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REVIEW

Microglial Mechanisms and Therapeutic Potential in Brain Injury Post-Intracerebral Hemorrhage

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Abstract: Intracerebral hemorrhage (ICH) is a particularly common public health problem with a high mortality and disability rate and no effective treatments to enhance clinical prognosis. The increased aging population, improved vascular prevention, and augmented use of antithrombotic agents have collectively contributed to the rise in ICH incidence over the past few decades. The exploration and understanding of mechanisms and intervention strategies has great practical significance for expanding treatments and improving prognosis of ICH. Microglia, as resident macrophages of central nervous system, are responsible for the first immune defense post-ICH. After ICH, M1 microglia is firstly activated by primary injury and thrombin; subsequently, reactive microglia can further amplify the immune response and exert secondary injury (eg, oxidative stress, neuronal damage, and brain edema). The pro-inflammatory phenotype transmits to M2 microglia within 7 days post-ICH, which plays a key role in erythrophagocytosis and limiting the inflammatory secondary injury. Microglial M2 polarization has significant implications for improving prognosis, this process can be mediated through crosstalk with other cells, metabolic changes, and microbiota interaction. Clarifying the effect, timing, and potential downstream effects of multiple mechanisms that synergistically trigger anti-inflammatory responses may be necessary for clinical translation. Analyses of such intricate interaction between microglia cells and brain injury/repair mechanisms will contribute to our understanding of the critical microglial responses to microenvironment and facilitating the discovery of appropriate intervention strategies. Here, we present a comprehensive overview of the latest evidences on microglial dynamics following ICH, their role in driving primary/secondary injury mechanisms as well as neurorepair/plasticity, and possible treatment strategies targeting microglia.
Keywords: intracerebral hemorrhage, microglia, brain injury, mechanisms, utilization strategies

Introduction

Intracerebral hemorrhage (ICH) has constituted a particularly common public health problem due to its high mortality and disability rates, yet no effective treatment has been identified.[1,2] An estimated one quarter of the global population is at risk of stroke during their lifetime, with ICH accounting for approximately 16% of all incidents. Shockingly, the mortality rate at 28 days following ICH is as high as 47%.[3,4] The incidence of ICH has substantially risen in low- and middle-income countries due to increased thrombosis, antithrombotic agents abuse, and the aging population.[5–7] Although methods for identifying the injury mechanisms of ICH and predicting the long-term vascular risk of patients have progressed in the previous decades, the effective clinical intervention for ICH is not yet available. The management guidelines of ICH focus on the management of risk factor (hypertension, antithrombotics, diabetes, and heavy alcohol use), surgical hematoma clearance, and medical management of secondary brain injury (seizures, hyperglycemia, elevated ICP and fever).[1,8] Apparently, interventions targeting microglia are significantly different from the conventional clinical treatment. Actually, the pathophysiology of ICH is extremely intricate and incorporates both primary brain injury and various secondary brain injury, for example, inflammatory response, oxidative stress, neuronal damage, and brain edema.[9,10] These injury mechanisms are all closely associated with the resident microglia. A comprehensive assessment of the injury mechanisms and effective intervening measures based on microglia for ICH remains necessary.

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Microglia, the resident immune cells of brain, comprise approximately 10–15% of all cells in the central nervous system (CNS).[11] These microglia are associated with multiple essential functions in the development and repairment of brain during homeostasis and diseases.[12] Furthermore, they are responsible for the brain's first immune defence after ICH. During homeostasis, microglia contribute to the synaptic formation and modification, neuronal protection, as well as neuronal and axonal excitability through several distinct patrolling modes.[13,14] Whereas in disease conditions, they can rapidly undergo clonal proliferation, become activated into phagocytic and/or proinflammatory states, and affect the recruitment of peripheral immune cells.[15,16] Microglia are myeloid cells that are derived from erythromyeloid progenitors, this lineage also includes monocytes/macrophages. Once fully activated, the infiltrated macrophages and resident microglia share many similarities, including phenotypic markers, signature genes, pro-/anti-inflammatory response and phagocytic function. Therefore, it is difficult to distinguish them, they are collectively known as microglia/macrophage.[17] Microglia/macrophage at the perihematomal site of cerebral hemorrhage can polarise and display dual roles in the injury and repair processes, including a pro-inflammatory phenotype (M1) and an anti-inflammatory phenotype (M2). Either the M1/M2 phenotype or pro-inflammatory /anti-inflammatory terminology is a commonly useful concept to understand the functional status of microglia/macrophage, and this will be used in this review for simplicity, despite the reality of the situation being more complex.[18,19] In this review, we will primarily concentrate on resident microglial activation, function and utilization strategies following ICH.

Mounting evidences have revealed the critical role of the immune cascade in the progress of brain injury and repair post-ICH. Following ICH, the entry of exogenous blood into the brain parenchyma constitutes the earliest trigger for homeostatic microglial activation through the composition of blood (thrombin, fibrous protein) and the mass effect of hematoma formation.[10,20] Subsequently, blood and its degradation products (hemoglobin, heme, and iron) further accelerate the immune response after brain damage.[21–24] Meanwhile, numerous secondary brain injury mechanisms have interacted with this inflammatory response, jointly contributing to both the brain injury and repair post-ICH. In the process of ICH, the transition of microglia from a pro-inflammatory to the anti-inflammatory phenotype also implies the changes of damage to repairment program of brain tissues. Targeted phenotypic modulation of microglia can inhibit inflammatory responses, promote hematoma clearance, and alleviate a variety of secondary brain injuries, which is a promising approach. Currently, many preclinical and clinical studies have focused on the immunotherapy post-ICH, including minocycline, statins, and sphingosine-1-phosphate receptor modulators.[25] The latest reports have displayed that a small-molecule drug candidate designed to target proinflammatory cytokines has been carried out for the phase 2a clinical trial of ICH.[26] The objective of this article is to summarize the latest evidences regarding the interaction of microglial inflammatory response and brain injury mechanisms after ICH, along with some effective utilization strategies directed towards microglia.

Microglia and ICH: Injury, or Repair?

The mechanisms of brain damage following ICH can be broadly classified into two distinct phases: the initial primary damage resulting from the infiltration of blood into brain tissue at the onset of ICH, and the subsequent secondary damages provoked by hematoma and its degradation products.[27] The primary brain injury after ICH is primarily attributed to the mass effect, which not only significantly contributes to clinical symptoms at the acute phase, but also serves as a critical prognostic indicator for patients.[28,29] As ICH progresses, brain tissue undergoes a series of intricate physiological and pathological alterations. Numerous studies have concentrated on investigating the mechanisms and intervention of secondary brain injury, which encompasses the coagulation cascade, oxidative stress, inflammatory response, neuronal damage, blood–brain barrier (BBB) disruption and brain edema (Figure 1). These factors are commonly recognised as crucial contributors to post-ICH brain injury and are closely associated with exogenous hematoma and its degradation products (hemoglobin, heme, and iron).[21–23]

Similar to the complicated mechanisms of secondary brain injury experienced over the time course of ICH, the microglial activation and its fate also displayed a temporal profile which was closely associated with the injury mechanisms. The latest microglial visualization study showed that the number of perihematomal microglia was dramatically decreased at 1 day after ICH and remarkably increased at days 3 and 7 in the autologous blood injected mice. This research also evidenced the distinguished contribution of iron and thrombin to microglial death and proliferation using the directly intracerebral iron or thrombin injected mice model, respectively.[20] The remarkable differences in the activation time and destiny of microglia based on the different injury factors implied the distinguished regulated pattern on microglia by various injury mechanisms during

