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Review

Microglia as Double-Edged Players in Ischemic Stroke

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Abstract

Stroke has long been a leading cause of death and long-term disability worldwide. In recent years, more and more research has revealed that microglial responses to ischemic injury are highly heterogeneous and exhibit dynamic evolution over time, across brain regions, and under different metabolic states. This endows microglia with a dual regulatory role in both neurotoxicity and neuroprotection after ischemia: on one hand, they drive inflammatory responses, exacerbating secondary neuronal damage, blood-brain barrier disruption, and synaptic loss; on the other hand, they orchestrate debris clearance, vascular rebuilding, and neural repair. The traditional pro-inflammatory versus anti-inflammatory dichotomy is no longer sufficient to fully describe their complex functions. In this review we summarize recent advances in understanding the dual regulatory roles of microglia after ischemic stroke, with a focus on key mechanisms such as metabolic reprogramming, lipid metabolism regulation, inflammasome activation, and epigenetic modification. Furthermore, emerging therapeutic strategies targeting microglia and the challenges they face are discussed.

Keywords: microglia; ischemic stroke; neuroinflammation; metabolic reprogramming

1. Introduction

Stroke remains a leading cause of death and long-term disability worldwide [1]. The sudden interruption of cerebral blood flow initiates a neuronal cascade of excitotoxicity, oxidative stress, and mitochondrial dysfunction, culminating in necrosis or apoptosis [2]. As the major resident immune cells of the central nervous system (CNS), microglia rapidly detect danger signals, shifting from homeostatic surveillance to an activated state [3,4]. This rapid transition establishes them as key players in the early neuroinflammatory response to ischemic injury. However, microglial activation after stroke manifests spatial heterogeneity, driven by multiple factors [5,6]. A pro-death phenotype dominates in the ischemic core, whereas a mixed or neuroprotective profile emerges in the penumbra and distal regions [6,7,8].

Stroke pathology unfolds in three stages: hyperacute (minutes-24 h; excitotoxicity, immune activation), subacute (3–7 days; multi-cell interactions, vascular/phagocytic remodeling), and chronic (>14 days; synaptic/white matter reorganization, persistent inflammation) [9,10]. Throughout, microglia exhibit a dual function, essential for clearance and repair, but capable of amplifying injury via dysregulated inflammation. This duality offers therapeutic opportunities but also poses significant challenges.

This review systematically summarizes the research progress on microglial heterogeneity and their multiple functions after ischemic stroke, revealing the close relationship among microglial functions, metabolic states, and epigenetic characteristics. These findings collectively challenge the traditional view of microglia solely as mediators of inflammatory responses, instead positioning them as highly plastic regulatory factors. Precisely modulating these cellular functions may become key to implementing stage-specific therapeutic interventions after stroke.

2. Spatiotemporal Dynamics of Microglial Responses After Ischemic Stroke

2.1 Hyperacute Phase (0–24 Hours)

Microglia are integral to the triphasic pathology of stroke (Fig. 1). In the hyperacute phase of ischemic stroke, rapid ion influx and metabolic failure mainly occur. Within minutes, voltage-gated channels are disrupted, and large amounts of adenosine triphosphate (ATP) flow out into the extracellular space. These danger signals are quickly recognized by purinergic receptors on microglia (including P2X7 and P2Y12), causing microglial processes to extend toward the lesion rich in ATP [11]. Simultaneously, microglial cells transition into an amoeboid state and commence the secretion of inflammatory mediators along with the phagocytosis of cell debris.

In terms of signal transduction, the activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways significantly promotes the expression of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-10 (IL-10), and various chemokines, facilitating the early recruitment of neutrophils and monocytes [12,13,14,15].

