Fig. 4).

In mice with ischemic stroke, treatment with the RTL551 molecule (I-A(b) linked to the MOG-35–55 peptide reduced the size of the lesion by approximately 50%, inhibited T lymphocyte accumulation, particularly macrophages/activated microglial cells, and DCs, and mitigated splenic atrophy [97]. Another animal study also showed that RTL551 effectively reduces infarct size and infiltration of harmful immune cells [96].

To enhance clinical significance, researchers determined the efficacy of humanized RTL1000, which contains a human MHC moiety (HLA-DR2) covalently linked to a human myelin peptide (hMOG-35–55) in experimental stroke in humanized DR2-Tg mice that express human TCR [97]. They found that RTL1000 protects against ischemic injury measured 24 or 96 days after stroke and improves long-term cognitive function 28 days after ischemic stroke in young male and female DR2-Tg mice [97–99]. They also confirmed that the combination of RTL1000 with rt-PA does not alter the ability of RTL1000 to reduce infarct size

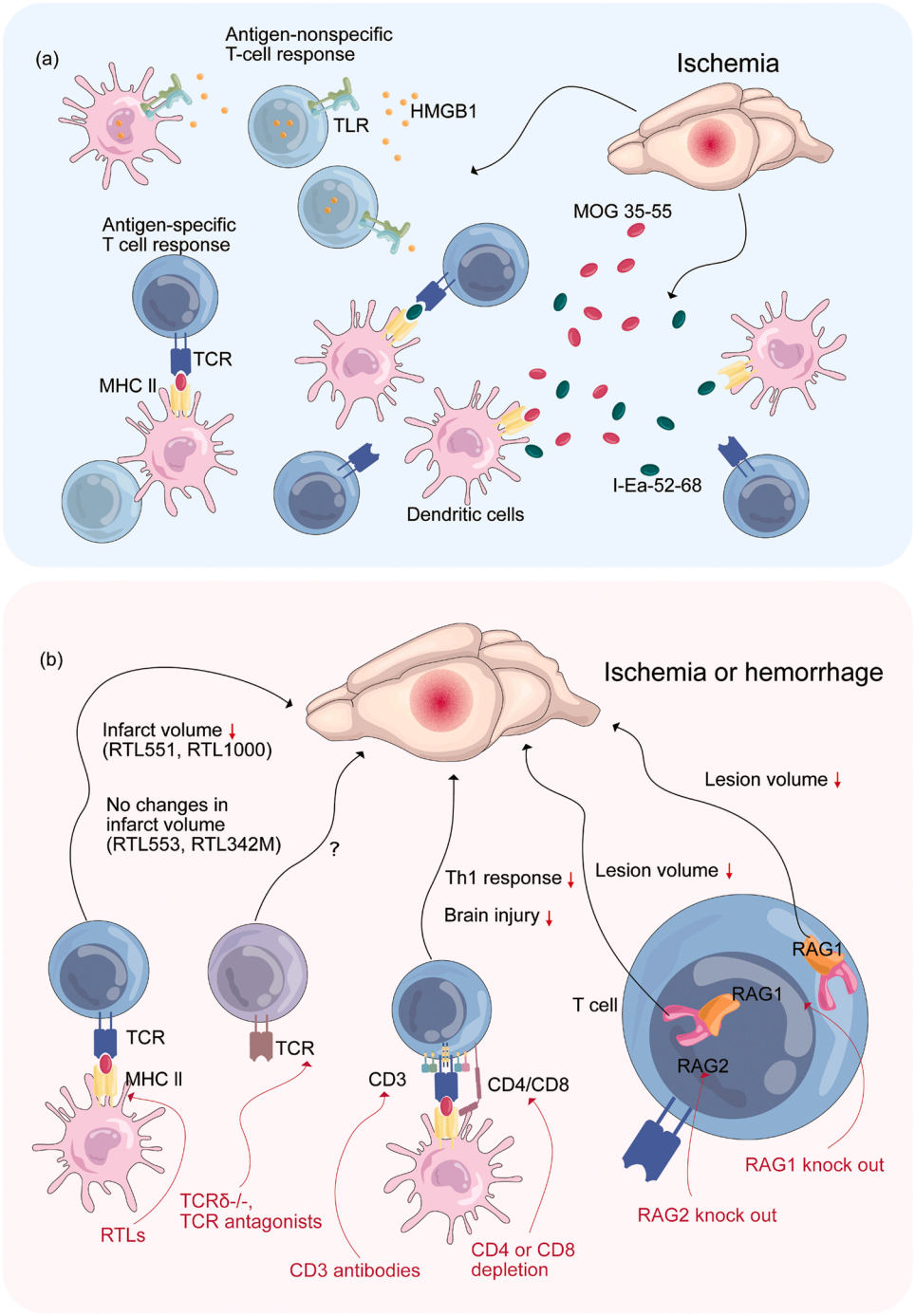

Fig. 4. The activation and function of TCR in stroke. T cells and APCs infiltrate the lesioned brain after the stroke onset. (a) T cell activation in ischemic stroke is antigen-dependent and -independent. Proinflammatory mediators such as HMGB1 or TLR can result in TCR-independent activation of T lymphocytes in animals and patients with ischemic stroke. Antigen-specific T-cell response also exits the ischemic brain. APCs such as DCs, macrophages, and B cells present MOG35–55 in T cells and activate T cells in the ischemic brain. How T cells are activated in ICH is unknown. (b) The TCR complex and its co-receptors are critical for brain injury after stroke. Treatment with the recombinant TCR ligand (RTL) linked to the MOG-35–55 peptide can reduce infarct size after ischemic stroke. Depletion of CD3, CD4, or CD8 can inhibit Th1 response or alleviate brain injury after hemorrhagic or ischemic stroke. Furthermore, knockout in Rag1 or Rag2 also provides neuroprotective effects. Although studies in other fields found that knocking out TCRδ or blocking TCR with TCR antagonists can inhibit T cell activation, their roles have not been investigated in stroke (the meaning of the symbol '?' in this figure). Abbreviations: APC, antigen-presenting cells; TCR, T cell receptors; MHC, major histocompatibility complex; HMGB1, High Mobility Group Protein 1; TLR, Toll-like receptors; RTL, recombinant TCR ligand; MOG, myelin oligodendrocyte glycoprotein; I-a52–68, I-a52–68 peptide.

[100,101].

However, with the same MHC moiety as RTL551 but linked to a non-neuroantigen peptide (I-Ea-52–68), RTL553 did not affect the infarct size in C57BL/6 mice [96]. Similarly, treatment with RTL342M, which has the same mMOG-35–55 peptide as RTL551, but a different MHC II moiety (HLA-DR2), did not reduce the infarct size [96]. Other studies on RTL further verified the role of CNS-specific antigens in T lymphocytes through TCR after ischemic stroke [102,103]. These studies suggest that modulation of the T lymphocyte response with RTL could be a potential strategy to treat stroke. However, the brain penetration ability of these RTLs and their effects in ICH may warrant additional verification.

Alternatively, the formation of the TCR-CD3 complex is essential to initiate the downstream signaling of TCR. However, very few studies have evaluated the influence of CD3 antagonism or depletion on the T lymphocyte response after ischemic stroke (Fig. 4). In mouse hemorrhagic stroke, anti-CD3 monoclonal antibodies alleviate Th-cell activation and inhibit Th1-type cytokine production, including IL-1β and IFN-γ [15]. Furthermore, some studies evaluated the roles of TCR co-receptors, including CD4 and CD8, in ischemic stroke (Fig. 4). They found that CD4 and CD8 depletion with specific antibodies inhibits the lymphocyte-related immune-inflammatory response and alleviates brain injury after ischemic stroke [16,104–106]. However, the effects of CD4 or CD8 deficiency on ICH outcomes warrant further investigation.

