Microglia-mediated neuroinflammation in intracerebral hemorrhage: Pathological mechanisms and implications for therapeutic development (Review)

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Abstract. Intracerebral hemorrhage (ICH), a life-threatening subtype of stroke accounting for 10-15% of global stroke cases, is characterized by high disability and mortality rates, imposing a heavy socioeconomic burden worldwide. Despite its clinical importance, no effective therapeutic interventions exist for this condition. As the resident immune cells of the central nervous system, microglia play a pivotal role in the pathophysiology of ICH. These cells can be activated to adopt either anti-inflammatory or pro-inflammatory phenotypes. Following ICH, pro-inflammatory mediators derived from microglia act as key drivers of neuroinflammation, thereby exacerbating secondary brain injury. By contrast, promoting the phenotypic shift of microglia toward an anti-inflammatory state has been shown to mitigate an inflammatory response and facilitate neurological recovery. In the present study, existing evidence was reviewed to propose that post-ICH brain injury and repair are orchestrated not by isolated cells, but by a highly dynamic neuroimmune network centered on microglia. Elucidating the spatiotemporal dynamics and key communicative nodes within this network represents a critical frontier. Moving beyond the classical M1/M2 dichotomy to target this network contextually offers a promising and precise therapeutic aim for future investigations.

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Abbreviations: ICH, intracerebral hemorrhage; PBI, primary brain injury; SBI, secondary brain injury; CNS, central nervous system; BBB, blood-brain barrier; PHE, perihematomal edema; TBI, traumatic brain injury; PPAR-γ, peroxisome proliferator-activated receptor γ; DAM, disease-associated microglia; Tg-AD, Alzheimer's disease-transgenic; hiPSC-NSC-Exos, exosomes derived from human-induced pluripotent stem cell-derived neural stem cells; tPA, tissue plasminogen activator; AMPK, adenosine monophosphate-activated protein kinase; AdipoR1, adiponectin receptor 1; CTRP9, C1q/TNF-related protein 9; GSK-3β, glycogen synthase kinase-3β; PRRs, pattern recognition receptors; TLR4, Toll-like receptor 4; cGAS, cGMP-AMP synthase; STING, stimulator of interferon genes; Mincle, macrophage-inducible C-type lectin; Syk, spleen tyrosine kinase; hUCMSC-exo, exosomes secreted by human umbilical cord mesenchymal stem cells; hADSCs-Exo, exosomes derived from human adipose-derived mesenchymal stem cells; MMPs, matrix metalloproteinases

Key words: ICH, brain damage, microglial polarization, neuroprotection, inflammation

Contents

1. Introduction

Intracerebral hemorrhage (ICH) accounts for 10-15% of all stroke cases, with >2 million patients worldwide annually. Characterized by complex pathophysiology and a one-month mortality rate of ~70%, ICH poses a severe clinical challenge (1-7). Globally, the incidence of ICH has demonstrated an upward trend with advancing medical understanding (8,9), driven by factors such as the increasing elderly population, widespread use of anticoagulants, antiplatelets and thrombolytics (10,11). While preclinical research using animal ICH models has yielded promising developments in potential treatments (12-15), the absence of evidence-based therapeutic strategies in clinical settings remains a critical barrier to improving ICH prognosis. This gap underscores the urgent need for translating preclinical advancements into clinically viable interventions to address the unmet therapeutic needs in ICH management.

Following ICH, rupture of brain parenchymal vessels leads to erythrocytes accumulation and hematoma formation, which directly compresses brain tissue and causes primary brain injury (PBI). In the hematoma, erythrocyte hemolysis releases toxic hemolytic products that induce secondary brain injury (SBI) and irreversible neurological deficits (16,17). Mounting evidence indicates that inflammatory responses are central to the pathophysiology of SBI (18). During this process, circulating monocyte-derived macrophages and resident microglia in the central nervous system (CNS) infiltrate the hemorrhagic site. These microglia/macrophages serve as key regulators of neuroinflammation and hematoma resolution mitigation in SBI (19,20), highlighting their critical role in shaping post-ICH neuroinflammatory trajectories and potential as therapeutic targets.

Microglia, the primary immune cells of the CNS, constitute 5-10% of brain cells and are often referred to as the 'resident macrophages' of the brain (21,22). They interact dynamically with neurons, astrocytes and oligodendrocytes under physiological conditions, playing a fundamental role in sustaining brain homeostasis (23). The highly plastic nature of microglia, including their phenotypic diversity, hinges on the type of stressor or neuropathology that they encounter (24). Specifically, during distinct pathological phases of ICH, microglia polarization generates pro-inflammatory (M1-like) or anti-inflammatory (M2-like) mediators, which directly influence the progression of ICH and neurological outcomes (20,25). This dual functionality underscores the central role of microglia in modulating neuroinflammation and tissue repair after ICH.

The hematoma and hemolysis resulting from ICH trigger robust microglial activation, exacerbating neuroinflammation (26,27). Chang *et al* (28) demonstrated that microglia rapidly respond to hemorrhagic insult within 1-1.5 h after ICH onset by initially adopting a protective phenotype, in which IL-10 mediates microglial phagocytosis of hematoma components and promotes hematoma resolution, thereby highlighting the early protective role of microglia in mitigating SBI. By contrast, microglial depletion exacerbates brain damage after ICH, manifesting as brain swelling, neuronal degeneration and worsened neurological impairments (29-31). Critically, emerging evidence suggests that microglia do not act in isolation. Therefore, the present review will discuss whether the pathological and reparative processes following ICH are determined not by any single cell type, but by a microglia-centered, spatiotemporally dynamic neuroimmune network. The present review systematically evaluated the microglial inflammatory response and its therapeutic targets after ICH, while integrating current understanding of their anti-inflammatory therapeutic potential. Notably, key hurdles to clinical translation were emphasized, including ICH-induced iron overload, mass effect, persistent inflammatory responses and oxidative damage.

2. Pathological changes following ICH

ICH-induced brain injury, characterized by a high risk of recurrent bleeding and ischemia, typically unfolds as a cascade of pathological processes comprising two successive stages: PBI and SBI (32,33). During the PBI stage, blood from ruptured vessels forms a hematoma within the first few hours, exerting a mass effect through mechanical compression of brain parenchymal structures. This process leads to elevated intracranial pressure and potential brain herniation, often managed clinically through advanced surgical interventions (33,34). The SBI stage follows, driven by hemolytic products from erythrolysis, including hemoglobin, heme, free iron, along with neuroinflammation, excitotoxicity and oxidative stress (35-38). Concomitant pathological changes include hemodynamic ischemia, cerebral edema exacerbation, direct cellular toxicity and blood-brain barrier (BBB) disruption (1,15,18,35,39,40). Hemolytic byproducts infiltrate the perihematomal region, activating microglia/macrophages for hematoma clearance (7,39,41,42), while thrombin activation contributes to vasculogenic edema via endothelial cell and BBB damage (43). Perihematomal edema (PHE), a hallmark of SBI linked to poorer prognosis, has emerged as a key therapeutic target in post-ICH pathophysiology (44-46). Additionally, intracranial hematomas can expand into adjacent brain tissue via perivascular spaces, white matter tracts and perineurium, distorting and disrupting nerve fibers beyond repair (7,47,48). Collectively, these SBI-related pathological changes culminate in permanent brain tissue damage and severe neurological deficits, underscoring the critical need for continuous focus on mitigating SBI mechanisms in ICH management (43,49).

3. Microglial polarization after ICH

The neuroinflammatory response following ICH is a highly dynamic and temporally regulated process, in which microglial polarization plays a central role. Post-ICH neuroinflammation evolves through distinct yet overlapping phases, each characterized by specific pathological drivers, shifting microglial phenotypes and unique molecular signatures. This chronological progression dictates the functional outcome of microglia, transforming them from sentinels of acute damage to modifiers of chronic recovery. Understanding this temporal regulation is therefore central for deciphering the dual roles of microglia in injury exacerbation and resolution, and for designing stage-specific therapeutic interventions.

