frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 17 July 2025
DOI 10.3389/fimmu.2025.1583274

OPEN ACCESS

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RECEIVED 25 February 2025
ACCEPTED 02 July 2025
PUBLISHED 17 July 2025

CITATION
Sun X, Wang J, Gu H, Guo M and Yang Z (2025) Uncovering a new mechanism of ischemic stroke: a study of the association between γδ T cells and immunoinflammation. *Front. Immunol.* 16:1583274. doi: 10.3389/fimmu.2025.1583274

Uncovering a new mechanism of ischemic stroke: a study of the association between γδ T cells and immunoinflammation

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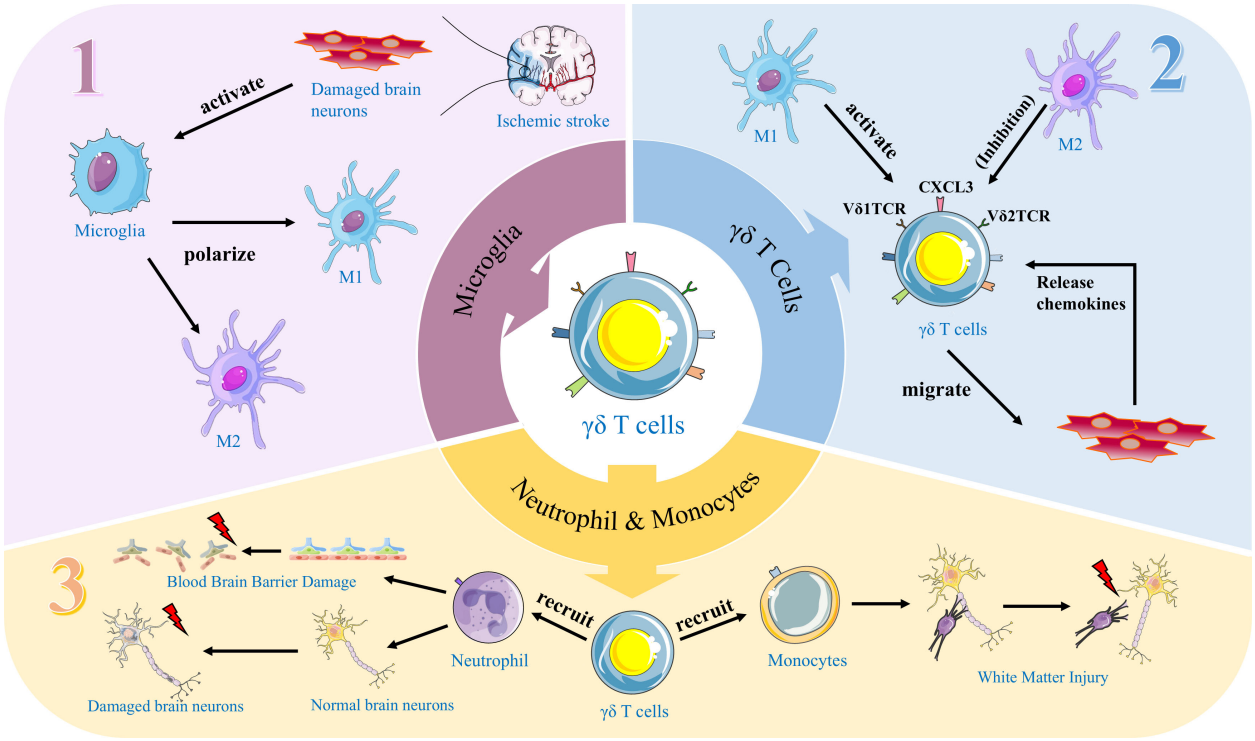
Ischemic stroke, characterized by high clinical mortality and poor prognosis, has been prioritized by the World Health Organization (WHO) for reducing the burden of non-communicable diseases. However, the pathogenesis of ischemic stroke remains complex and poorly understood. Recent studies have revealed the infiltration of γδ T cells within ischemic stroke lesions, accompanied by the upregulation of IL-17, IL-23, and other inflammatory cytokines, suggesting their involvement in the stroke's pathological process. Literature indicates that γδ T cells are recruited to the lesion site by microglia-derived chemokines and subsequently infiltrate the damaged brain tissue. This review summarizes current knowledge on the precise mechanisms underlying γδ T cell activation, migration, and ensuing immune-inflammatory responses in neuroinflammation, as well as their role in the progression of ischemic stroke. It further discusses the therapeutic potential of targeting γδ T cells to modulate neuroinflammation for ischemic stroke treatment, thereby offering novel therapeutic targets for managing neuroinflammation in this condition.

KEYWORDS

neurology, stroke, γδ T cells, microglia, immunity model category



GRAPHICAL ABSTRACT
This figure illustrates a cascade of immune responses mediated by γδ T cells subsequent to cerebral ischemic stroke. Section 1: Neurons compromised by brain injury secrete signaling entities that stimulate the activation of microglia. The activated microglia subsequently undergo phenotypic polarization, differentiating into M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes. Section 2: γδ T cells are activated by M1-polarized microglia, while concurrently, M2-polarized microglia exert an inhibitory effect on their activation. Additionally, neurons with compromised integrity release chemokines that facilitate the migration of activated γδ T cells toward the lesioned region. Section 3: Upon reaching the site of injury, γδ T cells summon neutrophils and monocytes, culminating in disruption of the blood-brain barrier and compromising the integrity of normal brain neurons and white matter.

1 Introduction

Stroke is a serious neurological disease characterized by the sudden onset of clinical syndromes and focal or global brain dysfunction, primarily caused by vascular lesions, with symptoms lasting more than 24 hours, often resulting in disability or death (1, 2). Ischemic stroke is predominant type of stroke. The pathological feature of ischemic stroke is cerebral vascular occlusion, accounting for approximately 80%-85% of all strokes. Its global burden continues to increase, placing significant pressure on social economies and healthcare systems (Table 1) (3, 4). Although hypertension (5), poor diet, and aging are major risk factors (6–8), current treatment options remain significantly limited.

Due to the rapid onset of ischemic stroke, timely, accurate, and effective medical decision-making is essential to prevent long-term disability and complications (9). The current core of ischemic stroke treatment is rapid vascular recanalization, including intravenous thrombolysis within 4.5 hours of symptom onset (such as recombinant tissue plasminogen activator alteplase) and endovascular mechanical thrombectomy within 6 hours (10). Although these methods can reduce the risk of disability, they have strict time window limitations and risks of complications such as intracranial hemorrhage (11, 12), limited overall efficacy, often poor prognosis, and techniques (such as mechanical thrombectomy) are highly dependent on operator experience. Therefore, a deeper understanding of the pathological mechanisms is key to developing more effective treatments. Oxidative damage, calcium overload, and inflammatory responses induced by ischemia-reperfusion injury synergistically exacerbate brain damage (13). Therefore, an in-depth analysis of its pathological mechanisms is key to developing more effective therapies. Given that inflammatory injury persists throughout the disease course and the limited efficacy of current thrombolytic therapies combined with anti-inflammatory drugs, it is urgent to explore new targeted anti-inflammatory mechanisms to provide novel strategies for the treatment of ischemic stroke.

Experimental evidence indicates that various immune cells and lymphocytes participate in the onset and progression of ischemic stroke. Notably, the post-stroke immune response exhibits significant spatiotemporal dynamics and complexity, involving both the immune environment within the central nervous system (CNS) and peripheral immunity (14). Following stroke onset, microglia within the CNS are the first to be activated and polarized, releasing

TABLE 1 Epidemiology and etiology of stroke.