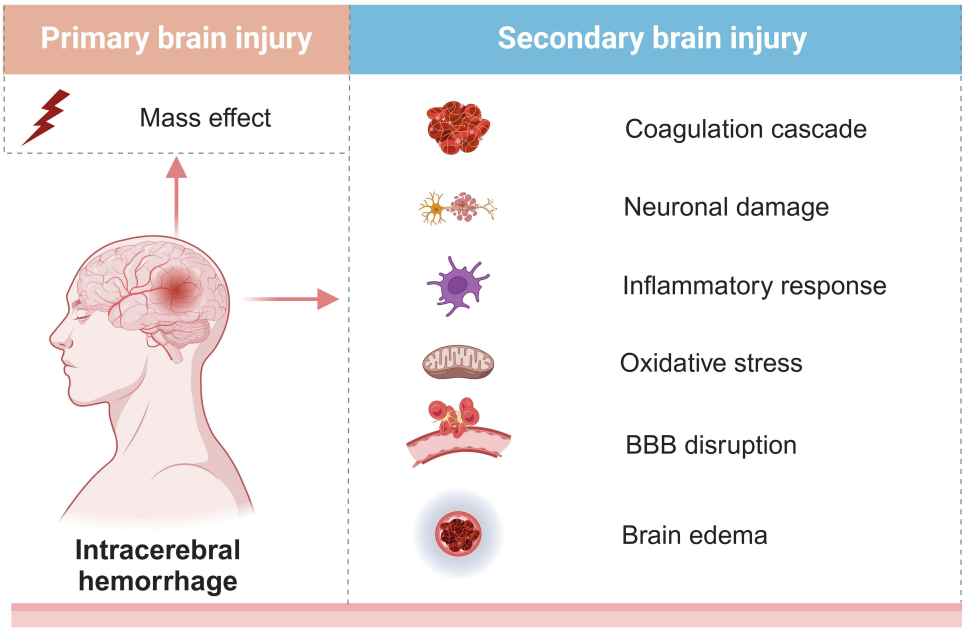

Figure 1 The mechanisms of intracerebral hemorrhage (ICH). Brain-damaged mechanisms following ICH can be roughly classified into the primary brain damage and secondary brain injury. The primary brain damage is primarily attributed to the hematoma formed mass effect. The secondary brain injury includes coagulation cascade, neuronal damage, inflammatory response, oxidative stress, blood-brain barrier (BBB) disruption, and brain edema.

the process of ICH. The next sections will describe how microglia elicit their immune or non-immune functions by interacting with the primary and secondary brain injury mechanisms after ICH.

Initial Microglial Activation Following ICH

When blood enters the brain parenchyma, microglia, as one of the first responders, play an important role in coordinating the disease-related perturbations. Microglial cells can be activated by a variety of intricate injury mechanisms after ICH under the imbalanced homeostasis.

The mechanical destruction induced by hematoma is highly temporally synchronized with early microglial activation. Similar to the immediately formed mechanical injury, the glia and neurons had been mechanically stretched by hematoma as early as 4 hours after ICH.[10] There was an observed increasement in the activated and polarized M1 phenotypic microglia that peaked in the ipsilateral basal ganglia at 4 hours following ICH.[30] Microglia, which possessed an innate ability to sense the mechanical information, presented a more intricate morphology and a migratory aptitude toward stiffer regions when cultured on a substrate with stiffness gradients.[31] It was reported that Piezo1 had mediated the effect of substrate stiffness-induced migration and cytokine expression of microglia.[32] Actually, the increased Young's modulus of brain tissues mediated by the hematoma mass effect can form a similar mechanical effect of substrate stiffness.[33] Meanwhile, the significant upregulation of Piezo1 protein in a balloon-inflated ICH model suggested the direct activation of mechanosensitive ion channels induced by primary injury mechanisms. Simple balloon implantation can not only create mechanical mass effect but also avoid the influence of hematoma and its products.[34] The direct regulating effect of primary injury on mechanically gated ion channel and the highly expressed Piezo1 in microglia both provide feasible avenues for further exploring the underlying molecular mechanisms in the process of mass effect mediated microglial activation after the acute phase of ICH.[35] Investigating the relevant mechanisms will be facilitated to further understand and intervene of this process.

Thrombin is the central participant in blood coagulation, and its production may reflect the activation of secondary hemostasis. Although clinical research had reported the positive correlation of plasma thrombin-antithrombin levels with ICH severity,[36] the accumulation of perihematomal thrombin after ICH in the silicone oil injected ICH model was reported to be associated with neuronal expression rather than systemic influx.[37] Controversially, the elevated thrombin activity in the blood injected rats has indicated the contribution of exogenous hematoma to thrombin increasement compared with the saline injected rat model.[38] It should be noted that thrombin production in the brain has been found to be increased immediately following cerebral hemorrhage

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or BBB breakdown in many kinds of brain injury.[39] Actually, the localisation of thrombin in CNS was not only on neurons but also on glial cells, which was considered to be the most powerful driver of various pathological inflammation of the brain, including ICH, ischemic, traumatic brain injury, Alzheimer's disease, and Parkinson's disease.[40,41] At lower levels (10 pM – 10 nM), thrombin can protect cells from a variety of insults through preventing glucose deprivation, edema or reactive oxygen species (ROS) formation after ICH. When increased to the upper 10-fold concentrations (100 nM – 10 μM), thrombin can be deleterious to the brain parenchyma by inducing tumor necrosis factor-α (TNF-α) upregulation, edema and neuronal damage.[42] Thrombin is considered as one of the central factors in the damage mechanisms of ICH, which can mediate various secondary brain injury, such as BBB disruption, brain edema, neuronal death and neuroinflammation. On the one hand, thrombin was capable of cleaving pro-IL-1α, generating matured IL-1α, and promoting the rapid recruitment of inflammatory cells. On the other hand, thrombin activated the protease-activated receptors (PARs) on microglia was able to facilitate the release of pro-inflammatory cytokines including TNF-α, interleukin 1α/1β (IL-1α/1β), IL-6, IL-12, cyclooxygenase-2 (COX-2), and upregulate surface CD40 expression.[38,43] Targeting thrombin activity has therefore been considered as a plausible mean to intervene in the proinflammatory process and improve neuronal prognosis. However, given the key role of thrombin in hemostasis after ICH, the irrational application of thrombin inhibitors is very possible to result in undesirable rebleeding or hematoma enlargement.[44] Evidence also suggested that delayed anticoagulant intervention did not increase hematoma volume in the collagenase-induced ICH model.[45] A previous study had confirmed that the overexpression of interleukin-1 receptor antagonist through adenovirus vector mediation was an efficient approach in decreasing inflammatory response and brain edema caused by thrombin following ICH.[46]

Microglia Mediate Inflammatory Secondary Injury

The inflammatory response driven by activated microglia that spreads throughout the brain is a significant contributor to the secondary brain injury following ICH. This process is triggered by the release of a series of inflammatory factors, including IL-1β, IL-6, TNF-α, COX-2, nitric oxide synthase 2 (NOS2), and ROS (Figure 2).[47] After ICH, the poor