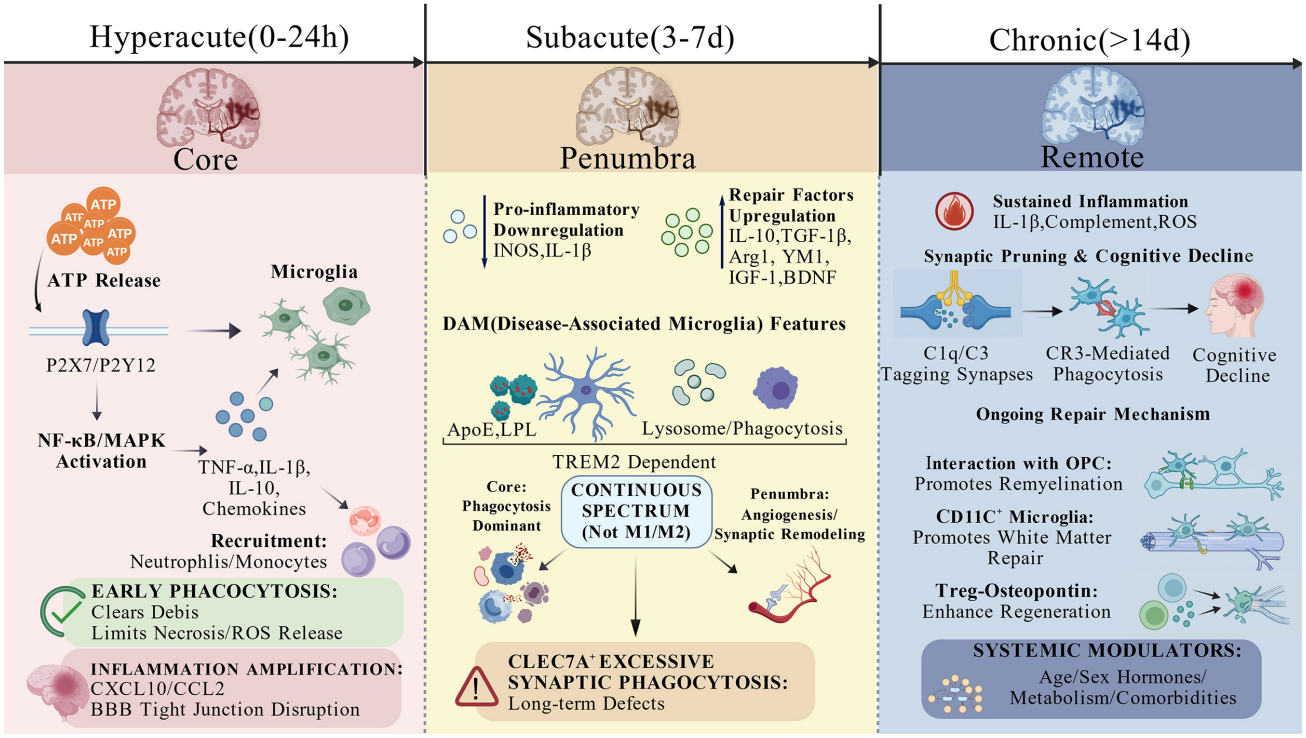

Fig. 1. The spatiotemporal heterogeneity of microglial responses across distinct brain regions after ischemic stroke. This schematic summarizes the stage-dependent pathological features and functional roles of microglia following cerebral ischemia. In the hyperacute phase (0–24 h) within the ischemic core, extracellular ATP and danger signals rapidly activate microglia via purinergic receptors and NF-κB/MAPK pathways, promoting early phagocytosis to clear debris but also amplifying inflammation, leukocyte recruitment, and blood-brain barrier disruption. During the subacute phase (3–7 days) in the penumbra, microglia undergo phenotypic diversification toward disease-associated microglia (DAM), characterized by TREM2-dependent phagocytosis, lipid handling, and upregulation of repair-associated factors (e.g., IL-10, IGF-1, BDNF). These responses support tissue remodeling but may become maladaptive if excessive synaptic engulfment occurs. In the chronic phase (>14 days), sustained microglial activation in remote regions drives complement-mediated synaptic pruning, oxidative stress, and cognitive decline, while simultaneously participating in remyelination, white-matter repair, and long-term neurovascular remodeling. Together, the figure highlights microglia as dynamic, context-dependent regulators of both injury and recovery after stroke. ATP, adenosine triphosphate; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; TREM2, triggering receptor expressed on myeloid cells-2; IL-10, interleukin-10; IGF-1, insulin-like growth factor-1; BDNF, brain-derived neurotrophic factor; iNOS, inducible nitric oxide synthase; TNF-α, tumor necrosis factor-α; P2X7, purinergic receptor P2X7; P2Y12, purinergic receptor P2Y12; IL-1β, interleukin-1β; CXCL10, C-X-C motif chemokine ligand 10; CCL2, C-C motif ligand 2; BBB, blood-brain barrier; TGF-β1, transforming growth factor β1; Arg1, arginase 1; YM1, chitinase-like protein 3; LPL, lipoprotein lipase; ApoE, apolipoprotein E; ROS, reactive oxygen species; CLEC7A^{+}, C-type lectin domain family 7 member A^{+}; M1/M2, macrophage type 1/macrophage type 2; C1q/C3, complement component 1q/3; CR3, complement receptor 3; OPC, oligodendrocyte precursor cell; CD11C^{+}, cluster of differentiation 11c^{+}.

This early inflammatory response is not inherently pathological. The rapid clearance of cellular debris can prevent secondary necrosis, minimize the extracellular buildup of reactive oxygen species (ROS), and help contain tissue damage [16]. However, if left unchecked, the response readily becomes detrimental, amplifying leukocyte infiltration (mediated by C-X-C motif chemokine ligand 10 (CXCL10)/C-C motif ligand 2 (CCL2)), aggravating tissue injury (through neutrophil proteases and ROS), and disrupting the blood-brain barrier (via endothelial activation) [17,18]. Thus, in the hyperacute phase, microglia play a paradoxical role: they are essential for initial protection but can exacerbate damage if their activation is excessive or prolonged.

2.2 Subacute Phase (3–7 Days)

During the subacute phase, microglia transition from an inflammatory activated state to a reparative state. At this stage, some components of the early pro-inflammatory phenotype still persist, but mediators such as inducible nitric oxide synthase (iNOS) and IL-1β are downregulated synergistically, while factors associated with inflammation resolution and repair are upregulated, including IL-10, transforming growth factor-β (TGF-β), arginase-1

(Arg1), chitinase-3-like protein 3 (YM1/Chi3l3), insulin-like growth factor-1 (IGF-1), and brain-derived neurotrophic factor (BDNF) [19,20,21].

This period is also marked by the emergence of a transcriptional profile in microglia that resembles the disease-associated microglia (DAM) phenotype. This profile features enhanced expression of genes related to phagocytosis, lipid metabolism (e.g., apolipoprotein E (*ApoE*), lipoprotein lipase (*LPL*)), and lysosomal function, an activation process largely dependent on the triggering receptor expressed on myeloid cells-2 (TREM2) signaling pathway [22]. Functionally, this reprogramming augments the capacity of microglia to clear apoptotic cellular debris and contributes to the stabilization of the blood-brain barrier.

It is important to note, however, that this transition is not a binary switch but rather involves the dynamic coexistence of both pro-inflammatory and pro-repair phenotypes [23]. This complexity exhibits spatial definition: microglia within the ischemic core are predominantly engaged in phagocytosing necrotic debris, whereas those in the peri-infarct region upregulate factors that support angiogenesis and synaptic remodeling to facilitate tissue reconstruction [8]. Notably, phagocytic activity can exert detrimental effects; for example, C-type lectin domain family 7 member A^+ ($CLEC7A^+$) DAM-like subsets have been shown to exacerbate long-term neurological deficits by mediating excessive synaptic elimination [24].

These nuanced dynamics highlight a critical therapeutic consideration: the necessity for precise temporal control. Broad, non-selective suppression of microglial activity during the subacute phase risks disrupting essential repair processes, such as debris clearance, trophic support, and vascular remodeling, thereby ultimately hindering functional recovery [25]. Consequently, future therapeutic strategies should aim for timed and phenotype-selective modulation, steering microglial responses away from detrimental inflammation and toward a defined, beneficial repair program.

2.3 Chronic Phase (>14 Days)

Following the acute and subacute stages, stroke enters a chronic phase characterized by persistent neuroinflammation, synaptic and white matter remodeling, and progressive neurodegeneration [26,27,28]. Microglia remain activated for weeks post-injury, sustaining the release of IL-1β, complement components, and ROS, thereby driving aberrant synaptic remodeling. Specifically, complement proteins complement component 1q (C1q) and complement component 3 (C3) tag synapses for elimination, facilitating their phagocytosis by microglia via complement Receptor 3 (CR3)-dependent pathways. When excessive or mistimed, this process leads to synaptic loss and cognitive deficits, a pathology akin to that observed in Alzheimer's disease [29,30,31]. Critically, complement component 1q-complement component 3(C1q-C3)-dependent synaptic pruning persists chronically after stroke, directly linking sustained complement signaling to long-term synaptic injury [32].

Despite their chronic inflammatory activity, microglia sustain a reparative repertoire that is vital for recovery. They orchestrate myelin regeneration via oligodendrocyte precursor cell (OPC) interactions, contribute to vascular integrity, and aid in circuit refinement [33]. This is exemplified by cluster of differentiation $11c^+$ ($CD11C^+$) microglia, which directly promote OPC differentiation and white matter repair [34]. The process can be augmented by immune signals, such as T cell-derived osteopontin, revealing a coordinated neuro-immune effort that underpins regenerative outcomes in the chronic phase [35].