Epidemiology and etiology	Main factors and rates
Increase in the global burden of stroke	Stroke events 70.0%
	Stroke deaths 44.0%
	Stroke prevalence 86.0%
	DALY 32.0%
16 main risk factors for stroke	High systolic blood pressure 56.8%
	Ambient particular matter 16.6%
	Cigarette smoking 13.7%
	High LDL cholesterol 13.1%
	Household air pollution 11.2%
	Diet high in sodium 10.6%
	High fasting plasma glucose 10.3%
	Kidney disfunction 9.3%
	Diet low in fruits 5.9%
	High alcohol use 5.2%
	Low temperature 4.8%
	High BMI 4.7%
	Secondhand smoking 4.4%
	Low physical activity 2.1%
	Diet low in vegetables 1.6%
	High temperature 1.1%

inflammatory cytokines and chemokines (15).his process simultaneously recruits peripheral immune cells to the lesion site, where they exert pro-inflammatory effects that exacerbate disease progression. γδ T cells, a distinct subset of peripheral innate lymphocytes, have garnered increasing attention. In ischemic stroke injury, they are recruited from the periphery to the CNS, leading to their activation and infiltration (16–20). Cytokines secreted by activated γδ T cells further recruit neutrophils and monocytes/macrophages to the lesion area, significantly amplifying intracerebral inflammatory damage (21–24).

However, compared to the extensive understanding of the role of γδ T cells in tumor immunotherapy, research on their function in ischemic stroke remains insufficient. Therefore, this review focuses on inflammation regulation to explore the central role of γδ T cells in the pathogenesis of ischemic stroke. Given the temporal-spatial specificity of γδ T cells in stroke-induced immunoinflammation namely, their time-dependent dynamics across different pathological stages and their spatial distribution and migration within the lesion – this article specifically examines the roles γδ T cells play during distinct phases of ischemic stroke. It further analyzes how they interact with other central and peripheral immune cells, collectively contributing to disease progression and driving inflammatory responses that exacerbate ischemic injury. This analysis aims to clarify the temporal transformation characteristics of γδ T cells across different pathological stages of ischemic stroke and their spatial migration/recruitment patterns within the immunoinflammatory context, while preserving an understanding of their involvement in processes within signaling networks during disease progression. The ultimate goal is to provide a theoretical basis for developing multi-target intervention strategies based on precise spatiotemporal modulation of γδ T cells, and to offer novel insights and approaches for the clinical treatment of ischemic stroke.

2 γδ T cells involved in ischemic stroke

2.1 Classification of mouse and human γδ T cells

Empirical evidence suggests that the ontogenetic origins of γδ T lymphocytes in murine and human species are not conserved, with each exhibiting distinct phenotypic attributes. In the murine paradigm, γδ T lymphocytes are derived from the thymic microenvironment and represent the inaugural T cell population to emerge within the embryonic thymus, with initial detection occurring as early as embryonic day 15 of murine gestation (25). In stark contrast, the presence of human γδ T lymphocytes is first ascertainable in the fetal hepatic tissue as early as 5–6 weeks into gestation (26, 27). The classification of γδ T lymphocytes is predicated upon the differential expression of T cell receptor (TCR) γ chains, including Vγ2, Vγ3, Vγ4, Vγ5, Vγ8, and Vγ9, as well as δ chains, encompassing Vδ1, Vδ2, Vδ3, and Vδ5 (28). In the murine model, γδ T cell subsets are delineated by the variability of TCR Vγ chain usage, with a predominance of $Vγ4^+$ and $Vγ6^+$ γδ T cells. In humans, however, γδ T cell subsets are primarily distinguished by the expression of Vδ chains, predominantly featuring $Vδ1^+$ and $Vδ2^+$ γδ T cells (29). The functional dichotomy of $Vδ1^+$ (mucosal-resident) and $Vδ2^+$ (blood-circulating) γδ T cells dictates their distinct contributions to post-stroke neuroinflammation: $Vδ2^+$ cells dominate early Interleukin-17 (IL-17)-driven neutrophil recruitment, while it is assumed that $Vδ1^+$ subsets may modulate late-stage repair via gut-derived metabolites (30, 31).

Most current single-cell RNA sequencing (scRNA-seq) studies have not identified γδ T cells because their transcriptomes at the single-cell level are unknown. However, there are publications that demonstrate the specific detection of human γδ T cells by high-resolution clustering of large scRNA-seq datasets and the combination of gene signatures in fresh tumor samples, allowing for the identification of their T cell receptor (TCR) Vδ1 and TCR Vδ2 subpopulations within large datasets derived from complex cellular mixtures (32–34). Furthermore, recent literature has introduced a TCR module scoring strategy for the identification of human γδ T cells, allowing for the determination of γδ T cell populations within the human body (35). This indicates that γδ T cells do indeed exist in the human body and can be subdivided at least into these two major subtypes based on their TCRs. The differentiation of human γδ T cells is influenced by tissue type and

the specific γδ TCRs they express (Table 2). Different types of γδ T lymphocytes can be formed; for instance, Vγ9 pairs with the Vδ2 chain to create Vγ9Vδ2 T cells, which are predominantly found in peripheral blood. Conversely, γδ T cells that express the Vδ1 chain can pair with various γ chains, resulting in a range of γδ T cells in the bloodstream (36, 37).

γδ T cells typically act as early responders to inflammatory lesions and are a crucial source of IL-17 and IFN-γ (38). Research indicates that γδ T17 cells are recruited to sites of inflammation 7–10 days prior to the antigen presentation required for $CD4^+$ T cell activation, allowing them to initiate antigen-dependent responses earlier (38, 39). In murine models, γδ T cells play a pivotal role in the pathophysiology of ischemic stroke, with distinct subsets performing different functions. Specifically, the γδ17 T cell subset rapidly infiltrates the brain during the early phase of stroke and releases IL-17A, thereby amplifying detrimental immune responses and exacerbating brain injury (40). The Vγ4 subset secretes pro-inflammatory cytokines such as IFN-γ and IL-17, activating inflammatory pathways in the brain; these subsets primarily exert their effects by exacerbating neuroinflammation and promoting brain damage. In contrast, the less abundant Vγ1 subset may confer protection by secreting TGF-β, thereby maintaining microglial homeostasis, suppressing hyperactivated neuroinflammatory responses, and mitigating brain injury (41). Consequently, in models of ischemic injury, the major γδ T cell subsets exhibit pro-inflammatory functions, and inhibiting γδ T cells or their markers significantly reduces brain damage by lowering levels of inflammatory mediators and neuronal apoptosis, thereby improving functional outcomes (42). Furthermore, in clinical studies of ischemic stroke, alterations in γδ T cell subsets are closely associated with disease progression and recovery in patients. Research indicates that during acute ischemic stroke, a reduction in the Vδ2 subset correlates with worse neurological status, manifested as higher deficit scores and adverse clinical outcomes (43). γδ T cells participate in both acute and chronic inflammatory processes post-stroke, and a decrease in the Vδ2 subset is associated with unfavorable long-term functional recovery (43, 44). Additionally, the role of γδ T cells in stroke pathophysiology includes regulating immune dysregulation; an imbalance between subsets may indirectly exacerbate brain injury by influencing inflammatory pathways and bone metabolism-related factors (45). These data indicate that γδ T cell subsets play a key immunomodulatory role in human stroke, directly impacting neuroprotection and functional recovery (43). (Figure 1).

TABLE 2 Subsets of mouse and human γδ T cells.