Additional studies on molecules that can regulate the function of TCR provide indirect evidence of the role of TCR in stroke (Fig. 4). The N-terminal region of RAG1 is essential for regulating the recombination of

V(D)J and lymphocyte development through multiple pathways, including controlling the balance between short- and long-range recombination [107]. One study showed that the infarct volume in RAG1$^{-/-}$ mice (without mature T cells and B cells) is smaller than in wild-type (WT) mice 1 day after tMCAO [91]. Furthermore, the inflammatory response in the hemorrhagic brain also decreases in mice with acute ICH [108].

In contrast, by promoting the inflammatory response via the FasL/PTPN2/TNF signaling pathway, the adoptive transfer of CD3$^+$CD4$^-$CD8$^-$ double negative (DNT) cells from WT to Rag1$^{-/-}$ mice increases infarct size. In addition, it worsens neurological severity scores and motor deficits [109]. Additional studies in *Rag1*$^{-/-}$ mice further demonstrate that the adoptive transfer of CTL, CD8$^+$ T lymphocytes, or NK cells from WT mice to Rag1$^{-/-}$ mice significantly increases infarct volume 7 days after pMCAO [110,111].

Similarly, as in RAG1$^{-/-}$ mice, there is no activation or infiltration of T cells into the brain during the chronic stroke phase in Rag2$^{-/-}$ OTII transgenic mice, which express only ovalbumin-specific TCR [75]. With Rag2$^{-/-}$ OTII transgenic mice, additional evidence has indicated that *Rag*2 deficiency also decreases infarct volume by inhibiting lymphocyte trafficking after stroke in mice [112,113]. Furthermore, the adoptive transfer of Treg cells to Rag2$^{-/-}$ and Cd3e$^{-/-}$ mice lacking in T cells suppresses excessive astrogliosis and the expression of neurotoxic markers after ischemic stroke. The results suggest that brain-specific Treg cells may provide a solid therapeutic strategy to alleviate neurologic deficits in stroke and other brain diseases [75].

Although mice deficient in γδ T cells showed better functional recovery after spinal cord injury, no studies have directly evaluated the function of TCR in animals deficient in TCR [114]. Some specific antagonists of TCR, including TCR1672 and AX-024, have recently been developed [115]. With these new compounds, it is reasonable to explore their function on the response of T lymphocytes associated with stroke (Fig. 4).

6. TCR and Th response in stroke

In the brain lesion, CD4$^+$ T cells account for a large proportion of infiltrated immunocytes [15,104]. Most Th responses associated with CD4$^+$ T cells are present after stroke, including Th1, Th2, Th17, Th40, Tfh, and Treg responses [13,116]. In addition, the cytokines necessary for differentiating different Th cells in the lesioned brain after stroke are expressed, such as IFN-γ, TGF-β, IL-4, IL-21, and TNF [6,116,117]. Furthermore, transcription factors essential for Th cell differentiation, including *T-bet*, *GATA3*, *RORγT*, *Foxp3*, etc., have also been detected in the injured brain after stroke [118,119]. Although antigen stimulation is crucial for differentiating different Th cells, studies on the role of TCR and TCR signaling in differentiating different subpopulations of Th cells after stroke are rare [13].

Only some indirect evidence may reflect the role of TCR and TCR signaling in Th cell differentiation after stroke. Furthermore, most studies concentrate on TCR's co-stimulatory or co-inhibitory molecules after stroke. The CD28 superagonist increases Treg cell proliferation in the ischemic brain of animals [120,121]. Furthermore, PD-L1 can specifically down-regulate the number of brain-infiltrating CD4$^+$ T cells and the percentages of Th1 and Th17 cells. However, it increases the rates of Th2 and regulatory T cells in the hemorrhagic brain of animals [108]. Exploring the regulatory effects of TCR and TCR signaling on Th cell differentiation after stroke is necessary. Future research in this direction may facilitate the identification of new targets for treating the immune-inflammatory response associated with stroke.

7. TCR-proximal signaling in stroke

As illustrated previously, PTKs in the proximal signaling of the TCR include Lck, Nck, Fyn, ZAP-70, ITAMs, etc. The expression and activity of Lck, Nck, and Fyn increase in the lesioned brain of animals with acute stroke [122–124]. PKCε has been identified as an upstream regulator of Lck and Fyn as a downstream target of Lck in ischemic stroke in mice [122]. Lck and Nck are the Src family kinase (SFK) gene family members. As expected, the Src kinase inhibitor PP1 blocked the increase in Src kinase activity at 3 h in the hemorrhagic brain of Sprague-Dawley rats. Interestingly, inhibition of SFK improved BBB function and functional outcomes after experimental ICH [123]. Therefore, the specific role of Lck and Nck needs investigation.

Furthermore, additional evidence has indicated that the administration of a nonspecific Src family kinase inhibitor (PP2) immediately after thrombin injections abrogated brain edema and BBB disruption in the focal ischemic brain of rats [124]. Unfortunately, none of the above studies investigated the relationship between Lck or Nck and the T lymphocyte response after stroke. Therefore, it is necessary to validate their causal relationship in the ischemic or hemorrhagic brain.

Few studies have measured the expression of ZAP-70 and ITAM in the ischemic or hemorrhagic brain [125]. Furthermore, the function of ZAP-70 and ITAM has yet to be explored in stroke. However, additional evidence indicates that the sphingosine-1-phosphate receptor (S1PR) may interact with TCR signaling through the hub genes of its network [74]. Although the results of a triple-blind placebo-controlled ICH trial (NCT03338998) are not yet available, the regulatory effect of S1PR modulators, including fingolimod and siponimod, on stroke, may also support the role of proximal TCR signaling in the response of T lymphocytes after stroke [15,126,127]. Additional studies on proximal TCR signaling will facilitate the discovery of new targets to regulate the T-cell response in stroke.

8. TCR-distal signaling in stroke

The molecules or protein kinases, including calcineurin, NFAT, PKCθ, IKK, NF-κB, RASGRP1, RASERK1/2, TSC1/2, mTOR, P38, JNK, etc., in the four distal signaling pathways of TCR, are expressed increasingly in the lesioned brain after stroke [128,129]. However, the expression of some of the above molecules or protein kinases is not specific to T lymphocytes. The roles of molecules in TCR-distal signaling in stroke pathology have only been broadly described [129–131].

A recent study showed that calcineurin expression and activity increase in the mouse hypoxic-ischemic brain at 6 and 24 h [131]. Furthermore, the NFAT pathways also participate in the immune-inflammatory response after ICH [128]. Without evaluating the immune-inflammatory response related to T lymphocytes, calcineurin inhibitors, tacrolimus (FK506), and SDZ ASM 981, were neuroprotective in the rat model of transient middle cerebral artery occlusion [131]. Additional research indicates that calcineurin may exert neuroprotective effects by promoting NFAT phosphorylation after ischemic or hemorrhagic stroke [129,130].