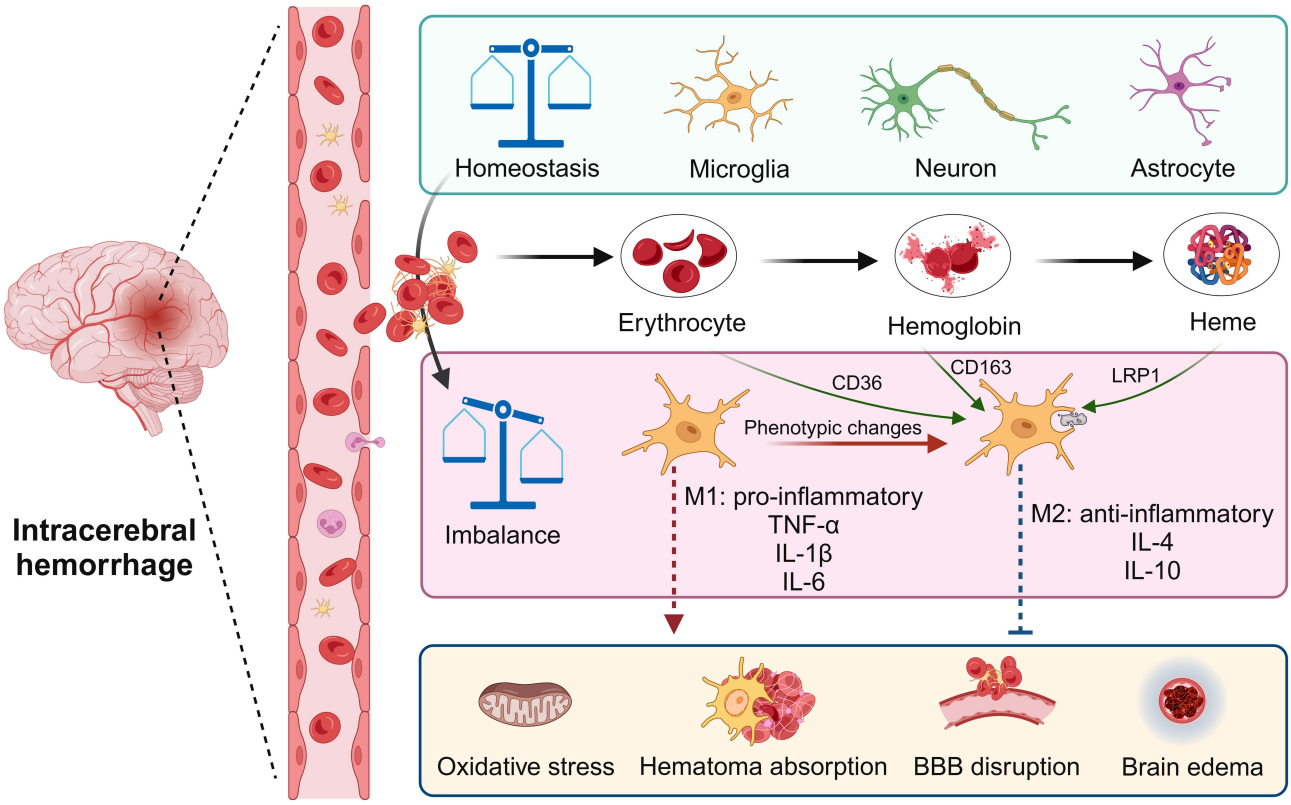

Figure 2 The correlation between microglia activation and the secondary brain injury. The M2 polarization of microglia can accelerate hematoma clearance through specifically phagocytosing the erythrocyte, hemoglobin and heme through CD36, CD163 and LRP1, respectively. Activated microglia can mediated the secondary brain injury via phenotypic changes and the release of a series of pro-inflammatory and anti-inflammatory factors.

prognosis is attributed to a range of secondary brain injury factors such as neuroinflammation, oxidative stress, perihematomal edema, and BBB disruption.[48–50]

Brain tissue is vulnerable to oxidative stress due to its high levels of lipids and iron but relative lack of antioxidants. Thus, oxidative stress is commonly considered as the pivotal factor for the secondary brain injury post-ICH, which can disturb the intracranial redox balance and result in activating multiple cell death pathways, including apoptosis, necrosis, necroptosis, excessive autophagy and ferroptosis.[51] Oxidative stress is defined as a disturbance in the balance between the generation and detoxification of reactive free radicals such as ROS (eg superoxide) and reactive nitrogen radicals (RNS, eg nitric oxide). Oxidative stress and inflammation have intimately interaction with each other. On the one hand, oxidative stress can directly induce the expression of proinflammatory cytokines (IL-1β, TNF-α and IL-6); on the other hand, the production of reactive species ROS/RNS production can be further mediated by the activated microglia after ICH.[52–54] NADPH oxidases (NOX) are the most important source of oxidants and have the primary function to catalyse the generation of ROS, which have been found to be upregulated in microglia after pro-inflammatory activation.[55] In vitro study has revealed that the ROS production in LPS treated microglia can be increased in an iron dose-dependent manner through NOX.[56] In the hematoma microenvironment after ICH, both the abundant activated microglia and the overloaded iron can provide an important boost for the production of ROS. In addition, the highly expressed inducible nitric oxide synthase (iNOS) on the activated microglia also can aggravate oxidative stress by producing nitric oxide and derivative oxidants.[57,58]

Perihematomal edema is considered as a quantifiable marker of secondary brain injury due to its radiological manifestation. Clinical statistical analysis had displayed that the absolute increase of perihematomal edema was a well-known predictor for clinical prognosis after ICH.[27,29] Numerous studies had explored the formation mechanism of brain edema, and most of these evidences had declared the significant effects of inflammation and oxidative stress mechanism.[59,60] Given the mutual connection between oxidative stress and inflammation, a central topic of this study will be the role of microglia to the formation of brain edema. Evidence indicated that vasogenic edema can be aggravated by metalloproteinase-9 (MMP-9) through degrading the basal lamina of the BBB. The MMP-9 increasement had been found to be induced by pro-inflammatory cytokines (IL-1β, TNF-α) in cultured microglia and astrocytes.[61–63] More than that, levels of MMP-9 also can be elevated by the activated microglia at the early stage of immune response. Research indicated that the pro-MMP-9 is generated by primary murine microglia, rather than astrocytes, when exposed to plasma extracellular matrix components of fibronectin and vitronectin in vitro.[64] Targeting activated microglia has been recommended as a therapeutic approach to prevent edema and BBB leakage. A recent study has revealed that activated MMP-9 can be significantly attenuated by inactivated and depleted microglia, and then ameliorate the BBB dysfunction.[65] Additionally, the available evidence displays that histone deacetylase 3 inhibitor can effectively mitigate brain edema and BBB leakage through reducing MMP-9 expression, decreasing neuroinflammation, and upregulating the tight junction proteins.[66] Another study indicated that the intervention effect of the inhibitors was directly targeted to microglia.[67] These results demonstrate the essential modulating function of activated microglia on the brain edema by elevating MMP-9 levels after ICH.

Except for vasogenic edema, the disruption of BBB also leads to hemorrhagic transformation and the infiltration of leukocytes, which plays a non-negligible role in the pathogenesis of ICH. Moreover, the inflammatory response induced by increased BBB permeability can further exacerbate BBB disruption and brain edema. Considerable evidences implicate that M1-like microglia released pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) are typically responsible for promoting BBB injury. Whereas M2-like microglia, produced anti-inflammatory cytokines (IL-10) are beneficial for tissue repair and BBB protection.[68–70] In inflammatory microenvironment, the pro-inflammatory cytokines TNF-α and its receptor have been considered as the crucial mediators on the endothelium for microglia induced endothelial necroptosis and BBB disruption. The anti-TNF-α inhibition has obviously reversed BBB destruction and endothelial necroptosis.[71] Meanwhile, conditional deletion of the IL-1 receptor had been shown to decrease BBB breakdown and neutrophil infiltration in ischemic stroke.[72] Oxygen and nitrogen-free radicals secondary to microglial activation were also reported to result in endothelial cell damage and regulating BBB permeability by mediating cell signaling pathways.[50] In animal models of ICH, pharmacological intervention with dexmedetomidine, a highly selective adrenergic α2 receptor agonist, has been shown to protect BBB integrity through reducing M1 associated markers and facilitating M2-like microglia polarization.[73] Therefore, promoting the phenotypic transition from M1 to M2 is a promising strategy for maintaining

BBB integrity and reducing secondary brain damage after ICH. This crosstalk between microglia and secondary brain injury constitutes the core of regulating brain injury and repair post-ICH.