Subset	Paired TCR δ/γ chains	Cellular localization
Mouse γδ T cells		
Vγ1	None	Lymphoid tissue, liver
Vγ4	Vδ4	Lymphoid tissue, lung, liver, dermis
Vγ5-DETC	Vδ1	Epidermis
Vγ6	Vδ1	Uterus, lung, tongue, liver
Vγ7	None	Intestinal mucosa
Human γδ T cells		
Vδ1	Vγ2, Vγ3, Vγ4, Vγ5, Vγ8 and Vγ9	Skin, intestine, liver, spleen and mucosal tissues
Vδ2	Vγ9	Peripheral blood
Vδ3	Vγ2, Vγ3	Liver and peripheral blood
Vδ5	Vγ4	Peripheral blood

Most chemokines expressed in brain neurons during ischemic stroke can recruit γδ T cells (Table 3). Chemokines are categorized into four subfamilies according to their structural variations: CC, CXC, CX3C, and XC (46). Once secreted, chemokines induce directed chemotactic migration by coupling to seven-helix chemokine receptors via G proteins on the cell surface, signaling cell migration (47, 48).

It was found that mRNA and protein expression of chemokine ligand 2 (CCL2) and chemokine receptor 2 (CCR2) significantly increased in the rat hippocampus 6 hours after cerebral ischemia-reperfusion injury (49). In particular, CCR5 is differentially upregulated in mRNA and protein expression in immune cells, astrocytes, and neurons during cerebral ischemia/reperfusion injury, playing a crucial role in disease progression (50). Similarly, the expression of chemokine (C-X-C motif) ligand12 (CXCL12) on the neuronal surface is upregulated after cerebral ischemic injury, while the expression of CXC chemokine receptors 4 (CXCR4) is upregulated in microglia and astrocytes, enhancing the inflammatory response to injury (51). Simultaneously inducing γδ T-cell infiltration. Therefore, these studies suggest that γδ T cells infiltrate the injury site in ischemic stroke by expressing these chemokine receptors.

γδ T cells are predominantly distributed in the intestinal lamina propria (LP) and epithelium. Specifically, γδ T cells and intestinal flora provide different signals for regulating host immune system effects or modulating phenotype (52, 53). As shown in Table 2, different subpopulations of human γδ T cells have been categorized (54). γδ T cells are expressed in the dermis as Vγ5 (dendritic epidermal cells) and Vγ4 TCR (skin γδ T cells) in skin inflammation, and when they migrate to the peripheral blood, they can express CCR6 and CCR2 (55–59). Additionally, Vγ1 and Vγ4 T cells develop postnatally and circulate in the lymphatic system and bloodstream (60). Studies indicate that γδ T cells originating from various sites like the intestine can migrate to the brain and could contribute to the γδ T cell population during ischemic stroke (61, 62).

2.2 Recruitment of γδ T cells

It has been demonstrated that γδ T cells infiltrate the brain parenchyma post-ischemic injury via chemokine gradients (e.g., CXCL12/CXCR4 axis) (63, 64). During the acute phase of ischemic stroke, levels of these chemokines are significantly elevated. Serum CXCL12 levels are elevated in patients with acute ischemic stroke,

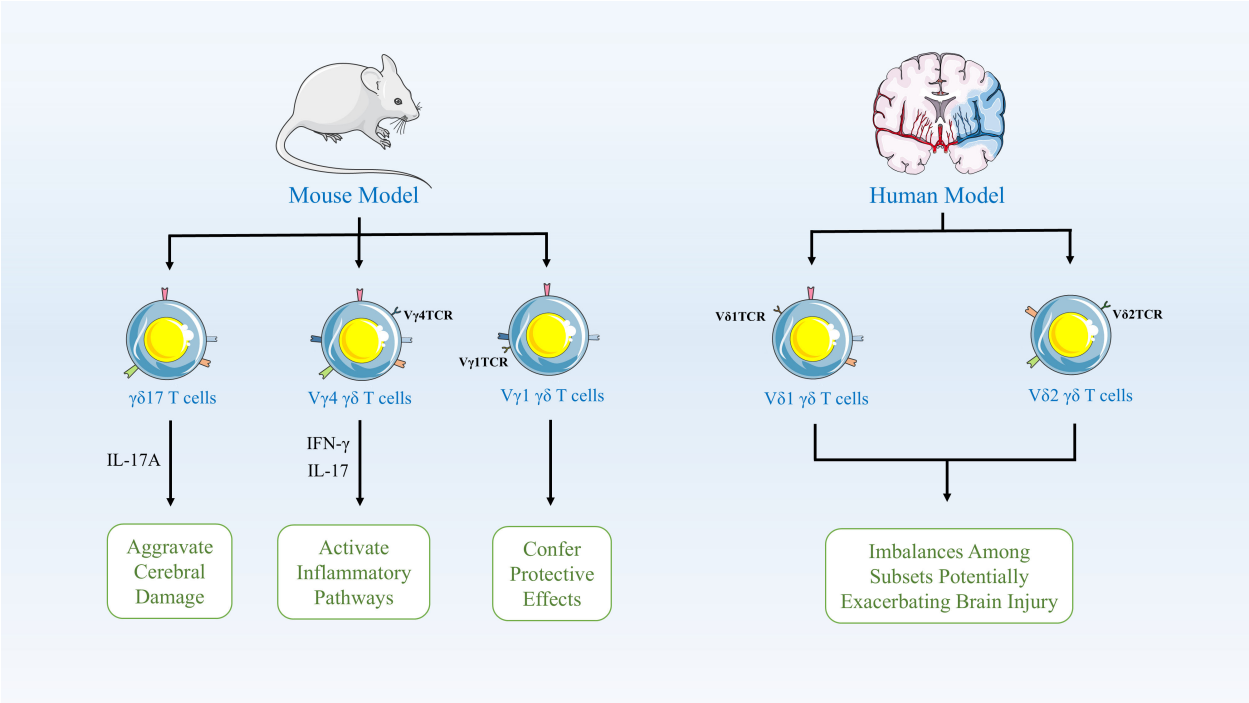


FIGURE 1
γδ T Cell Subsets in Ischemic Stroke Pathophysiology. In mouse models, γδ T cells critically modulate stroke outcomes. The γδ17 subset rapidly infiltrates the brain early post-stroke, releasing IL-17A to amplify neuroinflammation and injury. Pro-inflammatory Vγ4 cells secrete IFN-γ/IL-17, activating damaging brain inflammatory pathways, while Vγ1 cells may be protective. In humans, γδ T cell dynamics correlate with disease severity and recovery. Reduced Vδ2 subset frequency during acute stroke associates with worse neurological status (higher impairment scores) and poor long-term functional outcomes. γδ T cells regulate post-stroke immune dysregulation across phases; subset imbalances exacerbate injury via inflammatory cascades and bone metabolism factors.

showing a positive correlation with stroke severity (65); CXCL10 is increased in brain tissue or inflammatory responses, documented as an indicator of inflammation within 48 hours post-stroke, and is associated with neurological injury (66, 67). The critical role of γδ T cells in ischemic stroke-induced brain injury primarily involves cytokines released by γδ T lymphocytes, including IL-17, IL-21, IL-22, and IFN-γ, along with cytokine-recruited immune cells (68). Understanding how γδ T cells are activated and migrate, as well as how they induce an immune-inflammatory response, is crucial in ischemic stroke research.