Although PKC-θ may be involved in the pathophysiological process of ischemic or hemorrhagic stroke [132,133], its role in the response of T lymphocytes is unknown after stroke. mTOR expression is especially abundant in the lesioned brain after stroke [134,135]. mTOR signaling is activated at 30 min and returned to baseline 1 day after ICH [136]. Although it has multiple effects on the pathophysiological process of stroke, mTOR may regulate the response of T lymphocytes after stroke. Inhibition of mTOR with rapamycin in rats has several notable effects; it significantly improves the neurobehavioral deficit after ICH, increases the number of Tregs, increases IL-10 and TGF-β and reduces IFN-γ in peripheral blood and brain tissue [136]. Similarly, inhibiting rapamycin-induced activation of mTOR can significantly reduce lesion volume and improve behavioral deficits by inhibiting the infiltration of γδT cells and enhancing the anti-inflammatory activity of Tregs in the ischemic brain of rats [83].

Studies on the expression or functions of RASGRP1, RASERK1/2, and TSC1/3 on T lymphocyte response after stroke are rare [137]. Many studies have detected the expression of other molecules in the four distal TCR signaling pathways, including IKK, NF-κB, P38, and JNK, in the

ischemic brain [138–140]. However, these molecules are also expressed by neurons, microglia, astrocytes, etc., and not expressed explicitly by T lymphocytes [138–140]. From the available reports, it is difficult to conclude whether these molecules link TCR with the function of lymphocytes in stroke.

PDPK1 is essential in producing NF-κB mediated by TCR and T cell activation. Inhibition of PDPK1 effectively reduces the cytotoxicity of $CD8^+$ T cells after oxygen-glucose deprivation in *vitro* [113]. Additionally, inhibition of PDPK1 reduces infarct volume by suppressing Fas ligand (FasL)-mediated cytotoxicity of $CD8^+$ T cells in MCAO mice [113]. The expression of genes enriched in TCR signaling and specific T cells is negatively correlated with ICH volume but positively associated with relative perihematomal edema (rPHE), including PKCθ signaling in T lymphocytes, CD28 signaling in Th cells, ICOS-ICOSL signaling in Th cells, calcium-induced T lymphocyte apoptosis, and the Th1 pathway [74].

9. Co-signaling pathways of TCR in stroke

Recent studies have observed changes in the expression of the co-signaling molecules of the TCR after stroke. Additionally, the effects of these co-signaling molecules on T-cell activation after stroke are known and are summarized as follows (Table 2).

9.1. Co-stimulatory molecules

Ig superfamily members: Previous studies have explored the roles of CD28, ICOS-1, and CD84 in stroke. Peripheral blood $CD4^+CD28^-$ cells increase significantly in patients with acute ischemic stroke compared to healthy controls [141,142]. The increase in circulating $CD4^+CD28^-$ cells may be associated with an increased risk of stroke recurrence and death in patients with ischemic stroke [142]. Another study also showed that the number of $CD28^+$ CD4 cells significantly increased at 96 h in the spleen of mice with ischemic stroke [143]. There is no research on the frequency changes of $CD28^+$ cells in peripheral blood or lesioned brain after an ischemic or hemorrhagic stroke. However, the function of CD28 in stroke is known. In *vitro,* CD28 stimulation accompanying CD3 stimulation increases the proportion of $CD4^+$ T cells by increasing TrkC expression in peripheral blood mononuclear cells (PBMC) isolated from acute stroke patients [144]. In *vivo*, the CD28 superagonist monoclonal antibody (CD28SA) enhances the expansion and amplification of Treg cells in the ischemic brain of animals [120,121,145].

Regarding the effects of CD28SA on the inflammatory response, the severity of brain injury, and functional recovery, contradictory conclusions were obtained from animals with ischemic stroke [120,121,145]. However, blocking the B7–1/CD28 pathway reduces long-term brain damage by regulating immune and inflammatory responses in a mouse model of ICH [146]. Additional studies on the regulatory effects of CD28SA on different subpopulations of T lymphocytes may explain this difference after stroke.

Flow cytometry analyses in the brains of mice have identified IL-21-producing $CXCR5^+CD4^+ICOS\text{-}1^+$ T follicular helper cells (Tfh) early after tMCAO. Furthermore, $CXCR5^+CD4^+ICOS\text{-}1^+$Tfh may promote the pro-inflammatory response and aggravate brain injury after ischemic stroke. Although there was no statistically significant effect, ICOS-positive $CD4^+$ and $CD8^+$ T-cells increased slightly at 96 h in the spleen of mice with ischemic stroke [143]. There is also evidence that ICOS siRNA can protect brain tissues against ischemic injuries, improve movement and coordination of the limbs, reduce the mortality rate of rats, and inhibit T-cell-induced cytokine production [147].

As a member of the Ig superfamily, CD84 is also expressed on the surface of T cells. Mice lacking CD84 in T cells showed reduced cerebral $CD4^+$ T-cell infiltration and thrombotic activity after experimental stroke, reducing brain damage [148]. However, the roles of ICOS-1 or CD84 in hemorrhagic stroke still warrant further exploration.

TNF-TNFR superfamily members: Studies on the roles of members of the TNF-TNFR superfamily in stroke focus mainly on GITR, OX40, 4–1BB (CD137), and CD40L. $CD4^+GITR^+$T cells accumulate preferentially in the postischemic cortex, and treatment with GITR-stimulating antibody increases poststroke inflammatory responses and enhances neural stem/progenitor cell (iNSPC) apoptosis [149]. In contrast, blocking the interaction of the GITR-GITR ligand (GITRL) by the GITR-Fc fusion protein abrogates inflammation and suppresses iNSPC apoptosis [149]. Currently, few studies have explored the roles of GITR in hemorrhagic stroke.

CD137 (TNFRSF9, 4–1BB) expression in $CD4^+$ and $CD8^+$ T cells in peripheral blood or lymphoid tissues continuously increases from 6 to 72 h and peaks at 72 h after ischemic stroke in mice [150]. Furthermore, CD137 gene polymorphism is associated with the risk of ischemic stroke in the northern Han Chinese [151]. Moreover, it may be one mediating factor between diabetes and ischemic stroke [151]. In early cerebral ischemia, enhanced CD137 co-stimulation promotes T cell activation, upregulates the inflammatory immune response, and probably exerts deleterious effects. Consequently, blocking the CD137/CD137L pathway reduces ischemic brain damage [150]. Studies using C57BL/6 WT mice, CD137L-deficient mice (CD137L KO), and CD137-deficient mice (CD137 KO) mice identified a detrimental role of the CD137L-CD137 interaction in mediating inflammasome-associated brain injury and resulting neurological deficits after ischemic stroke. Therefore, pharmacological targeting of the CD137L-CD137 axis could be beneficial in limiting brain damage and neurological deficits after cerebral ischemia [152]. Although a study revealed an elevated CD137 mRNA and protein after SAH, which peaks on day 5 [153], no studies have examined CD137 expression in ICH.

Serum levels of CD40 are high in MCAO rats. A role for CD40/CD40L in inflammation-enhanced thrombosis in platelet and vascular endothelial cells is known in MCAO rats. However, the CD40 antagonist may decrease the volume of brain infarctions by signaling mTOR/S6K after focal ischemia/reperfusion [154]. Although this study did not detect the T cell response, the inflammatory response induced by CD40 and/or CD40L may aggravate brain injury after ischemic stroke. Serum sCD40L levels are higher in patients with ICH than in healthy controls. Furthermore, elevated serum levels of sCD40L are independently associated with the severity and clinical outcomes of ICH [155].