The role of microglia evolves dynamically with activation intensity and duration. Early on, they sense danger and initiate ambivalent inflammatory signaling. Progressing to the subacute phase, significant heterogeneity, metabolic reprogramming, and a damage-associated microenvironment emerge to balance debris clearance with tissue repair. Into the chronic phase, they simultaneously modulate processes spanning persistent inflammation, synaptic remodeling, and myelin regeneration. These complex outcomes are shaped by multiple factors, as illustrated in Fig. 1, summarizing their spatiotemporal heterogeneity following ischemic stroke.

3. Regional Heterogeneity of Microglial Responses After Ischemic Stroke

Ischemic stroke has a specific spatial structure, and the response of microglia closely corresponds to this tissue architecture. Neurons in the ischemic core region rapidly undergo necrosis, while the surrounding penumbra retains some perfusion and metabolic activity [36,37]. Accordingly, microglia in the ischemic core region are in a highly phagocytic and stressed state, with increased expression levels of lysosomal genes, autophagy regulators, and ROS detoxification pathways [8,38,39]. While these microglia initially serve a vital role by efficiently clearing necrotic debris and damaged oligodendrocytes, this reparative capacity can be subverted under prolonged, severe ischemia. In such maladaptive states, cells may activate pyroptotic pathways, thereby exacerbating tissue injury [40].

In the peri-infarct penumbra, microglia adopt a hybrid inflammatory-repair phenotype. These cells partially retain responsiveness to neuronal activity and continue to perform certain homeostatic surveillance functions. Through dynamic interactions with synaptic networks and vascular components, penumbral microglia actively shape processes such as axonal sprouting, angiogenesis, and astrocytic scar formation, thereby modulating both the spread of injury and the subsequent tissue repair [41].

Microglial activation extends beyond the infarct to distal regions like the hippocampus and contralateral cortex, exhibiting delayed but distinct patterns [42,43]. In

these regions, microglia adopt metabolic phenotypes linked to post-stroke cognitive impairments in learning, memory, and attention. The activation of microglia in the hippocampus disrupts neuroplasticity and subsequently cognitive dysfunction, thereby suggesting that prolonged microglial responses underlie chronic neurological sequelae [44]. Furthermore, microglia residing in white matter tracts are particularly prone to lipid droplet accumulation, increased fatty acid transport, and mitochondrial dysfunction [44,45,46]. These lipid-rich cells exhibit heightened susceptibility to oxidative stress and ferroptosis, predisposing them to a chronic inflammatory state that drives progressive white matter degeneration [47]. The overall spatiotemporal heterogeneity of microglial activation after ischemic stroke is summarized in Fig. 1.

4. Pathological Signaling Hubs and Their Dual Nature in Microglia Following Ischemic Stroke

Following ischemic stroke, microglial responses are modulated by a complex interplay of molecular signaling pathways that exert dual effects. This functional plasticity is governed by the intensity and spatiotemporal dynamics of activation, as well as the local cellular microenvironment, which collectively determine neurotoxic versus neuroprotective outcomes. Initially, pattern recognition receptors (PRRs) such as TLR4, NLRs, and RAGE detect damage-associated molecular patterns, triggering downstream inflammatory and metabolic programs [48,49,50]. TLR4 activation drives both classic pro-inflammatory signaling and lipid droplet formation [47,51]. In contrast, the TREM2 pathway coordinates lipid metabolism and suppresses excessive inflammation [52].

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is a key intracellular signal amplifier. Under ischemic stress, it assembles to activate caspase-1, cleave gasdermin D (GSDMD), and induce pyroptosis. These processes release IL-1β and interleukin-18 (IL-18), exacerbating neuroinflammation and neuronal damage as shown in Fig. 2 [53]. Its regulation is multifaceted, involving activation by cGAS-stimulator of interferon gene (STING), inhibition by neuronal fractalkine (CX3CL1), and epigenetic fine-tuning (e.g., m6A methylation) [54,55,56,57,58].

Microglial phenotypes are shaped by key regulatory circuits, including the JAK-STAT/type I interferon axis. Activated STAT1-IRF1 promotes inflammatory gene expression, yet chronic signaling may result in harmful synaptic loss [6,51,52,59].

Separately, the complement cascade serves as a critical mediator of synaptic pruning. Under pathological conditions post-stroke, proteins like C1q and C3 trigger excessive, CR3-dependent synaptic elimination by microglia [60,61,62,63,64]. Damage via the HMGB1-C1q-C3 axis is therapeutically targetable and is naturally counterbalanced by activity-dependent neuronal suppression of complement phagocytosis [29,65].

Thus, the aforementioned pathways collectively dictate the microglial response following stroke. Their concurrent and often opposing inputs generate a functional duality, rendering microglia a therapeutic double-edged sword. The net result is a pivotal determinant of the precise temporal, spatial, and microenvironmental equilibrium among these signals.

5. Microglial Protective Signaling After Ischemic Stroke

5.1 TREM2 and Lipid Metabolism

TREM2, as an important metabolic and immune checkpoint, enables microglia to adapt to the lipid-rich inflammatory environment of the ischemic brain. TREM2 links damage sensing with lipid metabolism and phagocytic activity by recognizing phospholipids, ApoE containing lipoproteins, and myelin debris [52,66,67,68]. Upon binding to a ligand, TREM2 recruits the adaptor protein DAP12 and activates the downstream Syk-PI3K signaling cascade, thereby supporting microglial survival, metabolic adaptation, and effective clearance of cellular debris [69,70,71,72].

TREM2 deficiency significantly compromises microglial function following ischemic stroke. In the absence of TREM2 signaling, microglia accumulate dysfunctional mitochondria, exhibit disrupted lipid metabolism, and demonstrate impaired phagocytic capacity, thereby exacerbating infarction after ischemic stroke [52]. Recent evidence further highlights the therapeutic potential of TREM2 signaling, showing that its soluble extracellular domain (sTREM2) can promote an anti-inflammatory microglial response, including elevated expression of cytokines such as IL-4 and IL-13, while also disrupting harmful pathological interactions like those between nNOS and PSD-95 [73]. These mechanisms contribute to sTREM2's observed neuroprotective effects. Therefore, targeting the TREM2 pathway represents a promising strategy to enhance neuroprotection, improve debris clearance, and support neural circuit remodeling after stroke.

5.2 Anti-Inflammatory Cytokines

Beyond pro-inflammatory signals, a protective network of anti-inflammatory cytokines critically shapes post-stroke recovery by tempering excessive inflammation and promoting repair. This is achieved through regulating microglial polarization, metabolic homeostasis, and redox balance [74,75,76,77]. A central mediator, transforming growth factor-β1 (TGF-β1), regulates cytokine expression and maintains microglial metabolic stability. Its inhibition exacerbates inflammation and disrupts lipid metabolism, increasing lipid droplet accumulation after insults like oxygen-glucose deprivation/reoxygenation (OGD/R) [52,78,79].