2.2.1 Activation of M1 and M2 microglia

M1/M2 microglial polarization is dynamically regulated by post-stroke inflammatory cues, Microglia are innate immune cells in the brain, constituting 5-20% of neuroglia (69, 70). As the resident macrophages within the central nervous system (CNS), microglia continuously perform immunosurveillance under normal conditions, removing microorganisms, dead cells, redundant synapses, protein aggregates, and other harmful substances, while secreting soluble factors that contribute to the immune response and tissue repair (71–73). They support normal neuronal physiological activity by providing nutritional support, removing apoptotic debris, and eliminating faulty synapses (74–77). Microglia are the first immune cells to sense ischemia and respond immediately following an ischemic stroke (21, 78, 79). Once activated and initiating the defense process, microglia enhance phagocytosis and express increased levels of receptors, cytokines, chemokines, and other inflammatory molecules, aiding in the recruitment of additional immune cells to the damaged area (80). (Figure 2).

Studies have shown that disruptions in brain homeostasis, such as inflammation and oxidative stress, lead to microglia activation. Following the onset of ischemic stroke, microglia are activated through damage-associated molecular patterns (DAMPs), including heat shock proteins released from necrotic cells, and non-protein alert proteins like adenosine triphosphate (ATP) (81–83). Toll-like receptors (TLRs) are key components of the innate immune system, acting as pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and DAMPs (84). This triggers immune responses, including the release of inflammatory cytokines and activation of downstream signaling pathways. These responses play a critical role in defending against infections, regulating tissue homeostasis, and bridging innate and adaptive immunity (85, 86). In ischemic stroke, TLR2 and TLR4 are particularly crucial in regulating microglia activation and play a key role in inducing neurodegeneration (87, 88). Studies using an apoptosis-associated speck-like protein (ASC) knockout mouse model with a C-terminal caspase-activation and recruitment domain (CARD) have shown that microglia sense PAMPs and ATP released from damaged neurons (89). When microglia sense PAMPs and ATP released from

TABLE 3 Chemokine and chemokine receptors related to murine γδ T.

CC/CXC	Chemokine	Chemokine receptor
CC chemokine/ receptor family	CCL17	CCR4
	CCL2 (MCP-1)	CCR5
	CCL3 (MIP-1α)	CCR5
	CCL4 (MIP-1β)	CCR5
	CCL5 (RANTES)	CCR5
	CCL20	CCR6
	CCL19 (MIP-3β)	CCR7
	CCL21 (SLC)	CCR7
	CCL25 (TECK)	CCR9
	CCL27	CCR10
CXC chemokine/ receptor family	CXCL5	CXCR1
	CXCL6	CXCR1
	CXCL8 (IL-8)	CXCR1
	CXCL9	CXCR3
	CXCL10 (IP-10)	CXCR3
	CXCL11	CXCR3
	CCL21 (SLC)	CXCR3
	CXCL12 (SDF-1)	CXCR4
	CXCL16	CXCR6

injured neurons, TLRs on microglia are stimulated, leading to the formation of intracellular IRAKM-caspase-8-ASC inflammasomes that secrete ASC-dependent IL-1β. This nonclassical inflammasome-derived IL-1β can expand microglia populations through autocrine signaling (89). Conversely, when injured neurons express high levels of TLR4, it activates the NF-κB and NMDAR/PSD95-nNOS pathways, releasing proinflammatory factors such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which activate microglia (90, 91). Experiments in mouse models have shown that TLR2 is similarly expressed in microglia in the lesion area, and that high expression of TLR2 exacerbates ischemic stroke lesions, increasing infarct size and further amplifying stroke-induced CNS damage (92).

Similar to the aforementioned studies, the current research on the mechanisms of stroke microglia is primarily conducted using animal models, including mice and rats. Upon activation, microglia can polarize into two states: M1 and M2. These polarization states are influenced by ischemic stroke factors, including transcription factors, receptors, and ion channels (93). Among these, NF-κB, STAT family members, TLR4, S1PR3 binding to S1P, and ROS can activate M1 microglia. Activated M1 microglia then release significant amounts of cytokines and chemokines, such as TNF-α, IL-1β, IFN-γ, IL-6, inducible nitric oxide synthase (iNOS), and matrix metalloproteinases (MMP9, MMP3) (83, 94, 95). This release exacerbates inflammation and impairs the blood-brain barrier, allowing monocytes and macrophages to migrate to the damaged area, which further aggravates the inflammatory response (96). Meanwhile, M1 microglia produce free radicals and oxidants, such as those generated by NADPH oxidase, which cause oxidative stress and have deleterious effects (97). Nrf2 transcription factors and PPARγ are associated with M2 microglia activation. Upon activation, M2 microglia work in conjunction with macrophages to secrete anti-inflammatory factors, including IL-10 and transforming growth factor β (TGF-β). These factors help suppress inflammatory responses and facilitate revascularization (98–100). Additionally, M2 microglia produce trophic factors, such as insulin-like growth factor 1 (IGF-1), which promotes neuronal proliferation, differentiation, and maturation, contributing to central nervous system repair after ischemic stroke (101–105). Additionally, interactions between microglia and other immune cells, such as T cells, modify the microenvironment created by DAMPs and neural antigens, influencing the state of the inflammatory response (99). Microglial cells have been shown to significantly impact the inflammatory response to stroke.

As discussed, the M1 polarization state of activated microglia mediates the inflammatory response exacerbated by neuronal injury. Several studies have shown that the ischemic milieu is a critical factor influencing microglia function and their activation phenotype (106, 107). Therefore, it is crucial to regulate T-cell infiltration, inhibit M1 microglia activation, and promote M2 microglia polarization to mitigate inflammation, improve the metabolic state and environment of the ischemic site, and provide neuronal protection. This approach is essential for maintaining CNS homeostasis (108). Ischemic stroke is a dynamically evolving disease process, necessitating different therapeutic approaches at various stages of the disease. Intervening in the dynamic transition between M2 and M1 microglia could be a key focus for future stroke treatments. Further research is needed.

2.2.2 Microglia-mediated activation of γδ T cells

Under normal conditions, microglia express a variety of scavenger receptors and TLRs as they continually monitor their environment for signs of injury or infection. As a significant component of the inflammatory response, γδ T cells, constituting 20% of total T cells, accumulate in the focal area within 24 hours after ischemic stroke, influencing the process (64, 109). Interactions between microglia and γδ T cells mainly involve the activation of γδ T cells by M1 microglial cells and the release of cytokines that either promote or inhibit microglial cell activation. The mechanism may involve TLR activation. Katja et al. demonstrated that M1 microglia activated by TLR-specific ligands upregulated CD69 and CD25, and secreted IL-17 (110). The supernatants, which contained ligands for TLR2, TLR4, TLR7, or TLR9, facilitated the activation of γδ T cells through the secretion of cytokines IL-1β and Interleukin-23 (IL-23). Microglia can induce IL-17 secretion from γδ T cells. However, M2 microglia produce IL-10, which limits IL-17A signaling (23). Within 24 hours post-ischemia, DAMPs (e.g., HMGB1) activate microglial TLR4, inducing MyD88-dependent NF-κB translocation and subsequent IL-1β/IL-23 secretion (111). These cytokines prime $V\gamma6^{+}V\delta1^{+}$ γδ T cells to produce IL-17A, which peaks at 72 hours and correlates with neutrophil influx (112). By contrast, beyond day

7, TGF-β from M2 microglia suppresses γδ T cell activity, favoring resolution phases (111, 112). Additionally, it has been shown that activated γδ T cells secrete IFN-γ, which activates the microglia-A1 astrocyte-C3-neuron C3aR neurotoxicity pathway, exacerbating neuronal injury (113). Thus, microglia-γδ T cell interaction in mice stroke involves activated microglia mediating γδ T cell activation, IL-17 secretion, and mutual influence on activation states (Figure 2).