As the ligand for OX40, a member of the TNFR family, OX40L is present in neurons. Furthermore, recombinant OX40 (ReOX40) attenuates neuronal cell death through the OX40-OX40L/PI3K/Akt pathway during the initial period of brain injury in the SAH rat model [156]. Furthermore, a high serum OX40 ligand level correlates with severity and mortality in patients with massive cerebral infarction [157]. However, few studies have evaluated its role in T cell response in stroke.

Integrin family members: As a member of the Integrin family, LFA is elevated in peripheral blood and brain lesions after ischemic stroke [158,159]. It mediates the firm adhesion of leukocytes to endothelial cells in the ischemic brain [158–160]. Furthermore, evidence also indicated that inhibition of junctional adhesion molecule-A/LFA interaction attenuates leukocyte trafficking and inflammation in brain ischemia/reperfusion injury in mice [161]. However, the expression and function of LFA have yet to be explored after ICH.

TIM family members: Studies on changes in TIM-1 expression in stroke are available. TIM-1 expression increases transiently 24 or 48 h after tMCAO [162]. In an analysis of 4591 subjects with a mean follow-up of 19.5 years, plasma levels of TIM-1 were positively associated with an increased incidence of all-cause stroke and ischemic stroke, respectively, after adjustment for cardiovascular risk factors [163]. Furthermore, genetic analysis that includes a 2-sample Mendelian randomization analysis further indicates that TIM-1 could be causally associated with stroke [163]. Functionally, TIM-1 blockade may ameliorate cerebral ischemia-reperfusion injury by inhibiting the inflammatory response related to T lymphocytes in *vitro* and in *vivo* [162]. First, however, we need to investigate the expression and function of TIM-1 in ICH.

Table 2
Interventions targeted on co-signaling molecules of TCR in stroke.

Co-signaling molecules	Stroke type	Drugs/reagents/ treatments	Species	The severity of brain injury	T lymphocyte response	Outcomes	References
Co-stimulatory molecules							
CD28	Ischemic stroke	Anti-CD3/CD28	PBMCs isolated from patients with acute stroke	N/A	Increase in the proportion of T cells expressing TrkC	N/A	[144]
	Ischemic stroke	CD28 superagonist monoclonal antibody (CD28SA)	Male C57BL6 mice and IL-10$^{-/-}$mice	Reduction in infarct size on day 7 after stroke	Increase in Treg numbers in the spleen and ischemic brain	Attenuation in functional deficit 7 days after stroke induction	[120]
	Ischemic stroke	CD28SA	Male C57BL/6 and Rag1$^{-/-}$ mice	Increase in lesion volume in WT mice, no change in the infarct volume in Rag1$^{-/-}$ mice that lack lymphocytes day 1 after onset	Increase in peripheral Tregs and ipsilesional CD4^{+} cells	Deterioration in functional outcome as assessed by the grip test, decrease in survival rates on days 1 and 3 in WT mice	[121]
	ICH	Anti-B7–1 antibody	Adult male ICR mice	No changes in cerebral edema	Alleviation in splenic atrophy and inhibition in T lymphocyte proliferation in the spleen, and reduction in the IFN-γ/IL-4 (Th1/Th2) ratio in peripheral blood and ipsilateral hemisphere day 3 after stroke	Improvement in learning and memory on days 18 and 20 after stroke	[146]
ICOS-1	Ischemic stroke	ICOS siRNA	SD rats (males and females)	N/A	Inhibition of ICOS expression in lymphocytes in *vitro*, and reduction in the serum levels of TNF, IL-1, and IL-17 in peripheral blood 48 h after stroke	Improvement in limb movement and coordination, and reduction in mortality rate on day 14 after stroke	[146]
CD84	Ischemic stroke	N/A	Rag1$^{-/-}$ mice, Cd84$^{-/-}$ mice, and human	*Rag1*$^{-/-}$ mice, Cd84$^{-/-}$ mice, and *Rag1*$^{-/-}$ mice reconstituted with *Cd84*$^{-/-}$ CD4^{+} T cells all showed smaller infarcts 24 h after tMCAO	Less CD4^{+} T cell infiltration into the ischemic hemisphere 24 h after tMCAO in Cd84$^{-/-}$ mice	Both *Cd84*$^{-/-}$ mice and *Rag1*$^{-/-}$ mice reconstituted with *Cd84*$^{-/-}$ CD4 + T cells had a better neurological outcome day 1 after stroke; however, elevated platelet CD84 expression levels were associated with poor outcome in stroke patients	[148]
GITR	Ischemic stroke	GITR-stimulating antibody and GITR-Fc fusion protein	Male CB17/Icr$^{+/+}$ Jcl mice and CB-17/ Icrscid/scid Jcl mice	GITR–Ab increases infarct volume whereas GITR–Fc reduce it on day 3 after stroke	CD4^{+}GITR^{+}T cells preferentially accumulated in the postischemic cortex, and mice treated with GITR-stimulating antibody augmented post-stroke inflammatory responses with increased iNSPC; blocking the GITRL interaction by the GITR-Fc fusion protein abrogated the above changes	GITR^{+}CD4^{+}T cells are the main deteriorating modulators of post-stroke neurogenesis	[149]
4–1BB (CD137)	Ischemic stroke	Anti-CD137L monoclonal antibody	Female C57BL/6 J WT mice	Reduction in infarct size 72 h after ischemia	Elevated surface expression of CD137 on T cells in both peripheral blood and lymphoid tissues 6 h after stroke	Alleviation in neurologic dysfunction assessed with the Zea Longa score day 3 after stroke	[150]
	Ischemic stroke	N/A	Male C57BL/6 J WT, CD137L-deficient (CD137L KO), and CD137-deficient (CD137 KO) mice	The infarct volumes in CD137L KO and CD137 KO mice were lower than those of WT controls on day 1 after reperfusion	Reduction in inflammasome signaling in the ischemic brain of CD137L KO mice and the CD137 KO mice compared to WT controls after 24 h of reperfusion	N/A	[152]
CD40L	Ischemic stroke	CD40 antagonist antibody	Male Sprague-Dawley rats	CD40/CD40L increase infarct volume 12 h after reperfusion probably through mTOR/S6K signaling after focal I/R	N/A	N/A	[154]
sCD40L	ICH	N/A	110 patients	Elevated serum levels of sCD40L are independently associated with the severity of ICH	N/A	Elevated serum levels of sCD40L are independently associated with the clinical outcomes of ICH	[155]
OX40	SAH	Recombinant OX40 (ReOX40) and OX40L siRNA	Male Sprague-Dawley (SD) rats	OX40 attenuates neuronal cell death through the OX40-OX40L/ PI3K/AKT signaling pathway	N/A	Improvement in short- and long-term neurological function deficits	[156]

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Table 2 (*continued*)