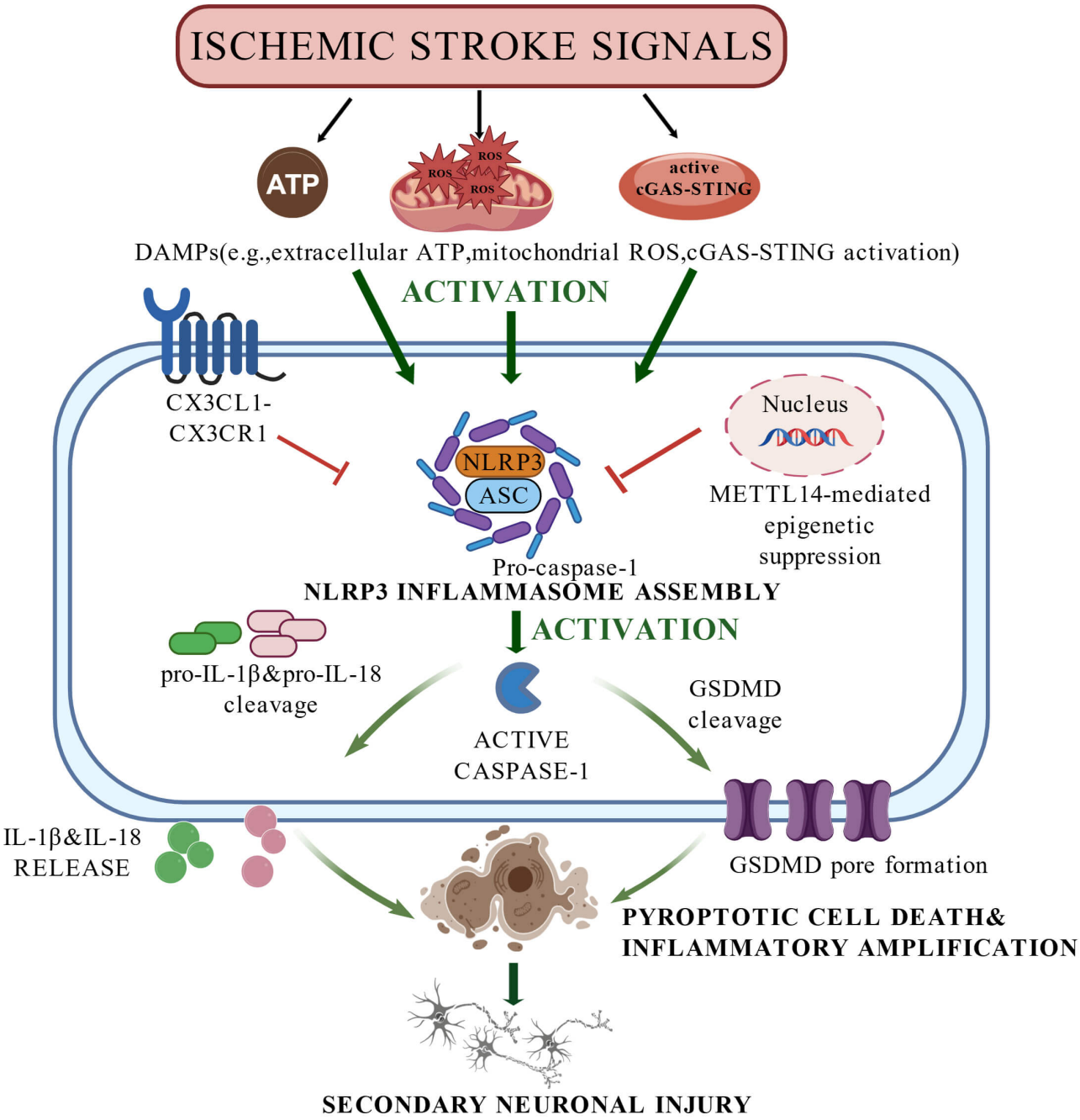

Fig. 2. NLRP3 inflammasome-driven microglial pyroptosis in ischemic stroke. This schematic illustrates the molecular mechanisms by which ischemic stroke–associated signals activate the NLRP3 inflammasome in microglia and drive pyroptotic cell death. Ischemic injury releases damage-associated molecular patterns (DAMPs), including extracellular ATP, mitochondrial reactive oxygen species (ROS), and activation of the cGAS–STING pathway, which collectively promote NLRP3 inflammasome assembly. The recruitment of ASC and pro-caspase-1 leads to caspase-1 activation, resulting in the cleavage of pro-IL-1β and pro-IL-18 as well as gasdermin D (GSDMD). GSDMD pore formation triggers microglial pyroptosis and facilitates the release of mature IL-1β and IL-18, amplifying neuroinflammation and contributing to secondary neuronal injury. Inhibitory regulatory pathways, including CX3CL1–CX3CR1 signaling and METTL14-mediated epigenetic suppression, restrain inflammasome activation and limit pyroptotic damage. NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated specklike protein containing a caspase recruitment domain; CX3CL1, fractalkine; CX3CR1, CX3C chemokine receptor 1; STING, stimulator of interferon gene; IL-18, interleukin 18; caspase-1, cysteine-aspartic acid protease 1; METTL14, methyltransferase-like 14.

Further modulating this network, bone marrow-derived mesenchymal stem cells (BMSCs) enhance microglial neuroprotection by upregulating IL-10, TGF-β, and CD206 while suppressing pro-inflammatory markers (e.g., iNOS, CD16/32, TNF-α) [80]. Beyond this immunomodulation, BMSCs also mitigate acute inflammation, promote neurogenesis, and support tissue repair [81,82], underscoring the broad therapeutic potential of harnessing the anti-inflammatory cytokine network to foster a pro-recovery microenvironment.

5.3 Neurotrophic Support

Beyond metabolic and cytokine pathways, microglia directly secrete neurotrophic factors such as BDNF, IGF-1, and glial cell-derived neurotrophic factor (GDNF) to mediate neurorepair [83,84,85]. Notably, an IGF-1 high/TREM2 high microglial subpopulation identified in ischemic tissue exhibits enhanced oxidative phosphorylation and a neuroprotective transcriptome, suggesting IGF-1 may regulate microglial metabolism and repair via TREM2 downstream signaling [86]. Meanwhile, BDNF not only supports synaptic plasticity but also directly suppresses microglial production of interleukin-6 (IL-6) and TNF-α [87,88,89,90,91]. This dual action indicates BDNF can modulate both the intrinsic state of microglia and microglia-neuron crosstalk.