Inhibiting the crosstalk between microglia and γδ T cells may be crucial for reducing secondary injury induced by ischemic stroke. Administering rapamycin within 6 hours post-focal ischemia, which targets the mammalian target of rapamycin (mTOR), or employing interferon beta (IFN-β) treatment in a transient middle cerebral artery occlusion/reperfusion (tMCAO/R) mouse model, or inhibiting perforin-mediated neurotoxicity, significantly reduces the proinflammatory activity of microglia at the site of brain injury in rats. These interventions also inhibit chemokine production by microglia, thereby reducing γδ T-cell infiltration (114–116). Additionally, experiments in rat models have demonstrated that poly (ADP-ribose) polymerase (PARP) inhibitors, minocycline, or histone deacetylase inhibitors (HDACIs) such as valproic acid and sodium butyrate has been shown to effectively inhibit microglia activation when administered for sustained periods following focal ischemia. This inhibition is crucial as it correlates with an enhancement in neuronal survival, suggesting a potential therapeutic strategy for neuroprotection (117–119). These findings confirm the close relationship between microglia and γδ T cells.

3 γδ T cell migration

γδ T cells develop from thymocyte precursors independently of TCR signaling and are influenced by the cytokine SRY-Box Transcription Factor 13 (Sox13) (120). Studies have demonstrated that subpopulations of γδ T cells producing IFN-γ, IL-4, and IL-17 are programmed in the mouse thymus before migrating to peripheral tissues. Upon leaving the thymus, they are transported through the bloodstream to secondary lymphoid organs and then to tissues, or they return from tissues to the circulation (121, 122). γδ T cells preferentially circulate through non-lymphoid tissues by rolling on the vascular endothelium to induce specific glycoproteins, followed by selectins and integrins that promote adherence to the endothelium, resulting in leukocyte arrest (123). The lymphocytes then migrate to endothelial cells at the intercellular junctions (124).

Unlike in mice, different subsets of human γδ T cells exhibit distinct patterns of migration. γδ T cells can be classified into Vδ1 and Vδ2 T lymphocytes based on the function of their δ-chain in human. Vδ1$^+$ T cells are predominantly located in mucosal regions, whereas Vδ2 T cells primarily circulate in peripheral blood and lymph nodes (125, 126). Most γδ T cell subsets found at the site of ischemic stroke injury are Vγ9 and Vδ2 T cells. Therefore, it is hypothesized that in human ischemic stroke injury, γδ T cells recruited and migrating to the injury site are more likely to originate from peripheral blood and lymph nodes. Both subpopulations may undergo inflammatory changes or respond to chemokines produced by γδ T cells, with Vδ1 T cells expressing PECAM-1$^+$CXCR4$^+$ in response to interferon-induced protein-10 (IP10/CXCL10) and using this molecule for migration. In contrast, Vδ2 T cells express NKRPIA and CXCR3 in response to stromal-derived factor (SDF-1/CXCL12) and use it for migration in endothelial cells (127, 128). Post-ischemia, the CXCL12 gradient peaks at 24–48 hours, coinciding with γδ T cell infiltration. Intriguingly, hypoxia-inducible factor-1α (HIF-1α) stabilizes CXCL12 transcription in peri-infarct astrocytes, while endothelial CXCR4 upregulation facilitates γδ T cell arrest via β2-integrin clustering (129, 130). Pharmacological blockade of CXCR4 in murine models reduces γδ T cell transmigration by 60%, highlighting this axis as a therapeutic checkpoint (131). (Figure 3).

Studies suggest that circulating γδ T lymphocytes may be sensitive to chemotactic or mechanotactic cues *in vivo*, allowing them to target damaged tissues. There are also experiments in brain diseases other than stroke to prove the mechanism of cell migration and promoting inflammatory response. Infiltration of γδ T cells at the damage site has also been observed in mice with experimental allergic encephalitis (EAE) However, administration of anti-γδ TCR did not deplete TCR signaling but rather inhibited it. Conversely, early γδ T cells secrete IL-17A, which enhances late Th17 cytotoxicity, suggesting their involvement in multiple sclerosis (MS) or EAE (132). γδ T cells exhibit a multifaceted role in MS progression in human samples (133). In mice with EAE, γδ T cells infiltrate the damaged brain parenchyma through integrin β2 (134, 135). Consequently, we conclude that the migration of γδ T cells is crucial for initiating inflammation.

4 γδ T cells orchestrate neutrophil and macrophage-driven inflammation

4.1 γδ T cells activate neutrophils to induce an inflammatory response

Within 24 hours after the onset of ischemic stroke, specific γδ T cell subsets (Vγ6$^+$CCR6$^+$ and Vγ9$^+$Vδ2$^+$), upon binding to IL-17R, release IL-17A and become the primary source of IL-17A (24, 136). Their activity peaks within 3 days post-stroke and serves as a key accelerator of disease progression (137). Furthermore, IL-17A synergizes with TNF-α to activate the ACT1-TRAF6 complex in astrocytes, driving sustained NF-κB-dependent CXCL1 production (138, 139). This CXCL1 recruits CD16$^+$CD62L$^+$ N1 neutrophils, which release MMP-9 and ROS, exacerbating blood-brain barrier (BBB) leakage (140). This cascade results in neutrophil infiltration into the injury site, where they invade the compromised brain parenchyma and impair its function (24, 136). Depletion of γδ T cells shifts neutrophil polarization towards an N2 phenotype (CD206$^+$Arg1$^+$), indicating the existence of a bidirectional crosstalk exploitable for immunomodulation (141). Additionally, interferon regulatory factor 4 (IRF-4)-expressing dendritic cells are recognized as the source of IL-23, which drives and sustains IL-17