Microglial Polarization

During ICH development, the presence of exogenous hematoma and its degradation products (Hb, Heme, and iron) provide a further boost for the activation of resident immune cells and infiltration of peripheral immune cells. The polarization of microglia and its phagocytosis of erythrocytes have been considered as a significant contributor to the clearance of both hematoma and cell debris (Figure 2).[57] If phagocytosis is not in a timely manner, erythrocytes will undergo hemolysis itself, and the balance between the two processes is critical for local redox homeostasis. Accelerated phagocytosis of erythrocytes and its degradation products is an effective strategy to ameliorate oxidative stress injury mediated by hematoma.[22] The recognition and phagocytosis of erythrocyte is carried out by CD36, a well-recognized membrane protein located on the surface of microglia. Unphagocytised erythrocytes will haemolyze and release the toxic degradation product hemoglobin to induce oxidative stress damage in response to complement activation, membrane attack complex and mass effect.[74,75] The released hemoglobin can be similarly phagocytosed by the glycoprotein of CD163 through binding with haptoglobin. Free hemoglobin released from erythrolysis is further degraded, resulting in the extracellular release of hemin. Hemin can specifically enter microglia via Low-density lipoprotein receptor-related protein 1 (LRP1) in the form of a high-affinity complex of heme-hemopexin.[22,76] Extensive neuroprotective and prognosis promoting effects have been demonstrated to be associated with the phagocytosis of these neurotoxins by microglia. There are evidences that simvastatin, bexarotene, and wogonin can activate the peroxisome proliferator-activated receptor-γ (PPAR-γ), and then enhance hematoma absorption through upregulating CD36 or CD163.[77–79] Impaired recycling of the pro-erythrophagocytic receptor CD36 was reported to negatively regulate the erythrophagocytosis of microglia.[80] However, the effects of CD163 knockout on prognosis had displayed distinct temporal differences during ICH, with early beneficial properties but delayed injurious effects.[81]

Additionally, microglia can also detect the conformational changed CD47 protein on erythrocyte and regard it as an "eat me" signal by the signal regulatory protein (SIRPα), and result to the phagocytosis of erythrocyte.[82] The intervention of CD47 blocking antibody had been found to be of great value in accelerating hematoma clearance and alleviating brain swelling and neurological deficits.[83,84] These authors also had verified their hypothesis that CD47 on erythrocyte may inhibit the polarization of microglia towards the M2 phenotype after ICH, as demonstrated by the blood injection of CD47 knockout mice.[82] Moreover, SIRPα variants can promote hematoma clearance and ameliorate brain injury through blocking the CD47-SIRPα interaction.[85] The M2 phenotype of microglia induced by hematoma and its degradation products contribute significantly to hematoma clearance and ICH recovery. Nevertheless, the proinflammatory effect associated with hematoma lysis still should not be ignored. A recent study using spatial transcriptomics indicated that heme was a potent inflammatoxin, which can result in obvious inflammation-related genes expression (eg, Ccl2 and IL-33) even in minimal doses of heme exposure (0.30 nmol). This harmful transcriptional response can be completely suppressed by the co-administered of hemopexin.[86] Hence, to prevent the subsequent brain injury following ICH, exploring the regulation of microglial activation and polarization specifically directed towards hematoma degradation products presents a promising avenue for further study.

Factors That Modulate Microglial Polarization

Crosstalk Between Microglia and Other Cells

The transition from pro-inflammatory to anti-inflammatory phenotype in hematomal microenvironment after ICH is not only dependent on microglia but is also closely associated with the crosstalk of surrounding brain cells (eg, astrocyte, oligodendrocyte, neurons) and multiple adaptive immune cells. The rapid activation of microglia is occurred in minutes after ICH, followed by the infiltration of neutrophils and peripheral macrophages into the injury site in the following hours to 1 day, which together constitute the inflammatory events after ICH. Many studies have now emphasized the important regulatory role of neutrophils in ischaemic stroke. The importance of neutrophils post-ICH has also received some attention.[87] Recent systematic reviews have revealed that the high neutrophil-to-lymphocyte ratio is significantly associated with the poor clinical outcomes of patients with ICH.[88] The depletion of neutrophils has reduced the infiltration of activated microglia/macrophages and decreased myelin fragmentation and axon damage.[89] Another study

found that microglia can promote neutrophils infiltration through releasing leukotriene B_4.[90] It can be seen that the infiltration process of microglia and neutrophils into the perihematomal site has an influence on each other. After ICH, neutrophils can be polarized towards the distinct pro- and anti-inflammatory phenotype based on the hematomal microenvironment.[91] Microglia-derived interleukin-27 has the effect of suppressing the production of pro-inflammatory products from neutrophils.[92] Although few studies have focused on the regulatory role of neutrophils in the inflammatory response after ICH, immunotherapy based on multiple immune cells crosstalk may be a valuable target to address the inflammatory injury post-ICH according to the importance of neutrophils in cerebral ischaemic injury.

Astrocytes are another key cellular component of neuroinflammation. On the one hand, astrocytes can restrict the entry of exogenous immune cells. On the other hand, astrocytes directly participate in the process of immune response. Astrocytes have two different types of activation states: neurotoxic A1 and neurotrophic A2. In general, the microglia-derived TNF, complement C1q and IL-1α are recognized as the necessary and sufficient for the activation of neurotoxic A1 astrocytes. The reactive astrocytes-derived proinflammatory cytokines (IL-1β, IL-6, interferon-γ, etc.) can further mediate the neuroinflammation.[93] Similar to the adaptive microglial phenotype, the conversion of A1 to A2 astrocytes exert neuroprotective functions by inhibiting inflammation after ICH.[94] Moreover, the astrocytes-mediated proinflammatory cytokine IL-15 upregulation has been revealed to activate the microglia toward a pro-inflammatory phenotype and increase the release of CD86, IL-1β, and TNF-α after ICH. Microglial depletion has effectively attenuated the augmentation of brain injury induced by astrocyte-derived IL-15.[95] Neurons also contribute to the activation and function of microglia. Previous in vitro studies have confirmed that the neuron-derived fractalkine can chemoattract microglia via the CX3CR1 receptor, and the knockout of receptor is associated with decreased microglial migration and delayed phagocytosis of synapses during development.[96] The increasement of fractalkine in perihematoma post-ICH can significantly promote the hematoma clearance and decrease hemoglobin content.[97]

Microglia Associated With Metabolic Changes After ICH

The CNS has long been regarded as a privileged metabolic niche isolated from the periphery by the BBB. Glucose is the primary oxidative fuel and energy source for the brain during metabolic process, brain function and its normal activities highly relies on the catabolism of glucose.[98] Extensive research has been conducted to examine the precise contribution of brain glucose metabolism in determining the physiological and pathological state of CNS, including the developing brain, traumatic brain injury, Alzheimer's disease, and other CNS diseases.[99–101] The metabolized dysfunction of unsaturated fatty acid was also reported to be associated with neuropathology as well as cognitive performance in neurodegenerative disease.[102] This section will explore the metabolic imbalance in the CNS after ICH and the microglial activation related metabolic changes.

The emerging field of immunometabolism has emphasized the intricated crosstalk between the immune responses and metabolic pathways. This means that when immune cells transform into an activated state, their metabolic pathways will also undergo alteration. Although lots of studies have investigated the important roles of immunity and the regulatory measures after ICH, the direct evidence of correlation between immunity and metabolism remains relatively insufficient.[17] Our previous works have revealed the obvious enriched of metabolic pathways induced by mass effect as early as 6 hours after ICH through proteomic analysis. The metabolic changes observed at early time points are consistent with the activation of microglia.[57,103] Therefore, this process of metabolic reprogramming is probably related to microglial activation and function. Another quantitative proteomic analysis conducted with collagenase injected rats has revealed the meaningful role of dysregulated energy metabolism based on nitrogen metabolism in ICH injury.[104] Except for microglial alteration in the innate immune system, the adaptive immune response cells of hematoma myeloid cells were also revealed an apparent expression of genes encoding glycolysis and immune factors.[105] While the involvement of microglial metabolic reprogramming in neurodegenerative environment has been widely recognized, and some key molecular mechanisms including TREM2, PI3K-AKT-mTOR, and AMPK.[106] Consequently, the exploration of clinical data and mechanisms on microglia metabolism after ICH is expected to provide some new evidence for clinical intervention.