Co-signaling molecules	Stroke type	Drugs/reagents/ treatments	Species	The severity of brain injury	T lymphocyte response	Outcomes	References
	Ischemic stroke	N/A	294 patients	OX40L levels were correlated with the Glasgow Coma Scale score	N/A	The level of OX40L was an independent prognostic factor for mortality at 60-days, after control of pulmonary infection, Glasgow coma scale score	[157]
LFA	Ischemic stroke	JAM-A antagonist peptide (JAM-Ap)	Male 10–12-week-old C57BL/6 mice	Reduction in infarct size on day 5 after stroke, and reduction in BBB permeability early after stroke	N/A	JAM-Ap increased survival time, improved neurological score day 7 after ischemia	[161]
TIM-1	Ischemic stroke	TIM-1-blocking mAb	C57BL/6 J mice	Anti-TIM-1 monoclonal antibody reduced infarct volume 24 h after tMCAO	Blocking TIM-1 substantially reduced CD3 in the lesioned brain	Anti-TIM-1 monoclonal antibody alleviated neurologic deficits 24 h after tMCAO	[162]
	Ischemic stroke	N/A	Ischemic stroke patients	N/A	TIM-1 was associated with an increased incidence of all-cause stroke	N/A	[163]
Co-inhibitory molecules							
CTLA-4	Ischemic stroke	Catecholamines	T cells isolated from stroke patients	N/A	Reduction in CTLA-4 in activated T cells	N/A	[165]
PD-1	Ischemic stroke	N/A	WT C57BL/6 mice, PD-1-deficient mice	Infarct volumes in the cortex, striatum, and total hemisphere were larger in mice deficient in PD-1- than in WT mice 96 h after tMCAO	PD-1 deficiency increases $CD3^+$ T cell infiltration in the lesioned brain	PD-1 deficiency worsens behavioral recovery on day 3 after tMCAO	[171]
	Ischemic stroke	PD-1 and CTLA-4 neutralizing antibodies	WT mice, PD-L1$^{-/-}$ and PD-L2$^{-/-}$ mice	PD-L2- but not PD-L1-deficient recipients of IL-10^+ B-cells had markedly reduced infarct volumes 4 h post-MCAO	Neutralization of PD-1 and CTLA-4 increases the proliferation of $CD8^+$ and $CD4^+$ T-cells in WT mice	N/A	[143]
	Ischemic stroke	PD-1 Abs	WT mice, PD-L1$^{-/-}$ and PD-L2$^{-/-}$ mice	PD-L1$^{-/-}$ and PD-L2$^{-/-}$ mice had smaller total infarct volumes 96 h after tMCAO compared to WT mice	The absence of PD-L1 rescues MCAO-induced splenic atrophy, inhibits the activation of splenic T cells, results in the loss of suppressor T cells from the spleen	N/A	[172]
	Ischemic stroke	Tregs isolated from WT or PD-L1$^{-/-}$ mice	C57BL/6 J male mice and PD-L1 (B7-H1)$^{-/-}$ mice	PD-L1 deficiency abolished Treg-afforded protection of BBB integrity at 24 h after MCAO	PD-L1 increases the suppressive effect of Tregs on neutrophil-derived MMP-9	PD-L1 deficiency led to a deterioration of neurological severity scores on day 3 after stroke	[173]
	ICH	Anti-PD1 monoclonal antibody	C57BL/6 (B6) male mice	N/A	Blocking the PD-1 pathway with an anti-PD1 monoclonal antibody prevented contraction of the T and NK cell compartments and spleen atrophy post-ICH, with reduced pulmonary bacterial burden	Anti-PD-1 treatment alleviated neurological deficits on day 3 post-ICH	[21]
	ICH	Anti-PD-L1 antibody and PD-L1 protein	Male C57BL/6 and Rag1$^{-/-}$ mice	Administration of the PD-L1 protein reduced brain water content and decreased lesion volume on day 3 after ICH	PD-L1 treatment significantly reduced $CD3^+CD4^+$ T cell counts, and the percentage of Th1 and Th17 cells in $CD4^+$ cells, whereas increasing that of Th2 and Treg cells on day 3 in ICH brain	PD-L1 protein significantly attenuated the severity of behavioral symptoms on day 3 after ICH induction	[108]
	ICH	N/A	PD-1$^{-/-}$ mice and WT mice	PD-1 reduced the brain water content after ICH	PD-1 decreased the mRNA and protein expression of TNF, IL-1β and IL-6 in the ICH brain	PD-1 improved neurological impairment induced by ICH	[174]
TIM-3	Ischemic stroke	N/A	Ischemic stroke patients	N/A	Tim-3 expression on $CD4^+$ T cells positively correlated with systemic IL-17 in patients with ischemic stroke	N/A	[175]
	Ischemic stroke	Nateglinide (NAT)	Male rats	NAT exhibited neuroprotective effects in rats through the downregulation of HIF-1α/TIM-3 inflammatory pathway	N/A	NAT pretreatment improved behavioral and motor functions in rats	[177]
	ICH	Specific siRNA for TIM-3 and recombinant human TIM-3	Sprague-Dawley rats	TIM-3 siRNA alleviated neuronal degeneration, neuronal cell death, and brain edema	Blocking TIM-3 by siRNA markedly reduced the secretion of inflammatory factors	Inhibition of TIM-3 improved short- and long-term neurological functions from day 3 to day 28 after ICH	[179]

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Table 2 (*continued*)

Co-signaling molecules	Stroke type	Drugs/reagents/ treatments	Species	The severity of brain injury	T lymphocyte response	Outcomes	References
	ICH	Galectin-9	Adult male Sprague Dawley rats	Increased Galectin-9 reduces brain cell death earlier after ICH	N/A	Galectin-9 promotes the short- and long-term recovery of motor and sensory functions	[180]

Abbreviations: N/A, not available; TrkC, the tropomyosin receptor kinase C; WT mice, wild-type mice; BBB, blood-brain barrier; IFN-γ, interferon-γ; IL-4, interleukin-4; HMGB1, high mobility group box 1 protein; TLRs, toll-like receptors; MOG, myelin oligodendrocyte glycoprotein; CD28SA, CD28 superagonistic monoclonal antibody; Th1 cells, helper T1 cells; Th2 cells, helper T2 cells; TFH, T follicular helper cells; Treg cells, regulatory T cells; ICOS, inducible T-cell costimulatory; TCR, T cell receptors; GITR, glucocorticoid-induced tumor necrosis factor receptor; PD-1, programmed death-1; SD rats, Sprague-Dawley rats; TNF, tumor necrosis factor alpha; IL-1, interleukin-1; IL-17, interleukin-17; GITR-Fc, GITR fusion protein; GITRL, GITR ligand; iNSPCs, ischemia-induced neural stem/progenitor cells; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; Tim-1, T cell immunoglobulin and mucin domain-containing protein 1; ICH, intracerebral hemorrhage; I/R, ischemia/reperfusion; mTOR, mammalian target of rapamycin; S6K: ribosomal protein S6 kinase; sCD40L, soluble CD40 ligand; OX40, tumor necrosis factor receptor superfamily member 4; OX40L, ligand of OX40; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; CTLA4, cytotoxic T-lymphocyte-associated protein 4; tMCAO, transient middle cerebral artery occlusion; MMP-9, matrix metalloproteinase-9; HIF-1α, hypoxia-inducible factor-1α.

9.2. Co-inhibitory molecules

Ig superfamily members: The roles of CTLA-4 and PD-1 in stroke are known [164]. However, few studies have evaluated the role of LAG-3 and TIGIT in stroke. Specifically, studies on CTLA-4 expression in peripheral blood T cells after stroke must be more consistent. A previous study showed that CTLA-4 is undetectable in peripheral blood T cells on days 1, 7, and 14 in 93 patients with ischemic stroke [165]. Another study found that CTLA-4-positive $CD4^+$ and $CD8^+$ T cells decreased significantly at 96 h in the spleen of mice with ischemic stroke [166]. By stimulating PBMCs obtained from ischemic stroke patients, mitogen PHA induces a strong upregulation of CTLA-4 in $CD4^+$ T cells, which is counteracted by adding catecholamines [165]. High concentrations of catecholamines in acute stroke patients could explain why CTLA-4 is not upregulated in activated $CD4^+$ T-cells [165]. In another study, the serum CTLA-4 level is higher in hypertensive patients with ischemic stroke than those without ischemic stroke [167]. Furthermore, an increased expression of CTLA-4 may represent an effective marker for predicting a better prognosis of ischemic stroke [167]. However, there are no studies on the expression and function of CTLA-4 in the brain affected by ischemic or hemorrhagic stroke.