ICH-induced hematoma represents a primary driver of brain injury. A rapid neuroinflammatory reaction emerges

within minutes to hours post-ICH ictus, characterized by glial population activation and the production of cytotoxic factors, reactive oxygen species, matrix metalloproteinases and related pro-inflammatory mediators (50). Single-cell RNA sequencing of peri-injury cortical tissue from patients with traumatic brain injury (TBI) and ICH identified five microglial subpopulations: (i) Homeostatic; (ii) pro-inflammatory; (iii) stressed; (iv) ribosome biogenesis; and (v) phagocytic (51). Specific knockout of microglial C5aR1 ameliorated neurological outcomes in mice with TBI and ICH, attenuating neuroinflammatory responses and reducing cerebral edema (51). Concurrently, within hours to days, extravasated erythrocytes in the hematoma release neurotoxic blood products, including cytotoxic iron, heme and hemoglobin, triggering SBI and inducing persistent cerebral edema and progressive tissue damage (52,53). Emerging evidence highlights regulatory mechanisms that may mitigate this process by modulating the CCR4/ERK/Nrf2 signaling pathway and activating peroxisome proliferator-activated receptor γ (PPAR-γ). These mechanisms facilitate microglial phagocytosis and phenotypic polarization toward immune homeostasis, offering potential therapeutic strategies to counteract SBI (34,54,55).

The breakdown of the BBB and subsequent cerebral edema represent life-threatening events in ICH (56,57). Microglia, through nuclear receptor subfamily 4 group A member 1, can alleviate neuroinflammation in the acute phase after stroke and ameliorate ischemic brain injury (58). Accumulating evidence highlights the key role of microglial activation in driving SBI after ICH (59,60). Microglial M1 polarization promotes the secretion of pro-inflammatory cytokines, exacerbating neuroinflammation (61,62). Chen *et al* (63) demonstrated that TNF-α derived from M1-type microglia induces endothelial necroptosis, resulting in BBB disruption. In ischemic stroke models, anti-TNF-α therapy significantly mitigated endothelial necroptosis, BBB damage and neurological deficits, underscoring the causal link between microglial inflammation and vascular pathology. Neuroprotective agents have been shown to attenuate lipopolysaccharide-induced NO release, TNF-α secretion and NF-κB activation in microglia, while promoting anti-inflammatory cytokine production to protect the BBB and facilitate neural repair (64-66). Similarly, cytokines such as IL-4 and IL-10 promote microglial polarization toward an anti-inflammatory phenotype termed M2, emerging as potential therapeutic targets for modulating BBB integrity after ICH (67).

Previously, microglial subtype termed disease-associated microglia (DAM) was identified through transcriptional single-cell analysis in the brains of Alzheimer's disease (AD)-transgenic (Tg-AD) mice and triggering receptor expressed on myeloid cells 2 (TREM2)$^{-/-}$ Tg-AD mice (68-70). The differentiation of microglia into DAM occurs in two distinct phases, including an initial TREM2-independent activation program, followed by a TREM2-dependent maturation stage. This specialized microglial subset exhibits the potential to limit neurodegeneration, offering critical insights for future therapy in AD and other brain disorders (70,71). Subsequent genome-wide transcriptomic analyses revealed the presence of DAM-like states across diverse pathological contexts, including aging and ALS (70). While DAM shares partial molecular overlap with the classical M1 pro-inflammatory phenotype, their transcriptional signatures exhibit distinct differences (72). Notably, transcriptomic profiling of microglial activation in AD and aging models has revealed that DAM co-expresses anti- and pro-inflammatory sub-programs, highlighting their dual functional complexity (73,74). The progressive transition from homeostatic microglia to reactive DAM is critically dependent on TREM2, a receptor predominantly expressed on microglial surfaces (75-77). After ICH, activated TREM2 in perihematomal regions mitigates neuronal loss, neuroinflammation and neurological deficits through the activation of the PI3K/Akt signaling pathway (78). The activation of TREM2 can significantly alter the phagocytic and inflammatory functions of microglial cells, making it a critical regulator of DAM polarization (79). Additionally, exosomes derived from human-induced pluripotent stem cell-derived neural stem cells (hiPSC-NSC-Exos) have been shown to suppress pro-inflammatory cascades in DAM within AD mouse models (80). Wang *et al* (81) further demonstrated that hiPSC-NSC-Exos stabilize the BBB by downregulating monocyte chemoattractant protein-1 secretion in astrocytes via the PI3K/Akt pathway activation, underscoring the therapeutic versatility of DAM-targeted interventions across neurological diseases (81). Moreover, Gao *et al* (74) reported that transcription factors such as IRF1, CEBPα and LXRβ modulated anti- and pro-inflammatory DAM gene expression through regulating the Erk signaling pathway. Collectively, these findings underscore the notable sensitivity of microglia to dynamic pathological cues in brain tissue, emphasizing their role as highly plastic sensors and effectors of CNS injury and disease.

Notably, several studies have explored the spatiotemporal specialization of microglial subsets during evolution and disease, leveraging single-cell analyses to define precise molecular signatures and cellular dynamics (82,83). Olah *et al* (84) identified that 9/10 myeloid clusters express high levels of microglia-enriched genes (such as C1QA, C1QB, C1QC and GPR34), and they identified these nine clusters as distinct microglial clusters. Ochocka *et al* (85) demonstrated microglial cellular and functional heterogeneity through scRNA-seq and flow cytometry by isolating distinct microglial clusters with unique gene expression profiles and functional roles, revealing that in naïve and GL261 glioma-bearing mice, reactive microglia exhibited spatially segregated distributions when analyzing CD11b^{+} myeloid cells. Furthermore, Hammond *et al* (86) and Li *et al* (87) revealed that microglial heterogeneity reaches its peak during early development, indicating that microglia exhibit diverse transcriptional states across development, homeostasis, aging and disease (88). These findings not only identify microglial subclasses linked to neurodegenerative diseases and behavioral disorders but also provide a framework to dissect the multifaceted roles of microglia in human brain pathologies (89).

Following ICH, modulators of microglial activation and polarization, including key signaling pathways, transcription factors and specific markers of M1/M2 subclasses, hold clinical and translational importance, providing a basis for modulating microglial function to mitigate brain injury (38). While the classical M1/M2 dichotomy has provided a practical conceptual framework for describing pro-inflammatory vs. anti-inflammatory microglial responses following ICH, it has