6. Crosstalk With CNS Compartments

6.1 Neuron-Microglia

Under physiological conditions, neurons exert tonic inhibitory control over microglia primarily through signaling mediated by C-X3-C motif chemokine ligand 1 (CX3CL1)/CX3C chemokine receptor 1 (CX3CR1) signaling pathway [92]. Ischemic injury rapidly diminishes neuronal CX3CL1 expression, unleashing microglial pro-inflammatory programs [93]. Exogenous administration of CX3CL1 can counteract this shift, suppressing pro-inflammatory genes and driving microglia toward an anti-inflammatory, reparative state. Specifically, recombinant soluble CX3CL1 (rCX3CL1) inhibits NLRP3 inflammasome activation, blocks GSDMD-dependent pyroptosis, and reduces microglial release of IL-1β and IL-18 [55]. Consequently, reinforcing this neuron-to-microglia signaling axis emerges as a novel strategy to support circuit repair and recovery after stroke.

6.2 Astrocyte-Microglia

Astrocytes critically influence microglial responses after stroke, playing a dual regulatory role.

On one hand, they can exacerbate injury: at the infarct border, $BST2^{+}$ astrocytes secrete complement C3 to recruit and activate $C3aR^{+}$ microglia, exacerbating neuroinflammation and neuronal damage [94]. Ischemia-reperfusion also induces histone lactylation in astrocytes, upregulating the RNA methyltransferase NSUN2 to drive m^5C-dependent neuroinflammation and microglial activation [95]. On the other hand, astrocytes can enhance microglial anti-inflammatory and repair functions, promoting a neuroprotective A2 state [96]. Additionally, astrocyte-derived IL-33 modulates microglial activation, and restoring the IL-33/ST2 signaling pathway alleviates gliosis and provides neuroprotection [97,98].

6.3 Oligodendrocyte-Microglia

Effective myelin regeneration and white matter repair after ischemic stroke are crucially linked to how microglia handle oligodendrocytes and myelin debris [34,35,99]. While microglia aid repair by clearing myelin-derived lipids like cholesterol, dysregulated lipid metabolism during ischemia can disrupt this process, fueling inflammation and impeding regeneration [44,100]. A key adaptive mechanism is TREM2-dependent lipid droplet formation, which facilitates myelin debris clearance and promotes regeneration, indicating the beneficial role of TREM2-driven lipid reprogramming [101]. Pharmacologically enhancing regulated lipid droplet formation can further improve clearance and suppress inflammation [102]. Conversely, excessive lipid droplet accumulation, marked by elevated PLIN2 and associated with increased pro-inflammatory factors (TNF-α, IL-6, IL-1β), impairs myelin regeneration [52], indicating that chronic lipid overload can lock microglia into a pro-inflammatory, repair-limiting state.

6.4 Blood-Brain Barrier Interactions

The role of microglia in post-stroke blood-brain barrier (BBB) integrity is a paradigm of context-dependent plasticity, capable of either damage or protection based on their phenotype [75,76,103,104]. Pathologically, they rapidly release MMP-9 upon activation, dismantling tight junctions and exacerbating vascular leakage and edema [105,106]. However, microglia can also be strategically reprogrammed to support repair, as evidenced by SHPL-49's ability to reduce endothelial toxicity and suppress MMP-9, thereby aiding BBB restoration [107]. This functional switch is orchestrated by internal metabolic regulators, microglial-specific PPARα overexpression, for example, curbs inflammation, limits endothelial injury, and promotes structural and functional BBB recovery [76].

7. Metabolic Reprogramming in Microglial Fate After Ischemic Stroke

Post-stroke microglial fate is governed by metabolic reprogramming across three interconnected fronts: (1) the energy balance, where glycolysis promotes inflammation [3] and oxidative phosphorylation favors repair [108,109]; (2) lipid homeostasis, whose disruption via phagocytic overload sustains inflammation and impedes recovery, is a process amenable to therapeutic restoration [110,111,112]; and (3) lactate-mediated epigenetic regulation, which can direct transcription toward either inflammatory [113,114] or reparative outcomes [115].

7.1 Glycolysis Versus Oxidative Phosphorylation

Metabolic reprogramming is currently considered a key factor determining the fate of microglia after ischemic stroke, as it directly links energy utilization with inflammation and repair functions [110,116]. The shift between glycolysis and mitochondrial oxidative phosphorylation (OXPHOS) has a significant impact on whether microglia adopt a neurotoxic or neuroprotective phenotype. Inhibiting pyruvate kinase M2 (PKM2) with TEPP-46 can suppress glycolysis in microglia and promote their transition to an M2-like reparative phenotype [108]. Resolvin D1 (RvD1) can reprogram microglial energy metabolism from aerobic glycolysis to mitochondrial OXPHOS, thereby increasing the ATP supply needed for phagocytosis and promoting the resolution of inflammation [109]. Chemokine-like factor 1 (CKLF1) activates the AMPK-mTOR-Hypoxia-inducible factor-1α (HIF-1α) axis, driving the shift from OXPHOS to glycolysis, which stimulates inflammatory activation of microglia and exacerbates neural injury [3].

Collectively, these findings demonstrate that a metabolic program dominated by glycolysis drives microglia toward pro-inflammatory and neurotoxic activities. In contrast, restoring or maintaining mitochondrial respiration, lipid catabolism, and OXPHOS promotes a reparative, inflammation-resolving phenotype. Therefore, precise regulation of microglial energy metabolism represents an effective strategy to steer their functional fate toward debris clearance, inflammation resolution, and tissue repair in the brain. Ultimately, after ischemic stroke, the inflammatory or reparative fate of microglia is determined by the dynamic balance between glycolysis and OXPHOS, as summarized in Fig. 3.

7.2 Lipid Metabolism

In addition to glucose utilization, lipid metabolism also plays an important role in regulating microglial function after ischemic stroke. After injury, microglia engulf large amounts of lipids derived from damaged myelin and necrotic neurons. However, excessive lipid engulfment severely disrupts lipid homeostasis within microglia, leading to a distinctive "stroke-associated foamy microglia" (SAM-foamy) phenotype, which triggers chronic neuroinflammation and impairs tissue repair [110].

Lipid overload is a primary driver of chronic microglial activation, with cholesterol metabolism gene upregulation preceding inflammation [110]. This dysfunction is worsened by impaired anti-inflammatory signaling; loss of the astrocyte-microglia IL-3 axis downregulates the key fatty acid oxidation enzyme CPT1A. Exogenous IL-3 rescues CPT1A expression, alleviates lipid overload, and restores functional homeostasis [111,112].

7.3 Lactate and Histone Lactylation

Metabolic reprogramming influences microglia epigenetically, with lactate acting as a central regulator linking metabolism to chromatin [117,118]. Zhang and colleagues [119] were the first to demonstrate that lactate produced by glycolysis promotes histone lysine lactylation during the late stage of M1 macrophage polarization, thereby establishing the conceptual framework of the 'lactate-epigenetics-repair' program. Lactylation has dual roles post-stroke: it can mediate acute injury (e.g., via astrocyte-derived lactate) [114] or foster repair (e.g., via microglial H3K18la activating Plxnb2) [115]. Excessive microglial glycolysis and H3K9 lactylation also drive inflammation [113], while lactate signals via pathways like HIF-1α-CCL7/NF-κB [117].