These interactions between microglial activation and metabolic processes (such as glycolysis, lipid metabolism and oxidation) have been elaborated in multiple CNS diseases, in which glycolysis has shown heavily implicated.[107] During homeostasis, all major metabolic pathways in the brain typically display a basal level. Whereas the changed energetic requirements after stress or activation will promote the immune cells to experience metabolic reprogramming. For

example, the main metabolic pathway of microglia can transform into aerobic glycolysis from oxidative glycolysis in neuroinflammatory condition, which is a pivotal step to adapt cytokine release and immune actions in the brain (Figure 3).[108,109] A recent publication based on positron emission tomography imaging revealed that the glucose metabolism of ipsilateral brain apparently decreased in the early stage but increased during the late stage after ICH.[110] With the shift of metabolism from oxidative phosphorylation to aerobic glycolysis, activated microglia can result in the apparent accumulation of a typical glycolytic product, that is lactate.[111] Significantly elevated lactate levels have been identified in both cerebrospinal fluid and serum following spontaneous ICH, which has been demonstrated to be correlated with the poor prognosis.[112,113] The increased glycolytic process resulting from microglial activation is probably to induce an energy crisis for other nerve cells; however, neurons are more likely to prefer the molecular basis of oxidative phosphorylation. The reduced glucose levels after ICH have also been found to have a negative correlation with the lactate levels in cerebrospinal fluid.[112,114] Consequently, it is essential to consider potential risks and avenues for prevention or intervention. Further investigation based on immunometabolism is expected to provide exciting therapeutic targets and improve clinical outcomes. However, in addition to microglia, other neural cells also exist in the microenvironment and interact with metabolites and various active substances. The regulation of metabolic pathways based on targeting microglia is probably not a binary switch of black or white, and the extensive flux between pathways needs to be exhaustively explored and evaluated.

Microglia and Microbiota Interaction

The bidirectional communication between brain and gut microbiome is mediated through a variety of pathways, including immune system, nervous system and circulatory system. Multiple studies have highlighted the interaction between microbiota-derived metabolites and the resident microglia in CNS involving microglial development, depression, Parkinson's disease, stroke, as well as other neurodevelopmental and neurodegenerative diseases.[115–118] Microbiome and its derived metabolites, as the pivotal active substances of gut, are a crucial factor affecting neurodevelopment and microglial function in the peripheral environment.

In the process of ICH, recent multi-omics studies revealed that the gut microbiome of ICH patients was obviously differences from that of the healthy population, and the related metabolites were closely associated with the severity of ICH.[119] Subsequent research indicates that microbiota dysbiosis caused by ICH can in turn affect the neuroinflammation and functional deficits of ICH through the immune mechanism (Figure 3).[120] The transplantation of fecal microbiota

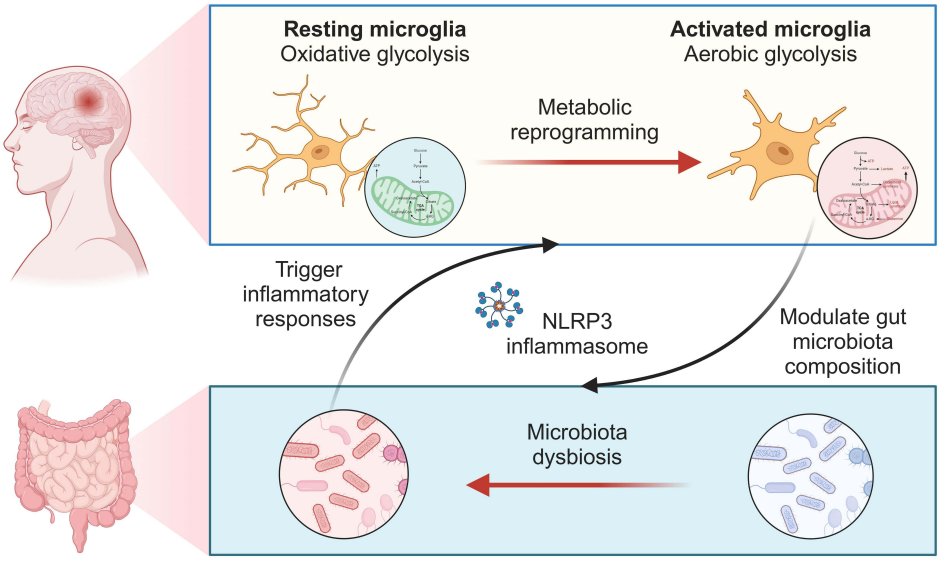

Figure 3 Microglial activation is associated with the metabolic reprogramming and gut microbiota dysbiosis. In neuroinflammatory condition, the main immune pathway of microglia can transform into aerobic glycolysis from oxidative glycolysis. The gut microbiota dysbiosis caused by microglial activation post-ICH can in turn affect the neuroinflammation and functional deficits of ICH.

from patients with post-stroke cognitive impairment to ischemia mice has revealed the central contribution of gut microbiota in cognitive impairment through mediating inflammation-regulating metabolites.[121] Evidence also suggests that microglial dysfunction in mice can be induced by microbiome-mediated disruption of intestinal barrier.[122] A typical example is the NLRP3 inflammasome, which is considered as an important linker between the brain and the gut. While the NLRP3 inflammasome signal can modulate the composition of gut microbiota, the gut microbiota can trigger neuroinflammatory response by activating the NLRP3 inflammasome.[123] The well-known anti-inflammatory agent berberine has been revealed to mitigate neuroinflammation post-ICH in a gut microbiota-dependent manner.[124] More than that, microglial transcriptomes are more preferentially influenced by the deficiency of gut microbiome compared with other nerve cells, which can be effectively reversed by microbial colonization.[125] Therefore, the regulating study based on the interplay mechanism between microglia and the gut microbiome may be one of the effective strategies to enhance the long-term prognosis after ICH.

Microglia Phagocytosis After ICH: The Gain and Loss

As mentioned above, numerous studies have investigated the essential role of M2-like microglia in the clearance of pathological microenvironment after ICH. However, is there only a positive role to play in clearing the battlefield? Whether there are some non-negligible negative effects will be further discussed in this section.

Phagocytosis is a natural metabolic process involving the cellular digestion of extracellular particles (such as cell debris, dying cells or pathogens) into the phagocytic cells. In the perihematoma after ICH, the important role of phagocytic cells in clearing exogenous hematoma and its degradation products (Hb, Heme, and iron) has been widely recognized. These products can be specifically engulfed through the receptor proteins of CD36, CD163 and LRP1, respectively.[126] In addition, many other specific phagocytic receptors and molecules associated with activating or inhibiting microglial phagocytosis, including TLR4, CX3CR1, P2Y12 and SIRP, are also located on microglia. These pathways have participated in various phagocytic processes.[127] Notably, microglia have also been claimed as an essential coordinator for intricate bidirectional communication with other brain cells (neuron, oligodendrocyte and astrocyte) during both homeostasis and disease. Microglia have been demonstrated to prune the presynaptic and postsynaptic inputs to establish appropriate neuronal connectivity through phagocytosis, which can modify the excitatory and inhibitory synaptic connection of neurons to regulate neural circuit connectivity and activity.[128] In addition to dead cells, the microglia-neuron crosstalk under disease and inflammatory states may also involve the engulfing process of viable synapses and neurons. The neuropathologic characteristics of a progressive loss of neurons with minimal dead or dying cells in the neurodegenerative diseases suggest that brain tissue is probably removed alive by the phagocytes, such as microglia, during disease process.[96] Evidence has confirmed that microglia can mediate the synaptic stripping and synaptic displacement of neurons in the LPS (a TLR4 agonist) induced neuroinflammation.[129]

As for neurons in pathological conditions, they can be activated by subtoxic doses of glutamate or neurons with tau aggregates, and then turn into ‘stressed-but-viable neurons’, which can be aberrantly removed via microglial phagocytosis due to its inappropriate expression or release of phagocytic signalling (ie find-me signals, eat-me signals, and don’t-eat-me signals).[96] In particular, the concentration of perihematomal glutamate has been found upregulated significantly after ICH.[130] This significantly increases the risk of stressed-but-viable neurons to be phagocytosed by microglia.[63] The ultrastructural pathology of brain tissues has demonstrated that there are many abnormal or lost synapses in perihematoma after ICH.[131] Targeting the excessive microglial phagocytosis of these stressed neurons has therefore been suggested as a promising measure to prevent neuronal loss and improve the long-term prognosis of ICH. Especially for the stressed but viable neurons, delaying or inhibiting microglial phagocytosis may be more preventable than neuronal death in acute phase. Although the regulation of neural phagocytosis during ICH has not been reported, the evidence of benefit from related molecular regulation in other diseases may provide some reference, such as the microglial $P2Y_6$ receptor knockout and the TMEM16F knockdown to inhibit phosphatidylserine expression.[132,133] It is important to note that the critical role of microglia in other injury mechanisms must be carefully considered when manipulating this process. Inhibition of microglial phagocytosis may somewhat hinder or even reverse its multiple beneficial roles in repairment post-ICH, including lessening the erythrolysis and removing debris, inhibiting

inflammation, promoting angiogenesis, and stimulating neurogenesis.[134] Block the specific targets of microglia and neurons associated with phagocytosis during distinct developmental phases of ICH is essential for precise regulation.