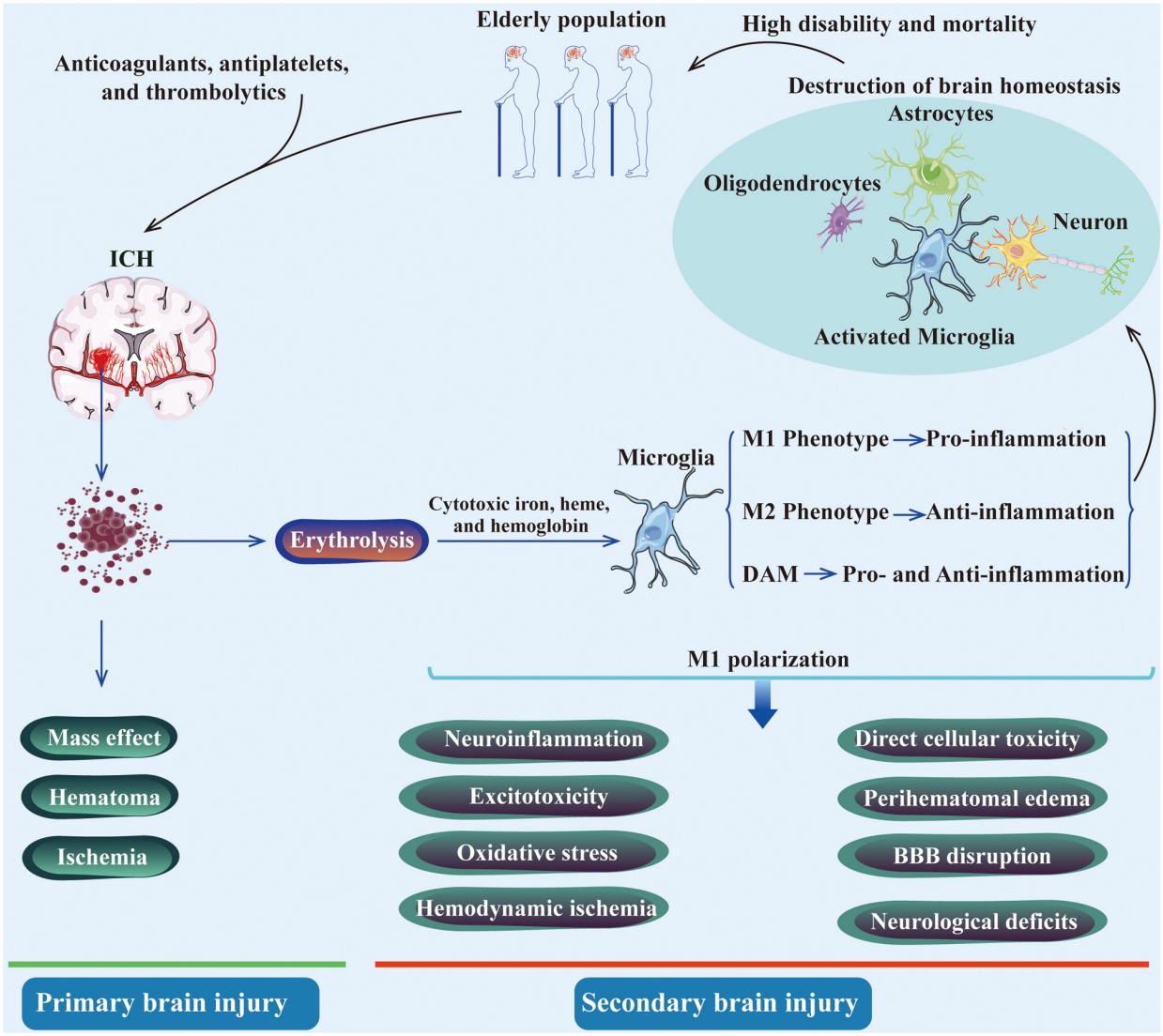

Figure 1. Polarization of activated microglia following ICH. After ICH onset, PBI and SBI occur sequentially. PBI begins with vessel occlusion, followed by rupture, erythrocytes extravasation and dynamic hematoma expansion, immediately compressing and damaging adjacent brain tissue, disrupting surrounding structures and causing early neurological dysfunction. SBI, emerging hours to days later, is driven by hemolytic products (such as ferrous ions, hemoglobin and heme), inducing oxidative stress, inflammation, excitotoxicity and death signals in neurons and glia. Microglial polarization in response to erythrocyte lysates post-ICH has three main types: (i) M1 phenotype, which elevates pro-inflammatory factors and promotes brain damage; (ii) M2 phenotype, primarily exerting neuroprotection; and (iii) DAM, identified via single-cell RNA sequencing and other omics, which can exhibit both neuroprotective and destructive phenotypes, requiring further investigation. ICH, intracerebral hemorrhage; PBI, primary brain injury; SBI, secondary brain injury; DAM, disease-associated microglia; BBB, blood-brain barrier.

become increasingly clear that this binary model oversimplifies the diversity of microglial states *in vivo*. Following ICH onset, pro-inflammatory microglia-derived mediators often overwhelm the reparative capacity of anti-inflammatory microglia (20). Thus, identifying these modulators and influencing factors is essential for promoting microglial polarization toward neuroprotective subclasses, offering novel insights into alleviating post-ICH microglial pathology. Based on the aforementioned analyses of microglial polarization in ICH and investigations into surface markers of microglial subtypes, shifting microglia from a pro-inflammatory to an anti-inflammatory state represents a critical strategy to improve outcomes after SBI (Fig. 1).

By integrating the microglial response in ICH within a dynamic continuum framework, the present review offers distinct added value over traditional classification perspectives. First, this framework can reconcile and unify seemingly contradictory findings in the literature. For example, the differential expression of the same marker in the injury core vs. remote regions, or at different time points, can be interpreted as positional shifts of the same cell population along the state continuum. Second, it emphasizes the critical importance of spatiotemporal dimensions by explicitly linking microglial states to proximity to the hematoma and specific disease stages. This directly suggests the existence of key time windows and spatial targets for therapeutic intervention. Finally, this paradigm points to new directions for future research: Encouraging the use of spatial transcriptomics to map the whole-brain landscape of microglial states post-ICH; employing single-cell multi-omics to identify key regulatory nodes driving state transitions; and ultimately designing next-generation smart therapies aimed at dynamically steering

microglia toward beneficial functional states, rather than simply suppressing or activating them. Therefore, adopting a dynamic continuum perspective not only more accurately reflects the biological reality but also serves as a conceptual prerequisite for advancing ICH immunotherapy from broad interventions toward precise modulation.

4. Microglia-mediated multicellular crosstalk in ICH

Microglia do not act in isolation but orchestrate a complex multicellular network with astrocytes, infiltrating immune cells and endothelial cells. This crosstalk constitutes a critical amplification loop of SBI and a potential therapeutic target after ICH.

Microglia-astrocyte crosstalk. Activated microglia and astrocytes form a bidirectional regulatory loop to modulate neuroinflammation and glial scar formation. Astrocytes promote an anti-inflammatory milieu by secreting costimulatory molecules such as CD200 and interacting with microglia to activate anti-inflammatory cytokines (90). In preclinical models, C5aR1 on microglia integrates local and peripheral C5a signals, triggering a cascade of neuroinflammation amplification, neurotoxic astrocyte polarization and neutrophil recruitment that culminates in cerebral edema (51). In ICH, the C3-C3aR signaling axis, formed by astrocytic C3 and microglial C3aR, mediates the inhibitory effect of A1 astrocytes on the phagocytosis of myelin debris (91). The release of IL-15 from astrocytes triggers a shift in microglia toward a pro-inflammatory phenotype, creating a feedback loop that exacerbates neuroinflammation following ICH (92). TRPA1 in astrocytes regulates neuroinflammation and neurological deficits post-ICH, by suppressing the MAPK/NF-κB signaling pathway, driving a shift toward the neuroprotective A2 astrocytic phenotype and enhancing the proliferation of phagocytic microglia (93). Bidirectional regulation between microglia and astrocytes serves as a key mechanism modulating the inflammatory response after ICH, primarily through influencing cytokine profiles and cellular phenotypic transitions. The crosstalk between microglia and astrocytes represents a focal point and cutting-edge area in immunology research, with their bidirectional modulation of phenotypic and functional states warranting particular attention in the field of ICH.

Microglia-immune cells crosstalk. Microglia serve as a bridge linking central and peripheral immunity after ICH. IL-10 modulates both microglial phagocytic function and the infiltration of monocyte-derived macrophages following ICH, with CD36 serving as a key phagocytic effector downstream of IL-10 signaling (94). Activin-A, derived from M2 microglia/macrophages, plays a crucial role in promoting oligodendrocyte differentiation and thereby fostering myelin regeneration, highlighting its potential as a therapeutic target for white matter injury following cerebral hemorrhage (95). In PHE, crosstalk between microglia-derived osteopontin and CD44-positive cells plays a critical role in regulating the local immune milieu, thereby influencing the pathological progression (96). Extracellular vesicles secreted by bone marrow-derived macrophages have the potential to boost microglial phagocytosis in the aftermath of ICH (97). Microglia act as an immune bridge, regulating phagocytic function and repair processes through specific molecules and responding to external signals such as extracellular vesicles. However, current findings largely remain as isolated mechanisms, and the mechanisms by which they integrate into a coordinated spatiotemporal network within the dynamically evolving ICH milieu remains unclear.