Although the association between metabolic reprogramming, epigenetic modifications, and microglial phenotypes is becoming clearer, many insights are still at the stage of identifying correlations. Direct *in vivo* causal evidence remains limited [110,116,117,118]. This gap underscores the need for caution when inferring causality from pharmacological or correlative studies [108,109,113,114,115,120]. Future research needs to use time-specific and cell type-specific genetic tools to elucidate the clear metabolic-epigenetic causal pathways in microglia after stroke and translate these mechanisms into precise therapeutic strategies.

8. Therapeutic Modulation of Microglia in Ischemic Stroke

Building on a deeper understanding of microglial functions in ischemic stroke, therapeutic strategies have evolved from non-specific immunosuppression toward the precise modulation of microglial fate. The dual role of microglia is shaped by a confluence of factors, including temporal dynamics, metabolic state, and the local microenvironment. Consequently, emerging interventions aim to operate across multiple regulatory levels, such as microglial survival and regeneration, inflammasome activity, metabolic and epigenetic reprogramming, and cell-specific drug delivery. Together, these approaches constitute a spatiotemporally guided, microglia-targeted therapeutic framework for ischemic stroke, as illustrated in Fig. 4.

8.1 CSF1R Inhibition

The colony-stimulating factor 1 receptor (CSF1R) signaling pathway regulates the survival, proliferation, and homeostasis of microglia. Small molecule CSF1R inhibitors (including PLX5622, PLX3397, and Ki20227) have become powerful experimental and therapeutic tools for modulating microglial populations [121,122,123,124]. Continuous CSF1R inhibition during the acute phase may suppress cell proliferation while exacerbating inflammation and impairing recovery [125]. Short-term partial inhibition can improve long-term functional outcomes [122]. In aging models, a 'clearance-replenishment' strategy has been shown to reduce lipid droplet accumulation and neu-

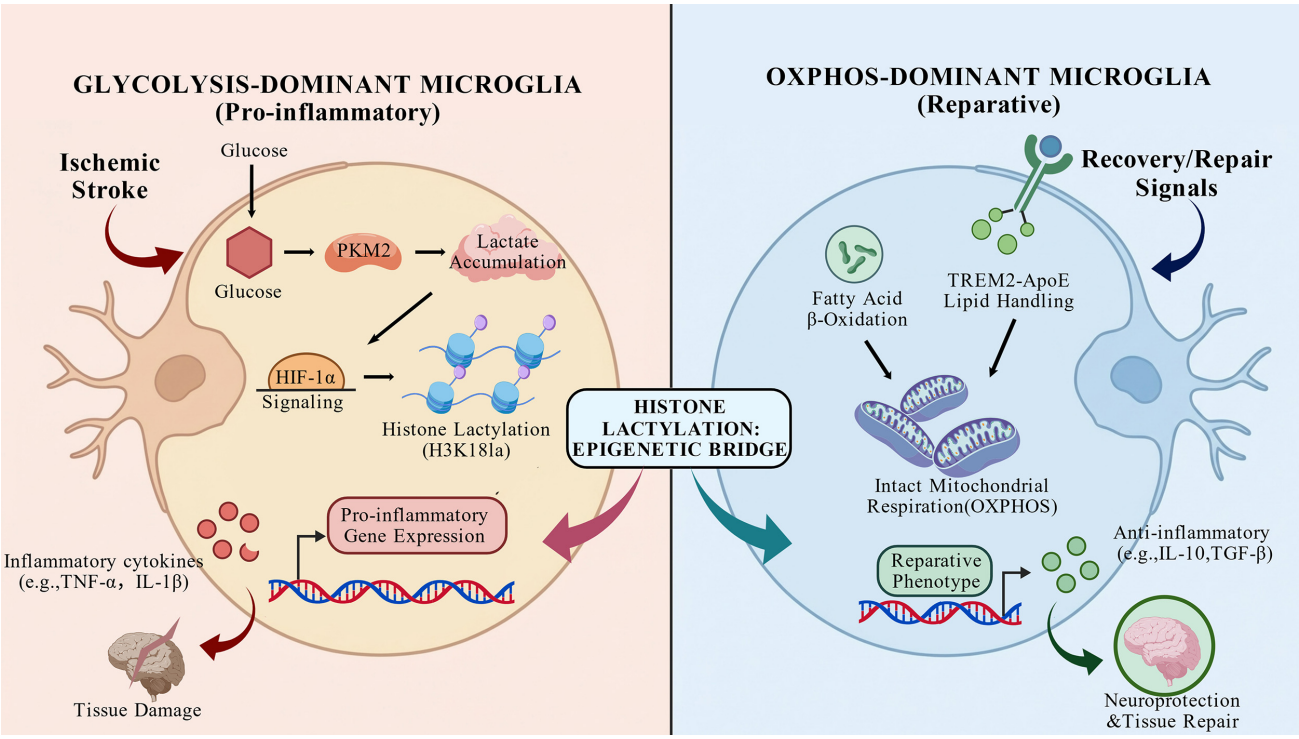

Fig. 3. Metabolic–epigenetic reprogramming shapes microglial fate after ischemic stroke. This schematic illustrates how ischemic stroke–induced metabolic reprogramming drives divergent microglial phenotypes through epigenetic mechanisms. In the left panel, ischemic stress promotes a glycolysis-dominant, pro-inflammatory microglial state. Enhanced glucose uptake and PKM2 activation increase lactate production, leading to lactate accumulation and activation of HIF-1α signaling. Elevated intracellular lactate fuels histone lactylation, particularly H3K18la, which transcriptionally promotes pro-inflammatory gene expression, including cytokines such as TNF-α and IL-1β. This metabolic-epigenetic axis reinforces inflammatory activation, exacerbates tissue damage, and contributes to secondary brain injury. In contrast, the right panel depicts an OXPHOS-dominant, reparative microglial state associated with recovery and repair signals. Enhanced fatty acid β-oxidation and intact mitochondrial oxidative phosphorylation support cellular energy homeostasis. Concurrently, TREM2-ApoE-mediated lipid handling facilitates efficient debris clearance and lipid metabolism. Under these conditions, histone lactylation acts as an epigenetic bridge linking metabolic status to reparative gene programs, promoting anti-inflammatory cytokine production (e.g., IL-10 and TGF-β) and a reparative transcriptional profile that supports neuroprotection and tissue repair. Together, this figure highlights histone lactylation as a key metabolic–epigenetic integrator that connects microglial energy metabolism to transcriptional programming, thereby governing the balance between neurotoxic and reparative microglial phenotypes after ischemic stroke. PKM2, Pyruvate Kinase M2; HIF-1α, Hypoxia-inducible factor-1α; H3K18la, H3K18 lactylation; OXPHOS, oxidative phosphorylation.

roinflammation, thereby promoting motor function recovery [126].