Therapeutic Opportunities Provided by Microglia

In addition to understanding the mechanisms of injury after ICH, the protection and repairment strategies are also an area of extensively researched. Microenvironmental regulation and neural remodelling around hematoma are considered as promising ways to reduce mortality and improve the long-term prognosis of ICH. For the improvement of microenvironment, it is easy to think of the clearance of hematoma and its degradation products.[135,136] In addition, measures such as inhibiting of inflammatory response, ferroptosis, and oxidative stress also can facilitate the survival of viable cells around hematoma to some certain extent.[2,137] Similarly, neural regeneration and neural network remodelling in the injured area are also crucial for long-term prognosis post-stroke.[138,139] It can be said that the ultimate goal of all research efforts is to provide powerful conditions for the orderly survival and development of existing and migrating neuron cells. Subsequently, we will further summarize the available opportunities based on microglia in the process of prognosis improvement following ICH (Table 1). Studies of microglial regulatory strategies in this review with detailed information on target, dose, delivery and outcome were included in Table 1, otherwise they were excluded.

Inhibition of Inflammatory Response

In the acute phase, multiple researches have explored the role of inhibiting the inflammatory response in ameliorating ICH injury. Many animal experiments have demonstrated the feasibility of various interventions in inhibiting microglial activation, reducing pro-inflammatory cytokines and improving long-term prognosis. While some evidence of deleterious has also been found in early microglial depletion.[148] Suppression of inflammatory response is usually targeted by a series of major aspects: first, inhibiting microglial activation; second, reducing the expression of inflammatory cytokines; and third, promoting microglia from a pro-inflammatory to an anti-inflammatory phenotype. Among them, inhibiting the activation of microglia has attracted multiple attention for long time. The physiological effect of minocycline on microglial inhibitory and neuroprotective effects has been discovered as early as 20 years ago. Clinical trials based on minocycline have evaluated its safety of application, but the neuroprotective and anti-inflammatory effects in ICH patients are still unresolved.[149] Microglia are the only cells in the brain that express the colony stimulating factor 1 receptor (CSF1R) and their proliferation depends on the activation of CSF1R. The treatment of CSF1R antagonist can significantly inhibit the microglia proliferation, reduce the pro-inflammatory factors release, increase IL-10 production and improve neurological function following ICH.[150] It should be noted that there is a close crosstalk between microglia and other cells in brain tissues. For example, the process of myelination is supported by microglial secreted factors that can stimulate oligodendrocyte progenitor cells recruitment and differentiation. The white matter remyelination of CSF1-/- mutant mice has been reported to be severely impaired.[151] Therefore, how to suppress the inflammatory response without affecting the regenerative activation induced by pathological conditions as well as potential downstream effects is still a problem to be solved. Several drugs have been demonstrated the effect of anti-inflammatory and neuroprotection in preclinical studies, with a representative regulatory factor of PPAR-γ pathway. The PPAR-γ agonist rosiglitazone has been shown to apparently upregulate the expression of phagocytosis-related genes such as CD36 and catalase, and significantly reduce pro-inflammatory gene of TNF-α, IL-1β, MMP-9, iNOS expression.[140] Many drugs targeting the PPAR-γ pathway have been revealed the function of suppressing inflammatory response and promoting hematoma absorption.[77,78] Recent studies have suggested that the regulatory effects of other signalling pathways, such as the PI3K/Akt pathway, the integrin αVβ5/AMPK pathway, and the Sirt3/Nrf2/HO-1 signalling pathway, also can reduce the inflammatory response in preclinical ICH models.[152–154]

Promoting the transformation of microglia phenotype from M1 to M2 can not only alleviate neuroinflammation but also promote the clearance of hematoma. The regulation of the pattern recognition receptor Dectin-1 has been reported to accelerate microglial polarization and functional recovery after ICH.[141] Another interesting example is naltrexone. Naltrexone, while promoting the transformation of inflammatory profile, also participates in the process of immunometabolic reprogramming, which is accompanied by an apparent cellular metabolic shift from glycolysis to mitochondrial oxidative phosphorylation in the LPS pre-treated microglial cells.[155] These are recent evidences of regulatory strategies

Table 1 Summary of the Latest Microglial Regulatory Strategies Mentioned Within This Review for the Injury Repair After ICH

Intervention	Target	Species (model)	Modeling Approach	Dose	Delivery	Outcome	Reference
Bexarotene	RXR/PPAR-γ	Mice (ICH)	Autologous blood or collagenase	5 mg/kg	Intraperitoneal	Enhanced erythrophagocytosis, reduced hematoma volume, improved neurological recovery	[77]
Wogonin	PPAR-γ	Mice (ICH)	Autologous blood	20 mg/kg	Intraperitoneal	Upregulated Axl, MerTK, CD36, LAMP2 expression, promoted hematoma clearance, improved neurological recovery	[79]
Rosiglitazone	PPAR-γ	Mice (ICH)	Autologous blood	0.1 mg/kg	Intraperitoneal	Promoted hematoma absorption, upregulated CD36 and catalase expression, reduced pro-inflammatory gene expression	[140]
Laminaria	Dectin-1/Syk/Card9/ NF-κB	Mice (ICH)	Autologous blood	250 mg/kg	Intraperitoneal	Induced the shift of anti-inflammatory phenotype, alleviated neurological dysfunction, facilitated hematoma clearance	[141]
Recombinant IL-10 protein	CD36	Mice (ICH)	Collagenase	0.1 μg/mice	Intranasal	Accelerated hematoma clearance, improved neurologic outcome	[142]
IL-4 NPs	IL-4/STAT6/ST2	Mice (ICH)	Autologous blood or collagenase	50 μg/kg	Intranasal	Facilitated hematoma resolution, improved long-term functional recovery	[143]
Vitamin D	Multiple	Mice (ICH)	Autologous blood or collagenase	1000 IU/kg	Orally	Promoted neurological recovery, facilitated hematoma clearance, elevated the levels of CD36 and PPAR-γ, accelerated differentiation toward macrophages	[144]
Anti-CD47 blocking antibody	CD47/SIRP α	Rat (IVH)	Autologous blood	10μg/ml, final concentration in blood	Intraventricular	Accelerated hematoma clearance, alleviated hemolysis and hydrocephalus	[84]
Fractalkine	CX3CR1/PPAR-γ/ CD163/HO-1	Mice (ICH)	Collagenase	300 nm	Lateral ventricular	Improved hematoma absorption and neurological recovery	[97]
Dexmedetomidine	NF-κB	Rat (ICH)	Collagenase	20 mg/kg	Intraperitoneal	Exerted neuroprotective effects, increased the numbers of surviving neurons, decreased brain water content, facilitated M2 polarization	[73]
rhCDNF	Multiple	Mice/rat (ICH)	Autologous blood or collagenase	5 μg/2 μl or 30μg	Intraventricular or intravenous	Accelerated hemorrhagic lesion resolution, reduced peri-focal edema, improved neurological outcomes	[145]
H_2S donor ADT	CBS-H_2S-complex I	Mice (ICH)	Autologous blood or collagenase	20 mg/kg	Intraperitoneal	Promoted microglial phagocytosis and hematoma resolution	[146]
Ceria NPs	Multiple	Mice (ICH)	Collagenase	0.5 mg/kg	Intravenous	Promoted remyelination and oligodendrocyte progenitor cell differentiation, increased mature oligodendrocytes	[147]

Abbreviations: ICH, intracerebral hemorrhage; RXR, retinoid X receptor; SIRP α, signal regulatory protein α; IVH, intraventricular hemorrhage; CDNF, cerebral dopamine neurotrophic factor; CBS, cystathionine β-synthase; NPs, nanoparticles.