Microglia-endothelial cells crosstalk. The communication between microglia and endothelial cells constitutes a critical axis within the neurovascular unit, fundamentally influencing the pathophysiology of ICH. This bidirectional crosstalk regulates central processes including BBB integrity, neuroinflammation and vascular repair, making it a pivotal focus for therapeutic intervention. Their functional interplay is facilitated by spatial proximity and involves both contact-dependent and soluble mediators. Activated microglia can directly influence BBB permeability through the release of inflammatory factors and proteases interacting with endothelial cells (67). In the context of ICH, endothelial cells lining the choroid plexus are prone to pyroptosis at the 24-h time point (98). ICH-induced pyroptosis in endothelial cells is accompanied by the release of pro-inflammatory cytokines IL-6 and IL-1β, which engage with microglia to activate the NF-κB signaling pathway and ultimately lead to increased transcriptional expression of Lcn2 and Msr1 (98). This initiates a cycle of endothelial damage activating microglia, whose response further exacerbates vascular dysfunction and inflammation. Hence, therapeutic strategies aimed at the microglia-endothelial axis, such as inhibiting key inflammatory pathways or protecting endothelial health, offer a promising avenue to alleviate SBI post-ICH.

5. Targeting microglial neuroinflammation post-ICH

Microglia play a dual role as both drivers of secondary injury and promoters of repair, which presents both challenges and opportunities for the treatment of ICH. This dual role not only poses complex challenges for the treatment of ICH but also identifies novel opportunities to achieve neuroprotection by modulating microglial functions. At present, although numerous molecular targets have been proven to regulate microglial functions, translating such findings from preclinical models to successful clinical applications faces a core issue: The need to shift from merely enumerating discrete mechanisms to prioritizing the development of therapeutic strategies based on translational feasibility, target specificity and their integration into the dynamic pathophysiology of ICH.

The pro-damaging properties of microglia have been widely validated. Soluble epoxide hydrolase expression is upregulated in microglia following ICH and potently drives neuroinflammatory responses, whereas its inhibition suppresses microglia-mediated inflammation (99). Additionally, deficiency of TWIK-related K^+ channel 1 exacerbates microglial and neutrophil recruitment and pro-inflammatory factor production in ICH-induced SBI (100). Furthermore, microglia-expressed integrin Mac-1, acting in conjunction with the endocytic receptor LRP1 in the neurovascular unit, promotes thrombolytic tissue plasminogen activator (tPA)-induced activation of platelet-derived growth factor-cc, thereby increasing BBB permeability in ischemic

stroke (56). These studies collectively indicate that targeting the pro-inflammatory pathways of microglia represents a viable therapeutic direction for alleviating early-stage injury.

The anti-inflammatory and reparative potential of microglia is equally prominent. The crosstalk between regulatory T lymphocytes and microglial neuroinflammation has been well documented. Studies have shown that regulatory T lymphocytes relieve ICH-induced neuroinflammation by enhancing a phenotypic shift from M1 to M2 microglia via modulation of the IL-10/GSK3β/PTEN signaling pathway (101-103). This Treg-mediated immunomodulation highlights the therapeutic potential of harnessing microglial plasticity to drive neurorepair following ICH. However, both Treg-based and M2-polarization strategies face notable translational hurdles in clinical translation, including the lack of robust, non-invasive biomarkers of microglial phenotype in humans, the potential risk of systemic immunosuppression and substantial uncertainty regarding the optimal intervention timing. Simple functional inhibition or promotion may be insufficient to address the spatiotemporal complexity of microglial dynamics following ICH. Therefore, future development of therapeutic strategies must undergo a fundamental shift in logic. It is hypothesized that prioritizing and integrating intrinsic regulatory targets that possess relative microglia selectivity, high druggability and well-defined therapeutic time windows. This approach should aim to develop precision interventions capable of adapting to the pathological progression of ICH, rather than merely describing isolated mechanisms.

Targeting intrinsic regulatory axes of microglia. Following ICH, the anti-inflammatory functions of microglia are mediated by diverse signaling axes that form complex networks intertwined with multiple biological processes. Elucidating these signaling pathways and their molecular foundations is critical for identifying promising therapeutic targets to mitigate neuropathological deficits in ICH. Among them, targeting intrinsic regulatory axes is particularly promising. This approach directly modulates the cell-autonomous mechanisms of microglia, including phagocytosis, polarization and inflammatory signaling, by acting on their intrinsic signaling pathways. Due to this cell-specific mode of action, it offers high target specificity with a potentially favorable systemic side-effect profile, representing the most promising direction for current clinical translation efforts in post-ICH neuroinflammation.

PPAR-γ. Studies have demonstrated that rosiglitazone-mediated activation of PPAR-γ protects against BBB damage and ameliorates hemorrhage transformation, potentially by promoting anti-inflammatory polarization of microglia (104,105). Phagocytosis is critical for enhancing hematoma resolution, promoting healing after ICH injury. Zhao *et al* (106) found that PPAR-γ activators significantly upregulated PPAR-γ-regulated genes such as CD36 catalase, while downregulating pro-inflammatory genes and alleviating neuronal injury by enhancing microglial phagocytosis, whereas PPAR-γ gene knockdown or anti-CD36 antibody treatment significantly impaired this phagocytic function following ICH. PPAR-γ activation also enhances the phagocytic capacity of anti-inflammatory microglia via CD36 (52). Building on preclinical research, PPAR-γ activators have entered clinical applications. Simvastatin-activated PPAR-γ improves microglia-induced erythrocyte phagocytosis and exhibits neuroprotective effects in patients with ICH (107,108). These findings highlight PPAR-γ as a pivotal regulator of microglial phagocytosis and inflammation, with therapeutic activators offering promise for clinical translation in ICH.

AMPK. Adenosine monophosphate-activated protein kinase (AMPK) regulates the balance between pro- and anti-inflammatory microglial subclasses by acting as a central sensor of brain injury (109,110). Adiponectin receptor 1 (AdipoR1), constitutively expressed in microglia, is activated by endogenous C1q/TNF-related protein 9 (CTRP9), which exhibits increased expression within the first 24 h after ICH. CTRP9 treatment upregulates AdipoR1 and phosphorylated (p-) AMPK protein levels while reducing inflammatory cytokines, thereby decreasing neuroinflammation by modulating the AdipoR1/AMPK/NF-κB signaling pathway (111). Following ICH, CTRP9-activated AdipoR1 further mitigates neuropathological damage and BBB dysfunction by engaging APPL1/AMPK/Nrf2 signaling, highlighting CTRP9 as a promising therapeutic agent for improving BBB integrity (112,113). Similarly, activation of melanocortin receptor 4 alleviates neuropathological deficits by regulating the AMPK signaling pathway (114). Future research should focus on developing brain-specific AMPK activators to enhance translational feasibility.

GSK-3β. Inhibition of glycogen synthase kinase-3β (GSK-3β) confers neuroprotective effects in *in vivo* experiments (115-117). By enhancing microglial phagocytosis and promoting M2-phenotype microglial differentiation, GSK-3β inhibition significantly improves hematoma resolution and cognitive deficits in rats with ICH (118,119). Additionally, lithium chloride treatment downregulated GSK-3β activity, reducing mature oligodendrocytes death and upregulating brain-derived neurotrophic factor expression (120). Thus, GSK-3β is classified as a medium-priority target, requiring time-window stratified studies and dose-optimization research to confirm its clinical applicability.