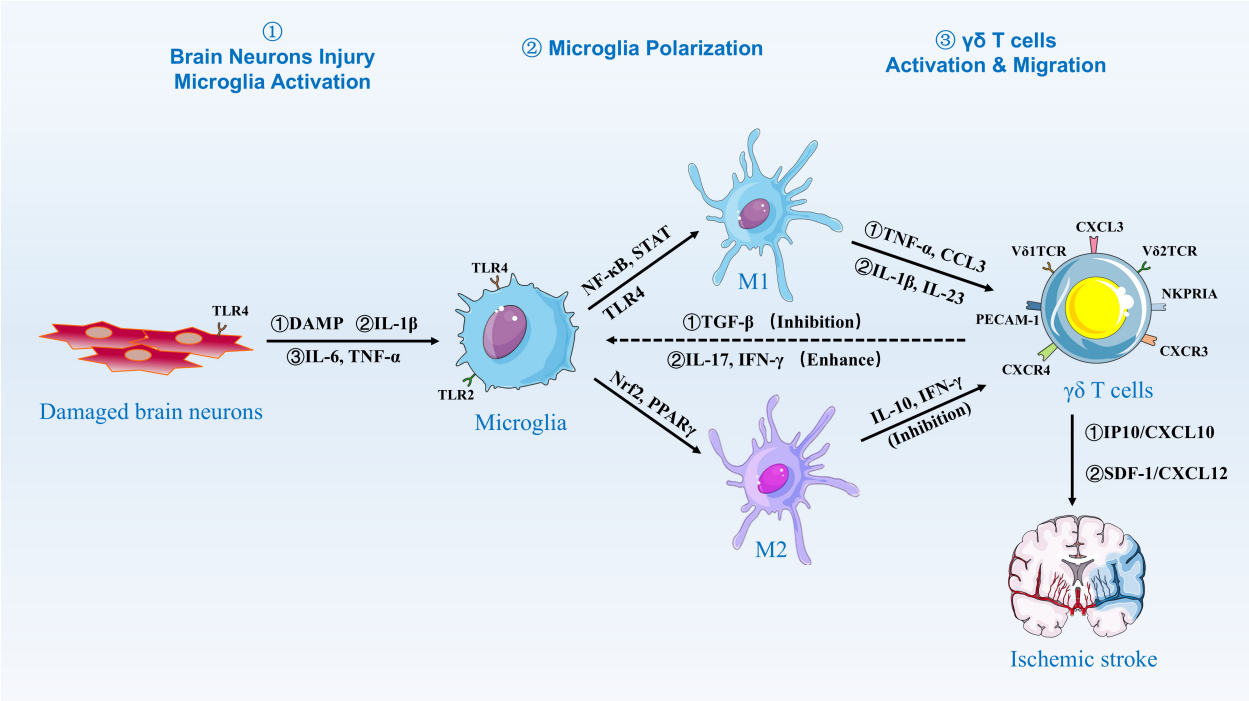


FIGURE 2
Activation and Migration of γδ T Cells by Microglia. Damaged brain neurons release DAMPs, IL-1β, IL-6, and TNF-α, which activate microglia via TLR2 and TLR4 signaling. Activated microglia then polarize into M1 and M2 phenotypes. M1 microglia are induced by NF-κB and STAT signaling, releasing pro-inflammatory cytokines such as TNF-α and CCL3, while M2 microglia are induced by Nrf2 and PPARγ signaling, releasing anti-inflammatory cytokines such as IL-10 and IFN-γ. The balance between M1 and M2 polarization is regulated by factors such as TGF-β, which inhibits M1 polarization, and IL-17 and IFN-γ, which enhance M1 polarization. γδ T cells are activated and migrate to the site of injury in response to chemokines such as IP10/CXCL10 and SDF-1/CXCL12, contributing to the inflammatory response and tissue repair in ischemic stroke.

production by γδ T cells, thereby inducing the neutrophil recruitment mechanism. Consequently, depleting dendritic cells or genetically disrupting the IL-23 signaling pathway reduces IL-17 production in γδ T cells, leading to a reduction in infarct size in murine models of ischemic stroke (136, 142).

The accumulation of neutrophils recruited to the site of central nervous system injury increases the production of cytotoxic molecules, such as pro-inflammatory cytokines, matrix metalloproteinases (MMPs), reactive oxygen species (ROS), and the multifunctional protein pyruvate kinase M2 (PKM2). These molecules initially disrupt the integrity of the blood-brain barrier (BBB) and further promote neuronal lysis and apoptosis, thereby exacerbating brain injury (143, 144). Studies have documented that in murine models of ischemic stroke, inflammatory cytokines TNF-α and IL-1β, along with hypoxia-inducible factor 1-alpha (HIF-1α) activation, induce the expression of MMP-9 and MMP-2. These MMPs are recognized as the principal proteases responsible for BBB disruption, subsequently degrading the basement membrane to facilitate neutrophil infiltration into the brain parenchyma (145–147). Furthermore, stroke induction triggers the nuclear translocation of PKM2 in neutrophils, mediating thrombo-inflammatory responses via STAT3 phosphorylation, which aggravates ischemia-reperfusion injury (148). Similarly, elevated levels of ROS generated by neutrophils directly damage junctional proteins and the endothelial cytoskeleton, further exacerbating the inflammatory injury response in ischemic stroke (149).

The release of neutrophil extracellular traps (NETs) by activated neutrophils also exacerbates damage in ischemic stroke. The formation of intravascular and parenchymal NETs peaks within 3–5 days after stroke onset. Depletion of γδ T cells promotes NET formation by neutrophils, which impairs vascular remodeling and disrupts the blood-brain barrier (BBB) during recovery from ischemic stroke (150–152). In the early phase of ischemic stroke, an elevated peripheral neutrophil count is associated with larger infarct volumes and poorer clinical outcomes and prognoses (153). The neutrophil-to-lymphocyte ratio (NLR) is considered the optimal predictor of post-ischemic stroke events (153). A higher NLR upon admission in patients with acute ischemic stroke, particularly within 48 hours of symptom onset, indicates a poorer prognosis at 3 months (154). Thus, γδ T cells clearly represent a crucial mechanism for neutrophil activation that drives the inflammatory response in cerebral ischemic stroke. This reveals significant bidirectional crosstalk between γδ T cells and neutrophils, laying the groundwork for future immunomodulatory therapies targeting this pathway.

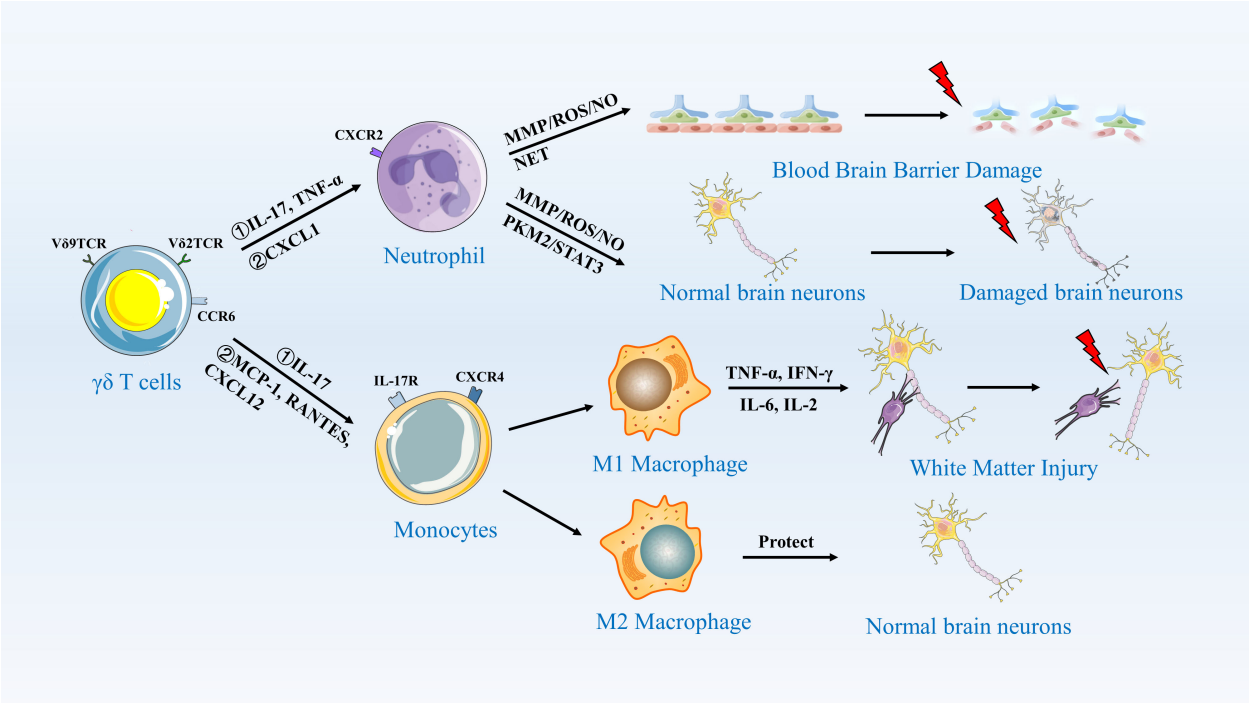


FIGURE 3
γδ T Cells Activate Neutrophils and Monocytes/Macrophages to Induce an Inflammatory Response. This figure illustrates the role of γδ T cells in central nervous system inflammation. γδ T cells, expressing Vδ9TCR and Vδ2TCR, recognize antigens and secrete cytokines such as IL-17 and TNF-α through CCR5. These cytokines activate neutrophils, which release MMP/ROS/NO and NET, leading to blood-brain barrier damage. Additionally, γδ T cells secrete MCP-1, RANTES, and CXCL12, which activate monocytes. Monocytes differentiate into M1 and M2 macrophages. M1 macrophages, through the secretion of TNF-α, IFN-γ, IL-6, and IL-2, further damage normal brain neurons, resulting in white matter injury. In contrast, M2 macrophages secrete protective factors that help maintain the integrity of normal brain neurons.