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regarding the inhibition of the inflammatory response, and clinical trials of these modulations have not been reported. For clinical trials in neuroinflammatory after ICH, a novel small-molecule drug candidate (MW01-6-189WH, MW189) has been highly expected. MW189 has been preliminarily assessed for its safety and is currently being tested for the utility of targeting neuroinflammation post-ICH.[26] Collectively, these findings indicate that inhibition of the inflammatory response has a significant positive impact on improving prognosis and also suggests that targeting immunometabolism may offer resultful therapeutic strategies for ICH. Differential results in inhibiting microglial activation also suggest that this intervention strategy is highly dependent on factors such as injury severity, treatment timing, target, and doses.

Hematoma Clearance

It is well known that the hematoma microenvironment suffers from hematoma and its degradation products over a long period of time. Many clinical and preclinical strategies have been applied to remove these toxic substances. The role of the protein CD163 and CD36 in hematoma clearance after ICH has been reported in many studies, and the pathways that regulate the expression of these two proteins are precisely the hotspot of current preclinical research.[17,156] Here, we mainly focus on how to manipulate microglia-related pathways to accelerate hematoma clearance (Figure 4). Erythrocyte is the first target in phased hematoma removal. Currently, evidence suggests that targeted delivery of the anti-inflammatory cytokine IL-10 to ICH-affected regions can effectively facilitate hematoma resolution, which is probably related to the activation of STAT3 pathway and the upregulation of CD36 protein.[142,157] Intranasal delivery of IL-4 nanoparticles also can accelerate hematoma scavenging through enhancing the expression of phosphor-STAT6 in microglia cells.[143] Vitamin D, on the other hand, has been reported to facilitate hematoma clearance via promoting reparative macrophage differentiation and upregulating the levels of CD36 and PPAR-γ in brain.[144] The "don't eat me" signalling molecule CD47, which is located on the surface of the erythrocyte membrane and is closely associated with phagocytosis, has also been the focus of research. Several approaches have been applied to block CD47 and promote hematoma clearance, including CD47 knockout and CD47 blocking antibody.[82,158] For hemoglobin derived from hematoma, the scavenger receptor CD163 is the focus of attention. Neuron derived fractalkine can facilitate erythrophagocytosis by microglia in vitro through the CD163 and HO-1 pathways, and the serum fractalkine levels are positively related with hematoma resolution in ICH patients.[97] The antioxidant regulator of Nrf2 also plays an important role in the process of microglial phagocytosis.[138] Intracerebroventricular administration of recombinant human cerebral dopamine neurotrophic factor was found to upregulate the Nrf2-HO-1 pathway, promote the expression of early scavenger receptors

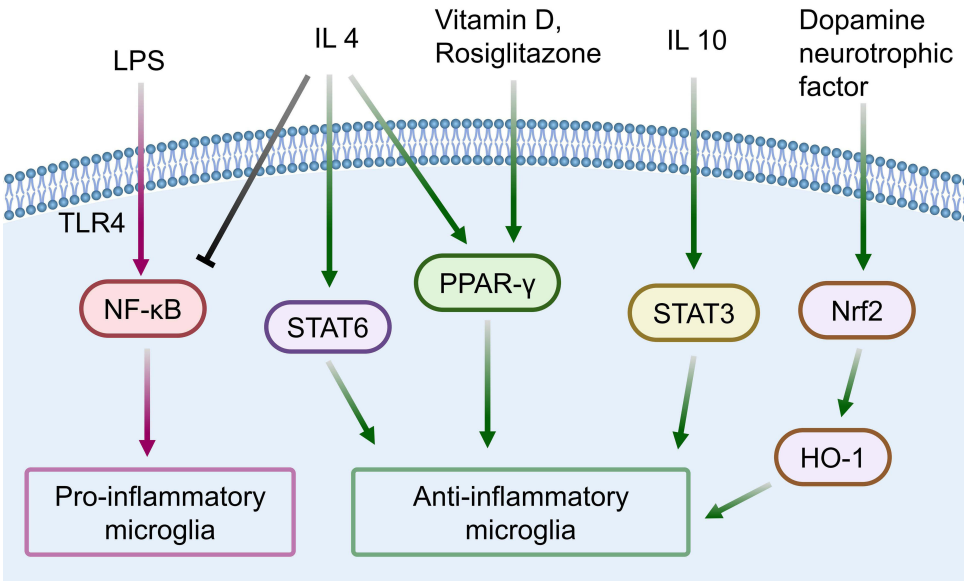

Figure 4 The intervention strategies targeting the microglial phenotypic transform post-ICH.

CD36 and CD163, and achieve beneficial effects in the collagenase-induced ICH animal model.[145] Additionally, enhanced UCP2 activation based on gasotransmitter hydrogen sulfide-induced superoxide production has been demonstrated to promote microglial continual phagocytosis of erythrocyte after ICH.[146] Understanding the regulatory pathway associated with these scavenger receptors may provide an efficient avenue for hematoma resolution and therapeutic intervention in ICH.

Remodeling Neural Network

Neural network remodeling is closely related to the long-term recovery of neurological function after ICH. The process of neural regeneration including neurogenesis, axonal regeneration, oligodendrogenesis, and angiogenesis.[138,159] Microglial functional changes under stress are strongly associated with neuronal network activity and contribute to pathological outcomes.[14] The most direct instance is microglial knockout or depletion, which has displayed that microglia can directly remodel synapses and increase neural circuit connectivity in the CNS with precise action.[15,128] Compared to vehicle, early microglial CSF1R inhibition resulted in more genes enriched in synapse function and dendritic spines in TBI, and improved neuronal maintenance and recovery.[160] Thus, the mechanism of neural network remodelling in the damage state may be a pathological extension of synaptic pruning during development. The proliferation and differentiation of oligodendrocytes, which are responsible for the myelination of neurons, are also affected by microglia. Inhibition of microglial polarization and astrocyte alteration has been reported to promote remyelination and oligodendrocyte progenitor cell differentiation after ICH.[147] Microglial activity and function also can affect the angiogenesis in perihematoma. LPS activated microglia have been observed to facilitate the migration, proliferation and angiogenesis of co-cultured retinal microvascular endothelial cells.[161] Microglia located perivascular of endothelial cells can not only survey the influent blood-borne components into the CNS but also promote angiogenesis, leukocyte extravasation, and BBB opening.[162] The latest analysis of single-transcripts of mice brains has revealed a new microglial phenotype associated with angiogenesis post-ICH.[163] Some neuroprotective agents have been verified to promote microglia phagocytosis and M2 polarisation, upregulate angiogenesis and functional recovery after ICH through glycogen synthase kinase-3β (GSK-3β) inhibition.[164] Therefore, the microglia-based treatment strategy for ICH may result from the combined action of multiple mechanisms, including inhibition of inflammatory response, improvement of hematoma microenvironment, and promotion of neural network remodeling.

Conclusion

Emerging evidence has accomplished great advances in understanding the mechanisms behind microglial inflammatory response associated with brain injury over the past few decades. It is becoming increasingly clear that the pro-inflammatory and anti-inflammatory phenotypes of microglia are closely related to the secondary brain injury and repair process after ICH, which is a key factor related to the prognosis of ICH. Different from the current conventional clinical treatment of ICH, the regulatory of targeting microglial phenotype transformation provides a wider range of recovery promotion strategies for the intervention research and clinical treatment post-ICH. Summarizing and reviewing the most up-to-date progress in microglial function and brain damage and repairment following ICH can provide reference for the future research directions. We highlight the significant therapeutic opportunities presented by microglia in their pro- and anti-inflammatory response states. Targeting microglial phenotypic transformation can effectively inhibit the inflammatory responses, promote hematoma clearance, and alleviate the secondary brain injuries. This synergistic intervention of multiple injury mechanisms is of great significance for improving the prognosis of patients and promoting clinical transformation.