8.2 Inflammasome Suppression

Targeting inflammasome signaling, particularly the NLRP3-caspase-1-GSDMD axis, is a highly attractive therapeutic strategy for ischemic stroke [127,128,129]. Inhibiting NLRP3 can alleviate brain injury and limit microglial pyroptosis [130]; blocking caspase-1 not only reduces infarct volume but also promotes microglial polarization toward a reparative phenotype [131]; inhibiting the GSDMD protein can likewise significantly reduce neuroinflammation [132].

While inhibiting pyroptosis is beneficial, complete suppression can be paradoxically detrimental by delaying tissue repair [32,133]. Therefore, the current focus has shifted to achieving spatiotemporally constrained inhibition. For instance, nanoparticles targeting $CD44^{+}$ microglia selectively block NLRP3 activation without disrupting phagocytic clearance [134]; meanwhile, pharmacologic agents such as dimethyl fumarate inhibit inflammasomes through Nrf2 signaling while maintaining overall microglial activity [135].

8.3 TREM2 Agonists

Targeting TREM2 has emerged as a compelling strategy to reprogram microglia post-stroke. Activation of TREM2 orchestrates beneficial functions, including enhanced clearance of debris, restoration of lipid metabolic homeostasis, and induction of an anti-inflammatory, repar-

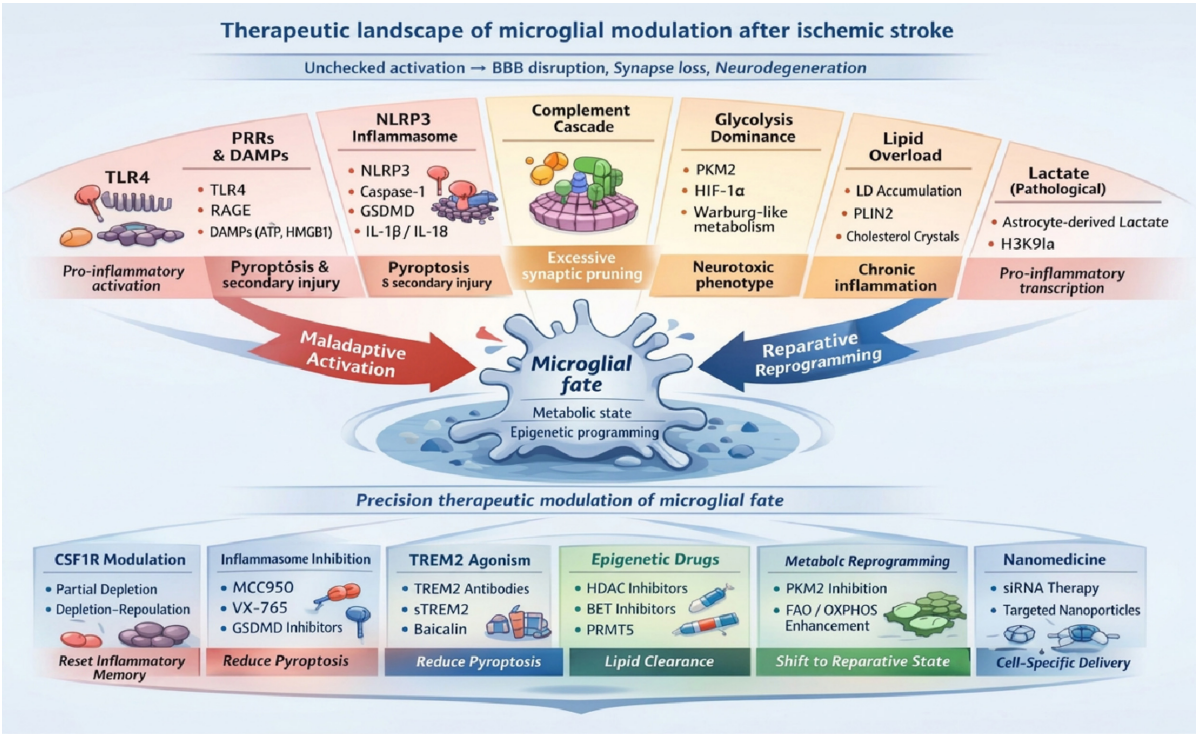

Fig. 4. Therapeutic landscape of microglial modulation after ischemic stroke. This schematic depicts the dual and plastic roles of microglia after ischemic stroke and outlines emerging strategies for precision modulation of their fate. The upper panel summarizes key pathology-driven pathways that promote maladaptive microglial activation. These include DAMP-PRR signaling, NLRP3 inflammasome activation, complement cascade induction, a glycolytic metabolic shift, lipid overload, and pathological histone lactylation. Together, these processes drive pyroptosis, excessive synaptic pruning, chronic neuroinflammation, BBB disruption, and subsequent neurodegeneration. At the center, microglia function as a fate-determining hub, influenced by metabolic and epigenetic states. Their plasticity allows a shift toward either neurotoxic or reparative phenotypes, reflecting their double-edged sword role in stroke. The lower panel highlights precision therapeutic approaches designed to steer microglia toward repair. These include: CSF1R modulation (partial depletion or depletion-repopulation) to reset inflammatory memory; Inflammasome inhibition to reduce pyroptosis; TREM2 agonism to enhance lipid metabolism and debris clearance; Epigenetic drugs (e.g., HDAC, BET, or PRMT inhibitors) to reprogram inflammatory transcription; Metabolic interventions that restore oxidative phosphorylation and fatty acid oxidation; Nanomedicine-based delivery of siRNA or small molecules for cell-specific targeting. Together, these strategies aim to suppress pathological microglial activation while promoting neuroprotective functions, thereby supporting BBB repair, synaptic preservation, remyelination, and functional recovery after ischemic stroke. CSF1R, colony-stimulating factor 1 receptor; HDAC, histone deacetylase; BET, bromodomain and extra-terminal domain; PRMT, protein arginine methyltransferase; PKM2, pyruvate kinase M2; HIF-1α, hypoxia-inducible factor 1α; LD, lipid droplet; PLIN2, perilipin 2; H3K9la, histone H3 lysine 9 lactylation; MCC950, a NLRP3 inflammasome-specific inhibitor; VX-765, a caspase-1 inhibitor; PRMT5, protein arginine methyltransferase 5; FAO, fatty acid oxidation; siRNA, small interfering RNA; PRR, pattern recognition receptor.

ative phenotype [52,72]. This is exemplified by the natural compound baicalin, which upregulates TREM2 to curb microglial hyperactivation and oxidative stress, leading to reduced infarction and improved recovery [136]. Parallel progress in antibody engineering showcases a complementary approach: a bispecific tetravalent TREM2 agonist (Ab18 TVD-Ig), designed for improved brain delivery via transferrin receptor, has proven effective in enhancing microglial phagocytosis and cognitive function in neurodegenerative models [137]. Together, these strategies highlight the potential of TREM2-targeted interventions to restore CNS homeostasis post-stroke.