4.2 γδ T cells activate monocytes/macrophages to induce an inflammatory responses

During the acute phase of ischemic stroke, the likelihood of Ly6C^{hi} monocyte-derived macrophages being present in the brain is low, but the number of monocytes in the blood increases dramatically (155). After ischemic stroke, immature proinflammatory Ly6C^{hi}CD43^{low}CCR2 monocytes in the peripheral circulation are recruited to the brain after neutrophils and infiltrate the ischemic brain tissue to reach the core of the lesion as tissue macrophages (156). Experimentally, it has been confirmed that monocyte recruitment and macrophage infiltration are regulated through the CXCL12/CXCR4 axis (157). In ischemic muscle tissues of mice, γδ T-cell depletion has been shown to lead to an increase in the number of proinflammatory M1 macrophages (151). IL-17R is highly expressed on Ly6C^{hi} monocytes, and IL-17A is able to induce cytokines and chemokines that are trophic for monocytes, including chemotactic protein-1 (MCP-1), RANTES, and CXCL12/CXCR4, enabling splenic and circulating monocytes to migrate through the endothelium to the damaged brain parenchyma and differentiate into tissue macrophages (Table 4) (158–160). It was found that IL-17 levels were reduced and circulating monocyte infiltration decreased by depletion of γδ T cells (161). Specifically, γδ T cells producing IL-17A serve as a major early source of this cytokine in the acute inflammation, and their ability to rapidly respond to damage signals surpasses that of Th17 cells (162, 163). In ischemic stroke, IL-17 produced by γδ T cells and by Th17 cells exhibits significant differences in timing, function, and context. Temporally, during the acute phase of stroke, γδ T cells rapidly release IL-17A following stroke onset to amplify early detrimental immune responses (164), while Th17 cells function throughout the stroke process, including in pathogenesis, induction of secondary injury, and regulation of late-stage repair (165, 166). Functionally, IL-17A derived from γδ T cells primarily exacerbates neuroinflammation and brain injury in the acute phase by promoting neutrophil recruitment and early immune amplification, worsening ischemic damage (164, 167), whereas IL-17A produced by Th17 cells has more diverse roles, not only promoting neuroinflammation and secondary injury (165, 168), but also potentially participating in repair processes during the recovery phase (167). Contextually, IL-17A levels in γδ T cells may be directly modulated by the gut microbiota and dietary factors, reflecting their responsiveness in local microenvironments (164), while IL-17 production by Th17 cells relies on more complex regulatory mechanisms, including extracellular signals (e.g., IL-23 activation), transcription factors (e.g., RORγt), RNA, and epigenetic modifications, all of which influence their differentiation and function in the stroke microenvironment (165, 169, 170).

TABLE 4 Summary of chemokines/signaling pathways for γδ T cell-mediated monocyte recruitment.

Stage	Chemokines/pathways	Function
Peripheral Monocyte Recruitment	MCP-1/RANTESCXCL12/CXCR4	Recruits monocytes from the spleen and circulation to migrate to brain injury sites, where they differentiate into macrophages
Macrophage Recruitment	MCP-1/PR3/ICAM-1/CCL2	Enhances macrophage recruitment
Macrophage Polarization	mTORC1-S6K1 TGF-β-PPARγ	Promotes M1 polarization Promotes M2 polarization
Macrophage Inflammatory Role	JAK2/STAT3&NLRP3 CX3CR1 (High Expression)	Releases pro-inflammatory cytokines and promotes cerebral edema Macrophages undergo phenotypic switching from M1 to M2

Moreover, γδ T cell-derived IL-17A binds on monocytes, activating the mTORC1-S6K1 axis to promote M1 polarization (171). Conversely, by day 7, TGF-β from M2 microglia suppresses mTOR signaling, enabling PPARγ-driven M2 transition (172). Targeting this temporal switch with rapamycin may balance pro-inflammatory and reparative responses. Additionally, MCP-1 released by neutrophils and endothelial cells mobilizes circulating monocytes to infiltrate the site of ischemic stroke injury, and protease PR3 released by neutrophils upregulates the expression of endothelial ICAM-1 and CCL2 to enhance macrophage recruitment (173, 174). In ischemic stroke, once vascular occlusion occurs, leading to intravascular hypoxia and inducing DAMP and ROS production, the endothelium becomes less responsive to the stress response. This, in turn, stimulates the expression of cell adhesion molecules in endothelial cells, disrupting the BBB and facilitating monocyte entry into the site of injury. A vicious cycle is formed, exacerbating disease progression (175).

It has been found that macrophages transform into different phenotypes at different times during ischemic stroke and thus play different roles. Their proinflammatory effects occur mainly 2–4 days after ischemic stroke, and MCAO examination detects circulating monocytes and monocyte-derived macrophages at the site of damaged brain tissue. Macrophage polarization at the site of damage induces an M1 proinflammatory phenotype that exacerbates oligodendrocyte death and demyelination, thereby worsening cerebral white matter injury (176, 177). Recent studies demonstrate that the JAK1/2 inhibitor, Ruxolitinib, reduces the release of proinflammatory factors by inhibiting the activation of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome in macrophages, as well as the JAK2/STAT3 pathway, thereby ameliorating brain edema after stroke (Table 4) (178). Macrophages subsequently undergo a phenotypic switch on day 7, transforming into M2 macrophages with tissue repair and remodeling functions, losing expression of Ly6C and CCR2 but highly expressing CX3CR1 (Table 5) (179).

5 Discussion

Neuroinflammation is a critical mechanism in ischemic stroke, involving the orchestrated participation of various immune cells that drive disease progression. This intricate immune regulation likely stems from the time-dependent (e.g., acute vs. chronic phases) and spatially specific (e.g., brain-infiltrating vs. peripherally recruited immune cells) nature of the post-stroke immune response. γδ T cells, endowed with unique innate immune properties, have emerged as pivotal initiators of neuroinflammation. During the early stages of stroke, γδ T cells primarily exert pro-inflammatory functions, while adaptive immune cells subsequently mount protective responses to curb inflammation and support neural regeneration (180–182). As rapid innate responders, γδ T cells recognize damage-associated molecular patterns (DAMPs) via TLRs, promoting microglial polarization toward the M1 phenotype. They are activated by cytokines such as IL-1β and IL-23 secreted by microglia (82, 83, 183). Chemotactically guided by CXCL10 and CXCL12, γδ T cells migrate into the ischemic region and secrete IL-17 to amplify inflammation (184). The IL-17 and CXCL12 produced by γδ T cells further drive neutrophil infiltration and monocyte/macrophage migration to the lesion site, respectively, exacerbating secondary injury and contributing to ischemic stroke progression (156, 157).