As aforementioned, regulatory T lymphocytes suppress the microglia-induced inflammatory response and improve neurological deficits by inhibiting NF-κB activation via the JNK/ERK pathway (38,101,121). Hyperbaric oxygen therapy has been shown to reduce the expression levels of pro-inflammatory cytokines and p-JNK, proposing a link between JNK signaling and downregulation of M1 microglial immune activity (122,123). Current clinical management of ICH faces notable limitations, including concerns about treatment efficacy, surgical trauma, complications and drug side effects, with few standardized interventions available. Hyperbaric oxygen therapy (HOT) emerges as a promising alternative approach, although the specific mechanisms by which HOT modulates ICH pathophysiology require further investigation and validation. These findings highlight the need to explore non-pharmacological, pathway-targeted strategies such as HOT to address unmet clinical needs in ICH treatment.

Intrinsic regulatory targets with high druggability and existing clinical repurposing potential should be prioritized for subsequent translational studies. AMPK and GSK-3β, while mechanistically promising, require specificity enhancement and clinical feasibility validation to advance toward clinical application.

Intercepting detrimental extracellular signals. Intercepting detrimental extracellular signals targeting microglial pattern recognition receptors (PRRs) is a key upstream intervention strategy. This approach aims to block the initial 'trigger' of microglial activation, thereby inhibiting downstream inflammatory cascades. However, PRRs are often widely expressed in myeloid cells, leading to potential systemic immune suppression, which poses a major translational issue for this class of targets.

Toll-like receptors. Toll-like receptor 4 (TLR4), a central player in innate immune responses, has been recognized as a key pattern recognition receptor (124). TLR4 deficiency attenuated perihematomal inflammation by reducing the infiltration of pro-inflammatory microglia in *in vivo* ICH experiments (125,126). By contrast, TLR4 activation impairs microglial phagocytosis of erythrocytes, delaying CD36-mediated hematoma resolution and exacerbating neurological deficits in ICH (127,128). Additionally, TLR4-driven microglial autophagy has been linked to exacerbated neuroinflammation in ICH mouse models (129). Collectively, these studies highlight the dual role of TLR4 in modulating both inflammatory recruitment and hematoma clearance after ICH. Targeting TLR4 signaling represents a promising therapeutic strategy to balance anti-inflammatory effects with enhanced phagocytic function, positioning it as a potential candidate for future ICH interventions.

cGMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) axis. DNA damage initiates the innate immune response, with cGAS, a key DNA sensor, detecting disease-associated damaged DNA to activate its downstream effector, STING. This cascade results in the upregulation of type I interferon production and phosphorylation of interferon regulatory factor 3 (130). cGAS acts as a critical regulator of inflammation and autophagy, with upregulated cGAS in striatal brain damage mediating inflammation via increased expression of pro-inflammatory genes (Ccl5 and Cxcl10) and activating autophagy through the major initiators LC3A and LC3B (131). In ischemic stroke models, tPA therapy enhances neutrophil extracellular trap expression in plasma and brain tissue. DNase I treatment or peptidyl-arginine deiminase 4 deficiency, both of which inhibit neutrophil extracellular trap formation, reverse tPA-induced cGAS upregulation. By contrast, in tPA-treated mice, cGAMP (a cGAS-derived second messenger) suppresses DNase I-induced anti-hemorrhagic effects by dampening STING and type I interferon signaling (132). Jiang *et al* (133) further demonstrated that cGAS knockdown furthers M2 microglial polarization and attenuates the inflammatory response by disrupting the cGAS-STING axis in stroke mice. Shi *et al* (134) extended these findings, demonstrating that a cGAS inhibitor delivered via immunosuppressive nanoparticles reduces microglial inflammation and enhances anti-inflammatory polarization in post-stroke rats. IronQ pretreatment confers mesenchymal stem cells (MSCs) with a synergistic effect to alleviate neuroinflammation and improve neurological function, achieved by inhibiting the cGAS-STING signaling pathway (135).

C-type lectin-like receptors. C-type lectin-like receptors, a family of transmembrane PRRs predominantly expressed in myeloid cells, play a critical role in innate immunity (136). Dysregulation of C-type lectin-like receptors following tissue injury can drive excessive production of inflammatory mediators and exacerbate inflammatory progression. Among C-type lectin-like receptors, microglial macrophage-inducible C-type lectin (Mincle), widely expressed on macrophages, binds nuclear spliceosome-associated protein 130 released from necrotic cells, potently enhancing the inflammatory response (137,138). In alcohol-induced liver injury models, Mincle activation via its downstream effector spleen tyrosine kinase (Syk) upregulates the expression levels of pro-inflammatory genes (139), while in Crohn's disease, the Mincle/Syk axis exacerbates intestinal mucosal inflammation through macrophage pyroptosis (140). Inhibiting this pathway attenuates inflammatory responses, highlighting its therapeutic potential. Preclinical studies across multiple neurological disorders have demonstrated that blocking the Mincle/Syk signaling axis confers neuroprotection (141). For example, interventions including the Syk inhibitor BAY61-3606, acupuncture and MSC transplantation suppress Mincle/Syk-mediated microglial activation, reducing neuroinflammation in *in vivo* stroke models (138,141-145). Collectively, these findings establish the Mincle/Syk pathway as a promising therapeutic target for ICH, offering a rationale for developing novel immunomodulatory strategies to mitigate post-ICH neuroinflammation and promote neurological recovery.

Autophagy. To date, autophagy exhibits dualistic functions, making it challenging to assess whether its effects after ICH are predominantly harmful or beneficial. Excessive autophagy exacerbates endoplasmic reticulum stress (ERS)-induced brain injury as early as 6 h following ICH. By contrast, at day 7 post-ICH in rats, autophagy strengthens ERS protective functions by clearing cellular debris (146). Tan *et al* (147) demonstrated that enhanced autophagy attenuates oxidative stress injury following ICH by upregulating antioxidant protein expression, while autophagy inhibitors reverse this neuroprotective effect. Previous studies further indicate that autophagy positively regulates the inflammatory response in the context of ICH (148,149).

IL. The levels of ILs during ICH progression are modulated by microglial functions. Xu *et al* (150) demonstrated that IL-4-loaded nanoparticles activating the IL-4/STAT6 axis promoted hematoma resolution and functional recovery in mice with ICH. By contrast, IL-15, a pro-inflammatory cytokine, regulates homeostasis and microglial immunoreactivity following CNS inflammatory events (92). Yu *et al* (151) showed that an IL-17A-neutralizing antibody attenuates microglial activation and blocks ICH-mediated pro-inflammatory cytokines. Shi *et al* (152) further revealed that IL-17A enhances microglial autophagy and neuroinflammation. Administration of an IL-17A-neutralizing antibody significantly reduced brain edema and improved neurological outcomes in mice with ICH, while genetic inhibition of autophagy-related genes ATG5 and ATG7 suppressed microglial autophagy and inflammation (153). Intraventricular injection of IL-33 alleviated white matter and neuronal injury by promoting microglial M2 polarization following ICH (154). Additionally, inhibiting the NF-κB signaling pathway through diverse interventions, including microRNAs (miRNAs or miRs), GATA-binding protein 4 and traditional Chinese medicines, can reduce neuroinflammation in ICH therapy (155-159). These findings highlight the bidirectional role of ILs and NF-κB in regulating