8.4 Epigenetic Drugs

Epigenetic regulation has become a powerful strategy for reshaping microglial transcriptional programs and neuroimmune responses [138,139]. The histone deacetylase (HDAC) inhibitor Scriptaid can selectively inhibit HDAC2 activity, promoting the polarization of microglia/macrophages toward the anti-inflammatory M2 phenotype and reducing the release of pro-inflammatory cytokines [140].

Targeting epigenetic ‘reader’ proteins can provide an additional layer of regulation. Bromodomain and extra-

Table 1. Overview and translational prospects of microglia-targeted intervention strategies.

Therapeutic strategy	Core targets	Level of evidence	Translational readiness	Major risks and challenges	References
Inflammation blockade	NLRP3/caspase-1	High (multicenter *in vivo* studies)	High (clinical trials initiated)	Long-term inhibition may impair debris clearance functions	[130,131,132]
Population modulation	CSF1R (partial depletion)	Moderate (evidence from animal models)	Moderate (requires strict control of therapeutic window)	Prolonged depletion may exacerbate neurodegeneration	[122,125,126]
Metabolic reprogramming	TREM2 agonists	Moderate (recent frontier discoveries)	Low (blood-brain barrier penetration remains a challenge)	Potential risk of inducing lipid overload	[52,136,137]
Epigenetic remodeling	HDAC/BET inhibitors	Low (mostly *in vitro* and early *in vivo* studies)	Low (lack of cell-type specificity)	Broad off-target effects and systemic toxicity	[140,141,142,143,144]
Precision delivery	Nanomedicines (siRNA)	Moderate (technology validation stage)	Low (clinical safety yet to be established)	Challenges in scalable manufacturing and human immunogenicity	[134,148,149,150]

terminal domain (BET) inhibitors, such as JQ1, not only suppress the transcription of pro-inflammatory cytokines, chemokines, and interferon response genes in activated microglia but also limit microglial migration [141,142,143]. The arginine methyltransferase PRMT5 translocates to the nucleus after ischemia, thereby altering chromatin-associated transcriptional programs. Inhibition of PRMT5 using EPZ015666 has shown significant neuroprotective effects in both *in vitro* and *in vivo* stroke models [144].

8.5 Nanomedicine

Nanomedicine-based strategies represent a frontier for precise therapeutic intervention on microglia post-stroke [75,145]. These approaches exploit intrinsic homing properties, targeting surface markers like P2RY12 and TMEM119, to achieve blood-brain barrier penetration and cell-specific delivery, thereby reducing systemic side effects [146,147]. Notably, siRNA-loaded nanocarriers have demonstrated compelling outcomes: polyethylene glycol–polylactic acid (PEG-PLA) nanoparticles with C3 siRNA curbed complement-mediated synaptic phagocytosis and improved neurological function [148]. lipid-polymer hybrids delivered CD11b or TLR4 siRNA for effective gene silencing [149], and PLGA nanoparticles carrying CX3CR1 siRNA alleviated microglial activation and pain [150], collectively underscoring the platform's versatility and therapeutic potential.

9. Clinical Perspectives and Challenges

Translating microglial modulation from preclinical promise to clinical reality faces significant hurdles [151,152]. A primary obstacle is the absence of reliable, non-invasive biomarkers for real-time tracking of microglial phenotypes. While second-generation TSPO-PET tracers detect global activation, they cannot distinguish neurotoxic from reparative states, limiting their utility for guiding precise therapy. Concurrently, substantial patient heterogeneity, stemming from species differences, comorbidities (e.g., diabetes, hypertension), age-related microglial senescence, and variability in stroke pathology (location, size, vascular status), undermines the predictive value of animal models and contributes to translational failures [152,153,154,155,156,157]. Moreover, strategies for precision reprogramming based on metabolic or epigenetic cues remain largely conceptual, challenged by technical barriers like BBB penetration. Future progress hinges on precise target stratification (see Table 1, Ref. [52,122,125,126,130,131,132,134,136,137,140,141,142,143,144,148,149,150]). Near-term efforts may pragmatically focus on broadly anti-inflammatory pathways already in development (e.g., NLRP3 inhibition). Long-term advancement will require human-relevant experimental platforms [158,159,160] and a shift toward precision immunomodulation, enabled by combining novel ligand imaging with integrated multi-omics analyses [161,162].

10. Conclusions

Microglia are intrinsically double-edged in ischemic stroke, essential for repair yet capable of driving secondary damage. Their function is not fixed but dynamic, shaped by temporal, spatial, metabolic, and signaling contexts. While early activation is beneficial, its dysregulation exacerbates injury. Thus, therapy must steer, not suppress, their responses. Single-cell and spatial omics have moved us beyond the M1/M2 dichotomy, revealing a continuum of states. Combined with immunometabolic and epigenetic insights, microglial fate emerges as a programmable target. Translational hurdles remain: species differences, patient

heterogeneity, and a lack of non-invasive biomarkers. The future lies in precision microglial medicine, using human-relevant models, advanced imaging, and subtype-specific strategies to transform microglia from injury amplifiers into active partners of recovery.

Abbreviations

ATP, adenosine triphosphate; NF-κB, nuclear factor kappa-B; MAPK, mitogen-activated protein kinase; TNF-α, tumor necrosis factor-α; IL-10, interleukin-10; IL-1β, interleukin-1β; CXCL10, C-X-C motif chemokine ligand 10; CCL2, C-C motif ligand 2; iNOS, inducible nitric oxide synthase; TGF-β, transforming growth factor-β; Arg1, arginase-1; YM1, chitinase-3-like protein 3; IGF-1, insulin-like growth factor-1; BDNF, brain-derived neurotrophic factor; ApoE, apolipoprotein E; LPL, lipoprotein lipase; TREM2, triggering receptor expressed on myeloid cells-2; ROS, reactive oxygen species; C1q, complement component C1q; C3, complement component C3; OPC, oligodendrocyte precursor cell; Treg, regulatory T cell; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon gene; CX3CL1, C-X3-C motif chemokine ligand 1; CX3CR1, CX3C chemokine receptor 1; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis associated specklike protein containing a caspase recruitment domain; IL-18, interleukin-18; GSDMD, gasdermin-D; PKM2, pyruvate kinase M2; HIF-1α, hypoxia-inducible factor-1α; H3K18la, H3K18 lactylation; OXPHOS, oxidative phosphorylation.

Author Contributions

SYL conducted the literature search for the manuscript and wrote and revised the manuscript, ZJL generated the images and table, YC revised the text and was involved in the interpretation of data. XYC designed the research project, reviewed and revised the manuscript and supported the financial for the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not Applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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