Increasing evidence also suggests a vital role of PD-1 in brain diseases [168]. PD-1 signaling suppresses the immune response of resident microglia and infiltrating peripheral immune cells [168,169]. PD-1 is present in almost all invading T lymphocytes in the ischemic brain of mice [20]. In peripheral blood from patients with ischemic stroke, PD-1 is highly expressed in $CD4^+$ T cells of different phenotypes after the acute phase and is associated with alterations in $CD4^+$ T cells. In particular, the PD-1 level is negatively correlated with the absolute number of central memory T cells among different phenotypes of $CD4^+$ T cells, which may be one of the underlying mechanisms of stroke-induced immunodepression [170]. In PD-1-deficient mice, the infarct volume is larger than in WT mice 96 h after tMCAO. The loss of PD-1 also promotes $CD3^+$ T cell infiltration and worsens neurologic deficits [171]. Blocking PD-1 and CTLA-4 signaling with neutralizing antibodies post-MCAO results in an increased proliferation of $CD8^+$ and $CD4^+$ T cells in WT mice and confirms the inhibitory effects of PD-1 and CTLA-4 on T-cell activation [143].

However, research on the PD-1 ligand revealed that PD-$L1^{-/-}$ mice have smaller total infarct volumes than WT mice [172]. $CD8^+$ T cells exhibit increased proliferation in PD-$L1^{-/-}$ mice compared to WT mice [143]. Furthermore, PD-L1 deficiency in mice abolished Treg-mediated brain protection and neurological improvements 3 days after MCAO [173]. The efficacy of PD-1 and its PD-L1 ligand on T lymphocyte response and severity of brain injury after ischemic stroke is contradictory.

In the brains of ICH patients and murine ICH models, PD-L1 decreases in the perihematomal area, associated with an increased level of soluble PD-L1 in peripheral blood [21]. Additionally, ICH induced a significant reduction in the number of T and NK cells in the periphery with upregulation of PD-1 in these cells. Blocking the PD-1 pathway with an anti-PD1 monoclonal antibody prevents contraction of the T and NK cell compartments and spleen atrophy after ICH, with reduced pulmonary bacterial burden and improved neurological outcome [21]. It suggests brain-derived PD-L1 as a new mechanism driving post-stroke immunosuppression so that anti-PD1 treatment could reduce the risk of post-stroke infections. Additional studies have shown that PD-1/PD-L1 exerts neuroprotection after ICH in animals. The underlying mechanism could be that the PD-1/PD-L1 pathway can reduce the number of $CD4^+$ T cells that enter the brain and the percentages of Th1 and Th17 cells. However, it increases Th2 and regulatory T cell rates in the hemorrhagic brain [108,174].

TIM family members: Increases in TIM-3 expression increases remarkably in brain tissue from MCAO mice and PBMCs from patients with ischemic stroke [175]. There is a significant correlation of TIM-3 expression in $CD4^+$ T cells with systemic IL-17 in patients with

ischemic stroke [175]. Furthermore, although T-cell-specific inflammation has not been observed, down-regulation of TIM-3 may inhibit the inflammatory response and alleviate brain injury in animals with ischemic stroke [176,177]. The effects of TIM-3 on neuroinflammation in ischemic stroke contradict its role as a co-inhibitory molecule illustrated previously. More studies are needed to evaluate the immunomodulatory effects of TIM-3 in ischemic stroke.

Similarly, TIM-3 mRNA expression in PBMCs also increases significantly and peaks on day 3 in the large group of ICH patients [178]. Furthermore, it is positively associated with TNF, IL-1β, and S-100B protein concentrations in the early phase of ICH and negatively related to the Glasgow outcome score at 30 days in patients with ICH [178]. However, in this study, TIM-3 expression increased slightly in $CD4^+$ T cells but decreased significantly in $CD8^+$ T cells in a large ICH group compared to the control group [178]. Negative regulation of glial TIM-3 inhibits the secretion of inflammatory factors and modulates microglia to the anti-inflammatory phenotype after experimental ICH in rats [179]. However, increased galectin-9, a TIM-3 ligand, alleviates brain injury and promotes recovery after ICH in rats by binding to TLR-4 [180]. Like its role in ischemic stroke, the dynamic expression of TIM-3 and the relationship between it and the response of T lymphocytes warrant further investigation after ICH.

TNF-TNFR superfamily members: As essential members of the TNF-TNFR superfamily, tumor necrosis factor receptors 1 and 2 (TNFR1 and TNFR2) increase in the brain parenchyma of stroke patients, and plasma levels are high in the acute phase of stroke [181,182]. Although elevated plasma levels of TNFR2 correlate with the immunosuppressive state in the periphery of patients with ischemic stroke, no relationship was found between plasma levels of TNFR2 and the outcome of patients with ischemic stroke [181,182]. However, in a nested case-control study that included 220 cases who experienced ICH and 244 matched controls, high plasma levels of TNFR1 and TNFR2 were associated with incident ICH, most clearly with ICH at the non-lobar location. The results suggest that TNF-mediated inflammation could be related to vascular changes before ICH [183]. Until now, few studies have explored the role of TNFR2 in the inflammatory response associated with T lymphocytes and the severity of brain injury in stroke animals.

10. Perspectives on translation

Several inhibitors of CTLA-4, PD-1, and PD-L1 that can increase the T-cell response and kill tumor cells have been approved by the Food and Drug Administration (FDA) to treat melanoma, small-cell lung cancer, etc. [184]. (Fig. 5). Unlike strategies to counteract cancer, almost all preclinical studies described above indicate that blocking stimulatory effects while increasing inhibitory effects of molecules in TCR signaling could be promising for alleviating immune-inflammatory injury after an ischemic or hemorrhagic stroke. However, stroke-induced immunodepression also worsens the prognosis of stroke [6]. Therefore, evaluating the influence of interventions aiming to down-regulate the T cell response on the systemic immune status and the appearance of infectious complications is critical. The following sections will summarize the adverse reactions of compounds that down-regulate targeted molecules of the T lymphocyte response in TCR signaling (Table 3).

Due to the lack of effective and safe antagonists, few studies have been designed to inhibit the T cell response by directly targeting TCR. Blocking mTOR, a molecule involved in TCR signaling, with sirolimus (rapamycin) reverses the skew of the pro-inflammatory lineage, including the expansion of Th17 and double negative T cells and contraction of Treg cells [185]. Furthermore, although sirolimus (rapamycin) mTOR blockade may benefit the treatment of autoimmune diseases such as systemic lupus erythematosus (SLE) [185], few studies have reported infectious complications of sirolimus. Similarly to mTOR blockade, inhibition of calcineurin, a molecule in one distal pathway of TCR, with ciclosporin or tacrolimus (FK506) also attenuates early activation of T lymphocytes [186,187]. Two clinical studies on multiple sclerosis with a small sample size have revealed that low blood levels of FK506 only decrease peripheral $CD25^+CD4^+$ cell counts but do not influence peripheral $CD45RA^+CD4^+$ cell counts and infectious complications [186,187]. For treating myasthenia gravis and autoimmune encephalitis, additional evidence has indicated that lung or urinary tract infections may not be the main complications of tacrolimus [188–191].