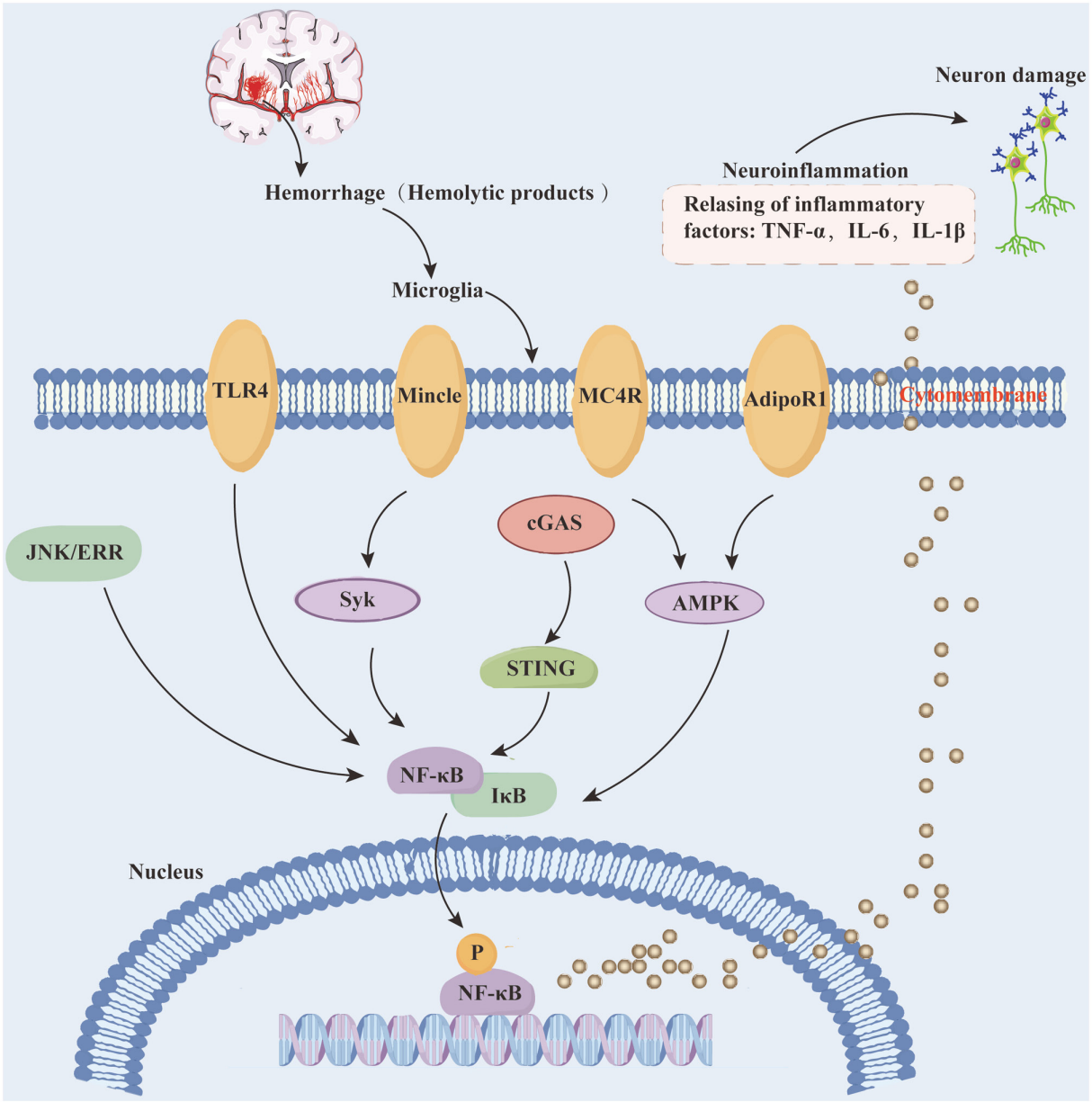

Figure 2. Mechanisms underlying activated microglia-mediated neuroinflammation. The mechanisms associated with intracerebral hemorrhage following microglial activation involve various signaling pathways, whose activation can exacerbate neuroinflammation.

microglial phenotypes and underscore their therapeutic potential in modulating neuroinflammation after ICH.

Intercepting extracellular signals via PRRs represents a rational upstream therapeutic strategy, yet its translational potential is constrained by insufficient target specificity and limited validation in ICH-specific models. Therefore, future research should focus on developing microglia-specific PRR modulators and conduct in-depth validation in clinically relevant ICH models. In summary, although extensive preclinical studies have made notable progress at the mechanistic level, successfully translating these findings into clinical applications requires further systematic investigation of promising interventions (Fig. 2).

Emerging precision therapeutics: Exosomes and miRNAs. Exosomes and miRNAs represent emerging precision therapeutic tools for modulating microglia after ICH, offering advantages such as low immunogenicity, high target specificity and the ability to regulate multiple pathways simultaneously, thereby effectively addressing the spatiotemporal complexity of microglial dynamics post-ICH. To translate these promising tools into precise therapies, a rational framework is required. This involves identifying key molecular targets within microglial dynamic continuum, categorizing them based on their pathological function, and employing engineered exosomes for spatiotemporally controlled delivery. Current evidence points to three strategic categories of targets: (i) Inflammatory initiators (for example, TLR4), the suppression of which quenches upstream danger signaling; (ii) polarization nodes (for example, CKIP-1 and C/EBP-α), the modulation of which actively reprogrammes microglia toward a reparative phenotype; and (iii) Cellular stress regulators (for example, mTOR), the intervention of which maintains microglial homeostasis. The convergence of exosome biology and miRNA targetology

offers a unique path to address these targets in a combined and specific manner.

Given their minimal risks of immunogenicity and tumorigenicity, exosomes secreted by human umbilical cord mesenchymal stem cells (hUCMSC-exo) represent a promising alternative to cell-based therapies. Evidence indicates that hUCMSC-exo administration can alleviate astrocyte inflammation and mitochondrial damage associated with ICH by inhibiting the TLR4/NF-κB signaling pathway (160). Exosomal PTEN-induced kinase 1 from hUCMSCs attenuates neurological deficits, dysregulated microglial M1/M2 polarization and inflammatory responses after ICH in mice (161). Exosomes derived from human adipose-derived mesenchymal stem cells (hADSCs-Exo) were successfully internalized by microglia cells and exerted robust anti-inflammatory actions by suppressing the exerted robust anti-inflammatory actions of inflammatory factors and promoting M1 to M2 transition (162). Exosomes, which are nanoscale vesicles measuring 30-150 nm in diameter, encapsulate a diverse cargo encompassing mRNA, miRNA, proteins and growth factors (163,164). Beyond serving as delivery vehicles, the specific contents of exosomes, especially miRNAs, are pivotal for their immunomodulatory effects. Consequently, identifying key miRNAs and elucidating their mechanisms in microglial polarization has become a major research frontier in developing RNA-based therapeutics for ICH.

Increasing genetic and epigenetic evidence highlights the critical role of miRNAs in modulating gene expression and microglial polarization following ICH (165). For example, let-7a modulates microglial M2 polarization by targeting CKIP-1 at day 3 post-ICH in mice. In the aforementioned study, let-7a overexpression reduced CKIP-1 protein levels, promoted M2 polarization characterized by increased expression of IL-10 and Arg-1, and alleviated neuroinflammation. By contrast, let-7a inhibition upregulated CKIP-1, driving M1 polarization (165). Similarly, miR-7 overexpression suppresses TLR4 protein expression, attenuating microglial inflammation in both ICH rats and lipoprotein-stimulated microglial inflammation models (166). Further research has demonstrated that targeting TLR4 through the inhibition of the Prx1/TLR4/NF-κB signaling axis at day 3 post-ICH provides neuroprotection against ICH-induced brain injury, presenting a promising anti-neuroinflammatory strategy (155). In stroke *in vivo* and *in vitro* experiments, miR-182-5p and miR-27a modulate inflammation by targeting TLR4, and their overexpression downregulates TLR4 protein levels while reducing the release of pro-inflammatory factors (167,168).

Previous evidence identified that integrin subunit β8, a direct target of miR-222, can be negatively regulated by miR-222 to alleviate microglial inflammation and apoptosis (169). Previously, miR-132 was shown to inhibit the cholinergic inflammatory response by targeting acetylcholinesterase. Zhang *et al* (170) reported that lentivirus-mediated miR-132 overexpression in the right caudate nucleus 14 days before autologous blood-induced ICH suppressed pro-inflammatory microglial activation, alleviated BBB dysfunction and reduced neuronal reduction at day 3 post-ICH. miRNAs also act as key mediators of autophagy-induced microglial inflammation, post-transcriptionally suppressing gene expression and function (171). It has been demonstrated that miR-144 enhances hemoglobin-mediated microglial autophagic inflammation by directly targeting the 3' untranslated regions (UTRs) of mTOR (171,172). Similarly, miR-124 promotes microglial M2 polarization and alleviates inflammation by targeting the 3'-UTR of C/EBP-α. In ICH mice, miR-124 mimic administration significantly reduced neurological deficits, brain water content (BWC) and C/EBP-α expression at day 3, compared with miR-124 inhibitor treatment. Consistent negative regulation of C/EBP-α by miR-124 was also observed in erythrocyte lysate-stimulated microglia transduced with miR-124 mimics or inhibitors (173).