Furthermore, during ischemic stroke, γδ T cells dynamically modulate the stroke immune microenvironment through interactions with other immune cells. This includes bidirectional regulatory circuits with αβ T cells, regulatory T cells (Tregs), dendritic cells (DCs), as well as microglia and NK cells. Literature demonstrates that γδ T cells serve as a critical nexus linking the innate and adaptive immune systems during ischemic stroke (137, 185). Specifically, γδ T cells typically exacerbate acute brain injury through IL-17A production, triggering a highly conserved innate immune response in the acute phase of stroke (23, 24, 137, 142). They further synergize with αβ T cells to promote cerebral tissue damage (142, 186, 187). Concurrently, interactions between γδ T cells and Tregs influence adaptive immunity (166, 188, 189). Conversely, Tregs suppress IL-17A production by γδ T cells indirectly via IL-10 signaling, while also restricting the pro-inflammatory functions of αβ T cells through modulation of IL-10 receptor signaling (23, 189). Additionally, synergistic interactions between γδ T cells and microglia amplify neuroinflammation. For instance, co-secretion of pro-inflammatory cytokines with M1-polarized microglia contributes to secondary injury (24, 168, 190), whereas Tregs and M2-polarized microglia foster anti-inflammatory responses (168, 180, 190, 191). In summary, through interactions with other cellular subsets within the immune network, γδ T cells orchestrate complex immunomodulatory mechanisms in the ischemic stroke microenvironment (192).

Therefore, targeting γδ T cells to modulate neuroinflammation represents a novel therapeutic strategy for ischemic stroke. Studies

TABLE 5 Key Experimental models and findings in ischemic stroke immunopathology.

Model category	Key findings	References
Human studies		
γδ T Cells	1. Increased infiltration of γδ T cells ($V\delta2^+$ subset) in ischemic brain tissue correlates with disease progression. 2. Human γδ T cell migration is mediated by the CXCL10/CXCL12-CXCR3/CXCR4 axis.	(27, 28, 30, 38)
Microglia	1. Microglia sense DAMPs (e.g., ATP) via TLR4, polarizing to a proinflammatory M1 phenotype ($CD86^+$/$iNOS^+$). 2. Post-stroke oxidative stress and inflammation drive microglial activation, exacerbating neuronal injury through IL-1β and TNF-α release.	(59, 60, 72)
Neutrophils	1. Elevated neutrophil-to-lymphocyte ratio (NLR) within 48 hours predicts poor 3-month outcomes. 2. Neutrophil-derived proteases (MMP9/MMP2) disrupt the blood-brain barrier (BBB), mediated by TNF-α and IL-1β.	(124, 127–129)
Murine models		
γδ T Cells	1. $V\gamma6^+$ γδ T cells rapidly infiltrate ischemic brain tissue within 24 hours, secreting IL-17A to recruit neutrophils. 2. IL-23 signaling sustains γδ T cell-derived IL-17 production; disrupting this pathway reduces infarct size.	(115, 135, 145)
Microglia	1. TLR2/TLR4 activation drives M1 polarization, releasing proinflammatory cytokines (TNF-α, IL-6) that disrupt the BBB. 2. Rapamycin (mTOR inhibitor) suppresses microglial inflammation and γδ T cell recruitment.	(74, 82, 101, 102)
Neutrophils & NETs	1. Neutrophil extracellular traps (NETs) peak 3–5 days post-stroke, exacerbating BBB disruption and impairing vascular repair. 2. Neutrophil depletion mitigates BBB damage and enhances post-stroke angiogenesis.	(132–134)
Rat models		
Microglia	1. CCL2/CCR2 expression surges in the hippocampus 6 hours post-ischemia, promoting monocyte infiltration. 2. M2 microglia secrete anti-inflammatory cytokines (IL-10, TGF-β) and neurotrophic factors (IGF-1) to support CNS repair.	(64, 88–91)
Therapeutic Targets	1. PARP inhibitors, HDAC inhibitors (e.g., valproic acid), and minocycline suppress microglial activation, improving neuronal survival. 2. JAK1/2 inhibition (ruxolitinib) reduces brain edema by blocking NLRP3 inflammasome activation in macrophages.	(104, 106, 160, 161)

demonstrate that blocking γδ T cells, IL-17a, or IL-21 confers significant neuroprotective effects against ischemic brain injury in murine stroke models, establishing them as promising therapeutic targets for mitigating ischemic brain damage (109, 193). Specifically, while IL-17A inhibitors (e.g., Secukinumab) are clinically used for autoimmune diseases, their application in stroke remains confined to animal studies. Conversely, γδ T cell agonists, such as α-GalCer, 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), and aminobisphosphonates, can activate immune responses under immunosuppressive conditions (194–196). Moreover, a potential link has been identified between γδ T cells and transient receptor potential (TRP) channels. TRPV1 modulates T cell activation and differentiation, which may indirectly affect γδ T cell activity (197, 198) and consequently influence post-stroke neuronal injury (199, 200). Blocking TRPV3 or TRPM2 shows potential for reducing brain damage and improving stroke outcomes (201, 202), an effect potentially linked to modulation of γδ T cell activity. This provides new perspectives on immunomodulation by regulating γδ T cell responses for ischemic stroke treatment.

Looking forward, the time-dependent and spatially specific role of γδ T cells in ischemic stroke, combined with advances in technology, holds promise for brain-targeted drug delivery using specialized encapsulation materials. This approach aims to enhance therapeutic precision and reduce peripheral side effects. Beyond pharmacological interventions, non-pharmacological approaches like dietary modifications (203–205) and electroacupuncture (206) also show efficacy in modulating immune responses. Consequently, by deepening our understanding of the inflammatory microenvironment regulation in ischemic stroke and its underlying mechanisms, we anticipate the discovery of effective novel therapeutic targets.

6 Conclusion

γδ T cells mediate post-stroke immunoinflammation through the TLR4/IL-17 axis, with their synergy with αβ T cells and interspecies heterogeneity presenting both therapeutic opportunities and challenges. Advancing multi-omics technologies and interdisciplinary collaboration will be critical to bridging the gap between mechanistic insights and clinical translation, ultimately enabling precision immune modulation in ischemic stroke.

To address current gaps, future research should prioritize: Cross-species mechanistic validation: Establishing humanized stroke models to compare functional heterogeneity among γδ T cell subsets. Metabolomic-epigenetic crosstalk: Combining metabolomics and chromatin accessibility profiling to elucidate how microbiota-derived metabolites (e.g., short-chain fatty acids) regulate γδ T cell plasticity via HDAC or mTOR pathways. Temporally targeted therapies: Developing phase-dependent strategies, such as acute-phase inhibition of IL-17/IL-23 signaling and recovery-phase enhancement of Treg activity to promote neural repair. Notably, multi-omics combined research overcomes the limitations of single-omics techniques, enabling a more

systematic and comprehensive analysis of the complex biological behaviors and molecular mechanisms of γδ T cells in ischemic stroke, but research on γδ T cells in ischemic stroke is still in the exploratory stage. Advancing multi-omics technologies and interdisciplinary collaboration will be critical to bridging the gap between mechanistic insights and clinical translation, ultimately enabling precision immune modulation in ischemic stroke. However, such studies also face numerous challenges, such as the integration of multi-omics technologies and the complexity of data analysis, requiring the establishment of standardized procedures and methods; as well as how to better translate animal experimental results into clinical applications. Nevertheless, with continuous technological advancements and deeper research, γδ T cells are expected to become a new target for immunotherapy in ischemic stroke, bringing new hope for improving patient prognosis and quality of life.

Author contributions

XS: Writing – original draft, Writing – review & editing. JW: Writing – original draft, Writing – review & editing. HG: Data curation, Writing – review & editing. MG: Data curation, Formal analysis, Methodology, Writing – review & editing. ZY: Methodology, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We are grateful to the pathology teaching and research group of Tianjin University of Traditional Chinese Medicine.

Conflict of interest

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

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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