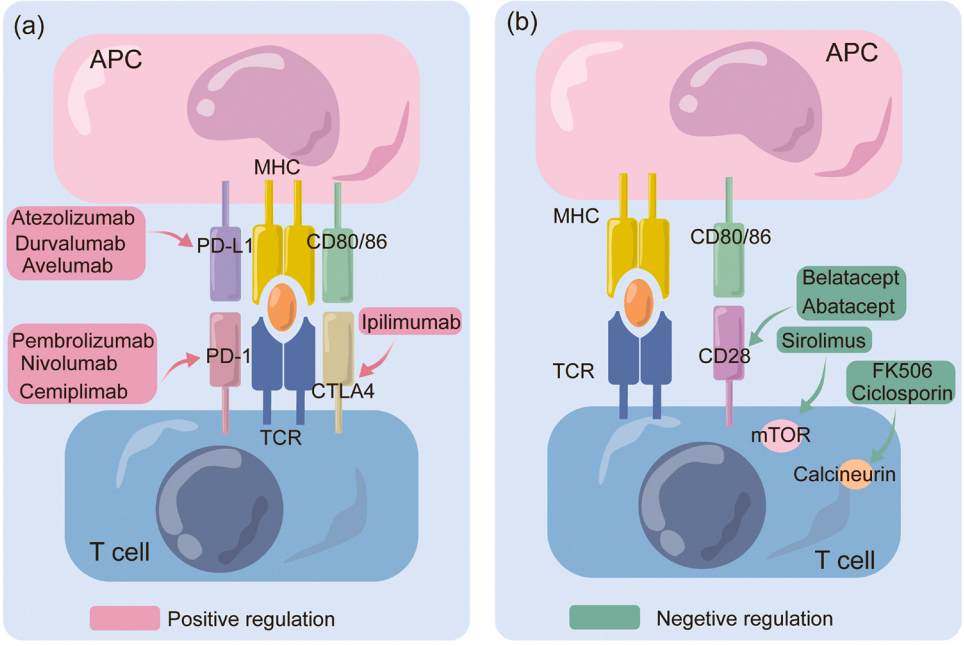

Fig. 5. Drugs approved by the FDA to modulate TCR signaling and T-cell response. Inhibition in co-inhibitory molecules, including PD-1 and CTLA-4, amplifies the T-cell response. In contrast, blockade in TCR signaling or its co-inhibitory molecules, including CD28, weakens the T-cell response. PD-1 and PD-L1 inhibitors, including pembrolizumab, atezolizumab, etc., have been approved by the FDA to treat colon cancer, melanoma, pancreatic ductal adenocarcinoma, etc. (a). In addition, Ipilimumab, a CTLA-4 inhibitor, was also approved by the FDA for treating melanoma (a). As mTOR and calcineurin are critical molecules in the distal pathways of TCR, the FDA has approved sirolimus (rapamycin), an mTOR blocker, and ciclosporin and tacrolimus (FK506), two calcineurin inhibitors, to treat some autoimmune diseases or lymphoproliferative diseases (b). Furthermore, by antagonizing the effects of CD28, FDA has approved abatacept and belatacept to control the T-cell response in kidney transplantation, giant cell arteritis, or rheumatoid arthritis (b). It is critical to evaluate further immunoregulation targeting TCR and T-cell response in stroke. Abbreviations: APC, antigen-presenting cells; TCR, T cell receptors; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1/2, programmed death ligand 1/2; CTLA4, cytotoxic T-lymphocyte-associated protein 4; mTOR, mammalian target of rapamycin.

Table 3
Adverse reactions of reagents that downregulate the T-lymphocyte response target molecules in TCR signaling.

Reagents	Targets	Diseases	Species	Adverse reactions	References
Sirolimus (rapamycin)	mTOR	Systemic lupus erythematosus (SLE)	Human	Few studies explored the infectious complications of sirolimus in patients with SLE	[185]
Tacrolimus	Calcineurin	Multiple sclerosis (MS)	Human	It may induce fatigue, headache, etc.; it did not increase infectious complications in patients with MS	[186]
	Calcineurin	Relapsing remitting (RRMS) and secondary progressive (SPMS) multiple sclerosis	Human	It may increase the appearance of neurotoxicity, hyperglycemia, and liver impairment; however, low levels of tacrolimus (FK506) did not increase infectious complications in MS patients	[187]
	Calcineurin (Inhibit transcription of the IL-2 gene mediated by TCR)	Myasthenia Gravis (MG)	Human	Lung or urinary tract infections may not be the main complications of tacrolimus; however, it may be related to the occurrence of nephrotoxicity, a high level of kidney failure, blood pressure, increased liver enzymes, increased blood glucose level, leukopenia, herpes zoster, herpes labialis, oral candidiasis, headache, dizziness, tremors, alopecia, and gastrointestinal discomfort, etc.	[188–190]
	Calcineurin	Autoimmune encephalitis (AE)	Human	Tacrolimus was well tolerated in the 17 patients and two patients adhered to treatment despite mild adverse events, including mild liver insufficiency and elevation of blood glucose	[191]
Abatacept	CD-80/CD-86	Rheumatoid arthritis (RA)	Human and animals	Studies on the influence of abatacept on infectious complications are currently controversial in patients with RA	[195,196, 199–201]
Belatacept	CD-80/CD-86	Immunosuppression after renal transplantation	Human	It may increase the risk of opportunistic infections including cytomegalovirus (CMV) infection and pneumocystis pneumonia, whereas its main complications are cardiovascular events and low eGFR after kidney transplant	[202,203]
CD40-TRAF6 inhibitor (6877002)	CD40-CD40L (CD40-TRAF6)	Development of heart failure (HF)	C57BL/6 male mice	Unknown in human	[204,205]
	CD40-CD40L (CD40-TRAF6)	Acute experimental autoimmune encephalomyelitis (EAE)	Lewis rats and C57BL/6 J mice	Unknown in human	[207]
SMI 6860766	CD40-CD40L (CD40-TRAF6)	Obesity	Male C57Bl/6 mice	Unknown in human	[206]
N/A	Induction in T cell exhaustion	Stroke and autoimmune diseases	N/A	N/A	[210–212]

Abbreviations: N/A, not available; mTOR, mammalian target of rapamycin; eGFR: estimated glomerular filtration rate.

As rapamycin, ciclosporin, and tacrolimus (FK506) have also been approved by the FDA to treat autoimmune diseases or lymphoproliferative diseases (Fig. 5) [192–194], the therapeutic value of mTOR blockers or calcineurin inhibitors may warrant further exploration in CNS diseases.