Exosomes and miRNAs represent more than just a list of promising entities; they form the core of an emerging precision immunomodulation paradigm for ICH. Moving beyond the generic suppression of neuroinflammation, this paradigm is defined by the rational selection of targets across the microglial functional spectrum (for example, TLR4, CKIP-1 and mTOR) and their precise manipulation via engineered exosomes loaded with specific miRNA combinations. The primary translational challenge no longer lies solely in target identification, but in optimizing these intelligent delivery systems to ensure their stability, targeting efficiency, and controlled cargo release, and in validating their synergistic efficacy in advanced disease models. This approach heralds a shift from broad anti-inflammatory strategies toward context-sensitive immune remodeling tailored to the spatiotemporal dynamics of ICH.

Modulating downstream effector molecules. Modulating downstream effector molecules targets the terminal pathological processes of microglial activation, aiming to block the final 'damage cascade' rather than regulating microglial function directly. This strategy is characterized by clear mechanisms of action but may lack specificity due to the widespread involvement of effector molecules in normal physiological processes.

Matrix metalloproteinases (MMPs). Matrix metalloproteinases (MMPs), a universal superfamily of structurally related zinc-dependent endopeptidases, are upregulated following ICH and contribute to extracellular matrix degradation. The role of MMPs in ECM disruption driven by inflammation serves as a pathological basis for stroke, as evidenced in numerous studies (174). Wells *et al* (175) investigated MMP function in ICH mice and found that MMP-12 was the most significantly elevated isoform, with experiments revealing that MMP-12 knockout mice exhibited substantial forelimb motor recovery compared with WT mice, while WT mice showed increased recruitment of $Iba1^+$ cells with macrophage morphology to the injury site, indicating that MMP-12 exacerbates SBI after ICH (175). Subsequent studies demonstrated that stem cell therapy or minocycline administration following ICH reduced perihematomal MMP-12 expression and attenuated microglia-infiltrated inflammatory responses (176,177), positioning MMP-induced microglial activation as a potential therapeutic target. For example, minocycline promotes the microglial phenotypic shift from pro-inflammatory M1 to anti-inflammatory M2 (178). However, while minocycline therapy effectively mitigates the early elevation of MMP-12 and TNF-α, its therapeutic efficacy diminishes by 1-week post-ICH. Additional studies have revealed that stem cell therapy notably reduces microglial infiltration and MMP-12 expression in perihematomal regions after ICH (177,179).

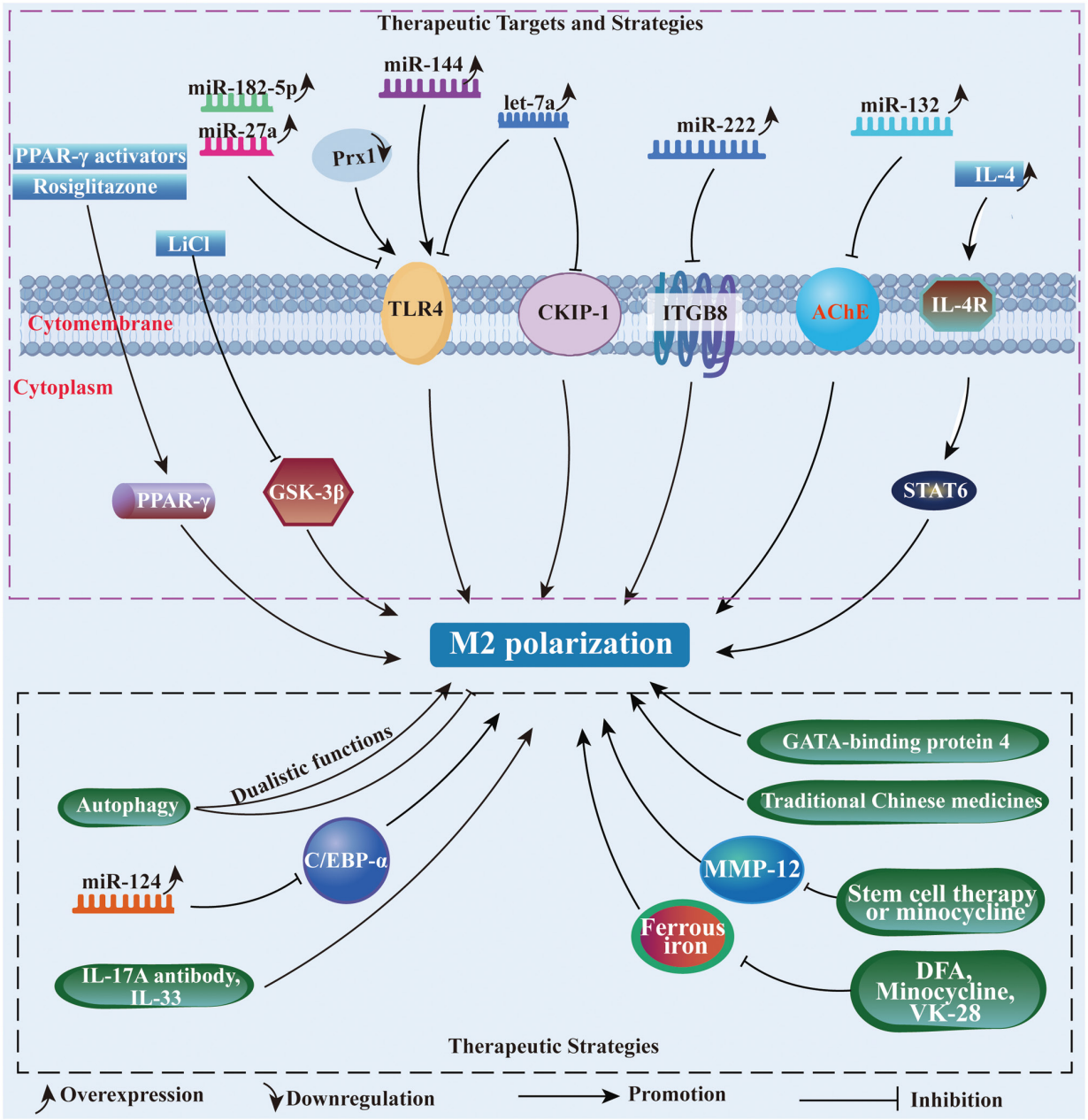

Figure 3. Summary of therapeutic targets and strategies for microglial polarization after intracerebral hemorrhage. Various interventions are available to suppress microglia-mediated neuroinflammation. These targets encompass signaling pathway proteins, individual proteins, genes and miRNAs. By modulating these targets, the pro-inflammatory microglial phenotype can be shifted toward the M2 phenotype. miR or miRNA, microRNA.

Iron. Increasing evidence indicates that ferrous iron released from hemolysis represents a key pathogenic factor in hematoma following ICH (180). Iron toxicity-mediated microglial activation and pro-inflammatory response are major contributors to brain injury after ICH. Deferoxamine, an iron chelator capable of crossing the BBB to bind iron, has been identified to moderately modulate microglial activation following ICH when administered intraperitoneally to decrease iron accumulation (181-183). As a microglial activation inhibitor, minocycline can also reduce iron levels to prevent neuronal death after ICH (184,185). Similarly, VK-28, a brain-permeable iron chelator, promotes microglial M2 phenotype polarization, reduces BWC, alleviates white matter injury and improves neurobehavioral deficits after ICH (186,187). Observational studies highlight the complexity of regulatory systems governing microglial function, underscoring the critical need to decipher phenotypic and genotypic variations to develop promising therapeutic strategies for ICH.

Modulating downstream effector molecules offers mechanism-specific intervention for post-ICH injury. Iron chelation is a high-priority strategy due to its ICH-specific mechanisms and existing clinical drug availability, while MMP-12 is limited by narrow intervention windows and poor specificity. For downstream targets, defining precise intervention timelines (aligned with pathological progression) is critical for balancing therapeutic efficacy and safety. Therefore, advancing these downstream strategies into the clinic critically depends on translational research that rigorously defines their optimal therapeutic windows in complex, time-course models (Fig. 3).

The core academic contribution of this review lies in the establishment of an innovative conceptual framework for the hierarchical targeted regulation of microglial neuroinflammation, which systematically categorizes regulatory strategies into four dimensions: Targeting the intrinsic regulatory axes of microglia, intercepting detrimental extracellular signals, implementing precise interventions with exosomes and miRNAs, and regulating downstream effector molecules, thus achieving a logical upgrade from mechanistic description to translation-oriented research. Its unique research perspective is reflected in taking translational feasibility, targeting specificity and pathological dynamic adaptability as the core criteria to clarify the regulatory priority and clinical translational potential of each signaling axis; it combines with the time dependence of pathological progression in ICH to distinguish the intervention windows and applicable scenarios of different regulatory strategies, and meanwhile focuses on the key challenges in translational medicine to analyze the clinical translational bottlenecks and optimization directions of various strategies. In summary, the present review systematically integrates the latest regulatory mechanisms of microglial neuroinflammation following ICH.

6. Radiological phenotypes and clinical biomarkers in ICH

ICH is distinguished by the concurrent presence of hyperdense and hypodense areas within a single hematoma, resulting in a 'blended' appearance, with hyperdense areas typically indicative of more coagulated or organized clots and hypodense areas often signifying relatively newly extravasated, incompletely coagulated blood (188,189). The upregulation of MAPT, CYCS, GAP43 and MAP1B, coupled with the enrichment of ferroptotic, mitochondrial dysfunction-related, oxidative stress-associated, inflammatory and cytoskeletal pathways, suggests that the intricate biological processes occurring within hematomas (190). While this association establishes a theoretical bridge between radiology and molecular biology, direct causal evidence verifying the mechanisms by which these genetic and pathway alterations drive the formation of hyperdense-hypodense regions remains scarce.

In terms of diagnostic and discriminative value, multiple molecular biomarkers exhibit promising performance in ICH management. Serum levels of matrix MMP-9, VEGF, GFAP and S100 calcium-binding protein B are significantly higher in patients with ICH, and the serum levels of these molecular biomarkers are correlated with a larger volume of PHE. The biomarkers GFAP, MMP-9 and APO-C1 independently discriminated between ischemic stroke and ICH within 24 h and markedly boosted the discriminative capacity of predictive models (191). The cerebral blood flow-based neurological score serves as an independent predictor of post-treatment ICH risk in adult patients with moyamoya disease (192). Despite these encouraging results, the specificity of these biomarkers remains incompletely validated. Notably, key inflammatory mediators such as MMP-9 and VEGF are also elevated in other acute cerebrovascular events and systemic inflammatory conditions. This overlap may limit their discriminative accuracy, especially in clinically heterogeneous patient populations. Furthermore, most supporting evidence originates from single-center studies with limited sample sizes. Therefore, multicenter, prospective validation is essential to confirm their true clinical applicability.

The association between molecular signatures and ICH prognosis further highlights the translational potential of these biomarkers. Elevation of inflammatory biomarkers is associated with adverse outcomes in ICH (193), and serum YKL-40 levels may serve as a candidate prognostic biomarker for the recurrence of cerebral amyloid angiopathy-related ICH (194). Moreover, the onset of acute anemia following ICH is prevalent, rapidly progressive and closely linked to inflammatory processes (195). Given that anemia development is associated with unfavorable clinical outcomes, it is proposed as a potential modifiable target to improve patient prognosis. The current understanding of anemia as a therapeutic target remains superficial as most studies only confirm the correlation between anemia and poor outcomes but lack interventional trials to verify whether correcting anemia can ameliorate ICH prognosis.

For early diagnosis and prevention, a panel of novel biomarkers has emerged as complementary tools when computed tomography and/or magnetic resonance imaging (MRI) are either unavailable or fail to reveal distinct signs of potential vascular rupture. To facilitate early diagnosis, ICH prevention and predict patient prognosis following hemorrhagic events, several parameters can be assessed including: Red cell distribution width, Red cell distribution width to lymphocyte ratio, resolvin D2 levels, C-reactive protein to albumin ratio levels, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels, and the precise and reliable assessment of circulating miRNAs, long non-coding RNA, circular RNA and mRNA expression in biological fluids (196-202). Furthermore, an in-depth investigation into differentially expressed inflammatory proteins, serum secretoneurin, and levels of soluble TLR4 and TLR2 in the early stage of ICH will facilitate an improved understanding of the pathogenic mechanisms underlying ICH, enable more accurate prediction of patient prognosis and facilitate the exploration of novel therapeutic strategies (198,203-205). A major difficulty in translating these biomarkers to clinical practice is the lack of standardized detection protocols, as different laboratories adopt varying assay methods, leading to inconsistent results that hinder cross-study comparison. Additionally, the optimal combination of these biomarkers for multi-marker diagnosis has not been systematically determined, and cost-effectiveness analysis is needed to evaluate their feasibility in resource-limited clinical settings.

7. Conclusion

Emerging evidence indicates that pro-inflammatory and anti-inflammatory microglial phenotypes exhibit divergent functions and implications, offering mechanistic insights into microglial regulation through intracellular and extracellular signaling pathways. Post-ICH brain injury and repair are not driven by isolated cellular responses, but are orchestrated by a highly dynamic, microglia-centered neuroimmune network. The functional regulation of microglia after ICH is a central therapeutic target for neuroinflammation. In the present review, a comprehensive overview of the cellular and molecular mechanisms governing microglial activation after ICH was provided. Substantial progress has been made in identifying signaling

molecular pathways linked to SBI following ICH in preclinical studies. PPAR-γ agonists, microglia-targeted exosomes and TLR4-specific inhibitors may represent the most promising directions in terms of current translational potential. However, extended clinical trials are essential for further validation.

The present review had several critical challenges which must be addressed. First, although animal models are widely used to investigate ICH etiology and pathophysiology, current models, predominantly rodent-based, do not fully recapitulate the complex etiology of human spontaneous ICH. Rodents exhibit robust spontaneous sensorimotor recovery and limited cognitive dysfunction, failing to reflect multifaceted clinical risk factors (such as hypertension and anticoagulant use). Second, experimental models do not fully replicate the pathological complexity of human ICH. To address this, preclinical research increasingly employs large animal models and advanced 3.0T MRI techniques to characterize key parameters such as hematoma expansion, white matter injury and hematoma evacuation, enabling cross-species comparisons with human disease. Third, most studies on ICH-induced brain injury focus on single-factor interventions. Future research should prioritize developing multi-targeted agents or combinatorial therapies to address the interconnected pathways driving neuroinflammation and tissue damage. While the current landscape of robust clinical trials remains limited and molecular genetic investigations into microglial phenotypic transitions are lacking, the present review offers an optimistic perspective on practical intervention strategies targeting microglial function in ICH. Further research into therapeutic strategies addressing microglial activation-driven neuroinflammation is critical for evaluating the translational potential of these promising approaches.

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Availability of data and materials

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Authors' contributions

GY, GC and XB conceptualized the study. XF, CP, LZ and OW wrote and prepared the original draft of the manuscript. DL and BZ wrote, reviewed and edited the manuscript. GY and XF prepared figures. XF, GY and XB acquired funding. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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