Evidence on the synergistic effect of co-signaling molecules has indicated that inhibition of the co-inhibitory pathways of T cells and stimulation of the co-stimulatory pathways could aggravate atherosclerosis and increase cardiovascular events [45]. However, anti-CD80-CD86 treatment combined with CTLA4-Ig, such as abatacept and belatacept, to competitively counteract CD28 effects, has been well developed as an FDA-approved immunosuppressive treatment for organ transplantation, giant cell arteritis, or rheumatoid arthritis in patients (Fig. 5) [195–198]. Although some studies indicated that infections are the most common adverse drug reactions of abatacept in patients with rheumatoid arthritis [199,200], a meta-analysis of 31 studies showed that abatacept treatment for patients with rheumatoid arthritis does not increase infections compared to patients who received biological DMARD (clinical protocols and therapeutic guidelines indicate disease-modifying drugs) [201]. Furthermore, compared to patients who received TNF inhibitors, patients who received abatacept also have a lower risk of cardiovascular events [201]. Regarding belatacept, studies have shown that it is not associated with an increased risk of serious infections, while it may be associated with a high cardiovascular risk after kidney transplantation [202,203]. Due to the survival and expansion of Treg cells sustained by the co-signals are essential for the induction of immunosuppression [35], it is worth exploring whether their different roles in Treg cells explain the difference in cardiovascular risk related to abatacept and belatacept.

By targeting CD40, the ligand of co-stimulatory CD40L, inhibition of CD40-TRAF6 interactions with small-molecule inhibitors can improve cardiac function or reduce complications of diet-induced obesity in mice [204–206]. Furthermore, small-molecule-mediated inhibition of the CD40-TRAF6 interaction can reduce the severity of experimental autoimmune encephalomyelitis, probably by lowering monocyte-derived macrophage infiltration into the CNS [207]. Similarly, with a blocker of co-stimulatory OX40, additional evidence also indicates that inhibition of OX40 can restore Treg function and suppress inflammation in pulmonary sarcoidosis [208]. However, the effects of CD40-TRAF6 or OX40 blockers on the pro-inflammatory response in the periphery or ischemic brain are unknown and warrant investigation. In addition, the adverse effects of these co-signaling antagonisms also need further evaluation. Notably, because of the lack of antagonists of other co-stimulatory molecules and agonists of the co-inhibitory molecules, studies on the negative regulation of T-cell response targeting the co-signals of TCR are limited. Therefore, more studies are needed to develop new compounds that counteract the function of co-stimulatory or co-inhibitory molecules.

T-cell exhaustion also downregulates immune response [209]. Recent research has proven that T-cell exhaustion facilitate tumor escape or aggravate infections. In addition, T cell exhaustion can be regulated by the transcription factor MYB, androgen receptors, nociceptor neurons, etc. [210–212]. Inhibition of T cell exhaustion represents a novel mechanism of resistance to immunotherapy. In contrast, whether the promotion of T cell exhaustion can alleviate the immune-inflammatory response associated with stroke may also deserve attention in the future. As illustrated previously, stroke-induced immunosuppression can increase infectious complications and worsen the prognosis of stroke. When trying to down-regulate the inflammatory response in patients with brain injury, efforts should be made to stabilize

the systemic immune status of patients with stroke. Further studies on the differential expression of molecules and their ligands that regulate TCR signaling or T cell exhaustion in the brain and periphery after acute stroke can help find joint targets that can alleviate brain injury induced by the inflammatory response but inhibit systemic immunosuppression at the same time.

Since T lymphocytes have multiple phenotypes and exert conflicting roles in brain injury and repair after stroke [6], further exploration of the potential treatment window of T-cell modulation therapy targeting TCR and its downstream signaling after stroke is critical. Specifically, to promote translation, it is necessary to assess whether an immunomodulator targeting T cells and TCR should be administered shortly after stroke onset. Given that ischemic and hemorrhagic stroke are pathologically different, it is also worth investigating whether the intervention window of the immunomodulator targeting T cells and TCR is different in treating ischemic and hemorrhagic stroke. Furthermore, immune systems, brain structure, and stroke pathophysiology can vary from species to species; translating findings regarding the downregulation of TCR activation in stroke from animal models to effective human therapies may represent another significant challenge we will face. Finally, more studies are needed to investigate the immunoregulatory effects of interventions targeting the TCR and T-cell response in different species with ischemic or hemorrhagic stroke.

11. Conclusions

The inflammatory response of T lymphocytes contributes to brain injury and brain repair during stroke. In addition, it is also related to systemic immune status and contributes to infectious complications after stroke. Therefore, regulating the T-lymphocyte response, including the inflammatory response associated with different T lymphocyte subsets, represents a promising strategy for treating stroke. The antigen-specific T cell response stimulated through TCR has been identified in the periphery and brain after stroke; it is vital to clarify more clearly whether it plays a decisive role in the T cell response after acute stroke. Subsequently, it may be reasonable to discern the antigens that trigger the T cell response and where T cells are activated, including peripheral organs or the lesioned brain, immediately after stroke. Additional studies to address these scientific questions may help identify a therapeutic strategy to alleviate immunosuppression in the periphery and inflammatory injury in the brain during stroke. It is an understudied research area.

TCR and molecules involved in TCR signaling may be essential for the proliferation and activation of T lymphocytes after stroke. Therefore, they may represent potential therapeutic targets for stroke immunotherapies; however, how TCR signaling and its co-stimulatory or co-inhibitory molecules regulate different T lymphocyte responses in stroke warrants further exploration. Furthermore, the efficacy of interventions targeting TCR signaling or co-signaling molecules on T cell response, brain injury, and functional recovery needs additional validation. Some molecules of TCR signaling are expressed not only by T cells. Therefore, verifying the causal relationship between these molecules and the T-cell response with techniques such as single-cell sequencing, spatial transcriptomics, and physically interacting cell sequencing (PIC-seq) is necessary after a stroke. Meanwhile, future research should also evaluate the adverse effects of interventions aimed at the inflammatory response associated with TCR in more detail. Further exploring these scientific questions may help find and pioneer novel immunomodulation strategies to treat ischemic and hemorrhagic stroke.

Literature research strategy

For TCR signaling and its co-signaling, we searched PubMed for articles or reviews published in English from 2019 to May 1, 2023 with the term 'T cell receptor'. For stroke and TCR signaling, we searched PubMed and the Cochrane Library for articles in English between 2000 and 1 May 2023, for 'Stroke' or 'intracerebral hemorrhage' and a second term, which was 'TCR', 'T lymphocytes', 'Co-stimulatory molecule', 'Co-inhibitory molecule', 'antigen', 'CD28', 'ICOS', 'GITR', 'OX40', '4–1BB', 'LFA', 'CD2', 'CD27', 'CD40L', 'Fas', 'CTLA4', 'PD-1', 'LAG-3', 'TIM-3', 'TIGIT', 'TNFR', 'Tim-1', 'BTLAs' or 'clinical trial'. The final reference list was generated based on relevance to the topics covered in this Review.

Chemical compounds studied in this article

AX-024 (PubChem CID: 56949412),
Siponimod (PubChem CID: 44599207),
Fingolimod (PubChem CID: 107970),
Rapamycin (PubChemCID: 5497196),
Tacrolimus (PubChem CID: 445643).

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CRediT authorship contribution statement

Jian Wang and **Chao Jiang** designed the review and provided supervision. **Chao Jiang** researched data for the article, and **Chao Jiang**, Yuanyuan **Liu, Shuai Chen, Jiewen Zhang**, and **Jian Wang** wrote the manuscript. **Shuai Chen** prepared the figures. **Simon Liu, Kevin L. Wallace**, and **Marietta Zille** revised the manuscript. All authors contributed substantially to the discussion of the content and reviewed and edited the manuscript before submission.

Declaration of Competing Interest

None.

Data Availability

No data was used for the research described in the article.

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