Although several effective preclinical studies have been reviewed, achieving successful clinical translation remains a challenge. There are still some open questions that impede a thorough understanding of microglial function, such as when and how to modulate the switch in microglial roles for maximum clinical benefits. In the early stage of ICH, the pathological state will spontaneously activate the body's immune response and the neural repairment mechanism of endogenous neural stem cells. Ultra-early immunosuppression will inhibit this spontaneous defense and repairment process activated by injury. Therefore, identifying the diverse temporal and spatial changes in the immune cascade mediated by microglia could be a crucial factor in contributing to the clinical prognosis of ICH. In addition, it should be

noted that the existing preclinical evidences are mainly obtained from animal models established by the autologous blood injection or collagenase injection. Actually, the pathogenesis of ICH involves complex risk factors, such as hypertension, antithrombotics, diabetes, and heavy alcohol use. How these factors influence the course of immunotherapy all need to be clarified. Moreover, to obtain the temporal and spatial information of immune activation and phenotypic transformation in the real pathological environment post-ICH, the multi-omics research of human spontaneous ICH may provide a more reliable basis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no competing interests.

References

1. Magid-Bernstein J, Girard R, Polster S, et al. Cerebral hemorrhage: pathophysiology, treatment, and future directions. *Circ Res*. 2022;130(8):1204–1229. doi:10.1161/circresaha.121.319949
2. Zille M, Farr TD, Keep RF, Romer C, Xi G, Boltze J. Novel targets, treatments, and advanced models for intracerebral haemorrhage. *EBioMedicine*. 2022;76:103880. doi:10.1016/j.ebiom.2022.103880
3. Wu S, Anderson CS. A need to re-focus efforts to improve long-term prognosis after stroke in China. *Lancet Glob Health*. 2020;8(4):e468–e469. doi:10.1016/s2214-109x(20)30086-3
4. Chen Y, Wright N, Guo Y, et al. Mortality and recurrent vascular events after first incident stroke: a 9-year community-based study of 0·5 million Chinese adults. *Lancet Glob Health*. 2020;8(4):e580–e590. doi:10.1016/s2214-109x(20)30069-3
5. Selim M, H D. Unmet needs and challenges in clinical research of intracerebral hemorrhage. *Stroke*. 2018;49(5):1299–1307. doi:10.1161/STROKEAHA.117.019541
6. Wu S, Wu B, Liu M, et al. Stroke in China: advances and challenges in epidemiology, prevention, and management. *Lancet Neurol*. 2019;18(4):394–405. doi:10.1016/s1474-4422(18)30500-3
7. Carpenter AM, Singh IP, Gandhi CD, Prestigiacomo CJ. Genetic risk factors for spontaneous intracerebral haemorrhage. *Nat Rev Neurol*. 2016;12(1):40–49. doi:10.1038/nrneurol.2015.226
8. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. 2015;46(7):2032–2060. doi:10.1161/str.0000000000000069
9. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet Neurol*. 2012;11(8):720–731. doi:10.1016/s1474-4422(12)70104-7
10. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373(9675):1632–1644. doi:10.1016/s0140-6736(09)60371-8
11. Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med*. 2017;23(9):1018–1027. doi:10.1038/nm.4397
12. Borst K, Dumas AA, Prinz M. Microglia: immune and non-immune functions. *Immunity*. 2021;54(10):2194–2208. doi:10.1016/j.immuni.2021.09.014
13. Augusto-Oliveira M, Arrifano GP, Delage CI, Tremblay M, Crespo-Lopez ME, Verkhratsky A. Plasticity of microglia. *Biol Rev Camb Philos Soc*. 2022;97(1):217–250. doi:10.1111/brv.12797
14. Li B, Yang W, Ge T, Wang Y, Cui R. Stress induced microglial activation contributes to depression. *Pharmacol Res*. 2022;179:106145. doi:10.1016/j.phrs.2022.106145
15. Ball JB, Green-Fulgham SM, Watkins LR. Mechanisms of microglia-mediated synapse turnover and synaptogenesis. *Prog Neurobiol*. 2022;218:102336. doi:10.1016/j.pneurobio.2022.102336
16. Cserep C, Posfai B, Denes A. Shaping neuronal fate: functional heterogeneity of direct microglia-neuron interactions. *Neuron*. 2021;109(2):222–240. doi:10.1016/j.neuron.2020.11.007
17. Ren H, Han R, Chen X, et al. Potential therapeutic targets for intracerebral hemorrhage-associated inflammation: an update. *J Cerebr Blood F Met*. 2020;40(9):1752–1768. doi:10.1177/0271678x20923551
18. Ransohoff RM. A polarizing question: do M1 and M2 microglia exist?. *Nat Neurosci*. 2016;19(8):987–991. doi:10.1038/nn.4338
19. Guo Y, Dai W, Zheng Y, et al. Mechanism and regulation of microglia polarization in intracerebral hemorrhage. *Molecules*. 2022;27(20):7080. doi:10.3390/molecules27207080

20. Ye F, Yang J, Hua Y, Keep RF, Xi G. Novel approach to visualize microglia death and proliferation after intracerebral hemorrhage in mice. *Stroke*. 2022;53(11):e472–e476. doi:10.1161/STROKEAHA.122.040302
21. Wilkinson DA, Pandey AS, Thompson BG, Keep RF, Hua Y, Xi G. Injury mechanisms in acute intracerebral hemorrhage. *Neuropharmacology*. 2018;134(Pt B):240–248. doi:10.1016/j.neuropharm.2017.09.033
22. Xia F, Keep RF, Ye F, et al. The fate of erythrocytes after cerebral hemorrhage. *Transl Stroke Res*. 2022;13(5):655–664. doi:10.1007/s12975-021-00980-8
23. Lu C, Tan C, Ouyang H, Chen Z, Yan Z, Zhang M. Ferroptosis in intracerebral hemorrhage: a panoramic perspective of the metabolism, mechanism and theranostics. *Aging Dis*. 2022;13(5):1348–1364. doi:10.14336/ad.2022.01302
24. Zheng Y, Tan X, Cao S. The critical role of erythrolysis and microglia/macrophages in clot resolution after intracerebral hemorrhage: a review of the mechanisms and potential therapeutic targets. *Cell mol Neurobiol*. 2023;43(1):59–67. doi:10.1007/s10571-021-01175-3
25. Xue M, Yong VW. Neuroinflammation in intracerebral haemorrhage: immunotherapies with potential for translation. *Lancet Neurol*. 2020;19(12):1023–1032. doi:10.1016/s1474-4422(20)30364-1
26. Avadhani R, Ziai WC, Thompson RE, et al. Clinical trial protocol for BEACH: a phase 2a study of MW189 in patients with acute nontraumatic intracerebral hemorrhage. *Neurocrit Care*. 2024;40(2):807–815. doi:10.1007/s12028-023-01867-2
27. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet*. 2018;392(10154):1257–1268. doi:10.1016/s0140-6736(18)31878-6
28. Teo KC, Fong SM, Leung WCY, et al. Location-specific hematoma volume cutoff and clinical outcomes in intracerebral hemorrhage. *Stroke*. 2023;54(6):1548–1557. doi:10.1161/strokeaha.122.041246
29. Murthy SB, Moradiya Y, Dawson J, et al. Perihematomal edema and functional outcomes in intracerebral hemorrhage: influence of hematoma volume and location. *Stroke*. 2015;46(11):3088–3092. doi:10.1161/STROKEAHA.115.010054
30. Wan S, Cheng Y, Jin H, et al. Microglia activation and polarization after intracerebral hemorrhage in mice: the role of protease-activated receptor-1. *Transl Stroke Res*. 2016;7(6):478–487. doi:10.1007/s12975-016-0472-8
31. Bollmann L, Koser DE, Shahapure R, et al. Microglia mechanics: immune activation alters traction forces and durotaxis. *Front Cell Neurosci*. 2015;9:363. doi:10.3389/fncel.2015.00363
32. Zhu T, Guo J, Wu Y, et al. The mechanosensitive ion channel piezo1 modulates the migration and immune response of microglia. *iScience*. 2023;26(2):105993. doi:10.1016/j.isci.2023.105993
33. Gong Y, Gong Y, Hou Z, et al. Establishment of an experimental intracerebral haemorrhage model for mass effect research using a thermo-sensitive hydrogel. *Sci Rep*. 2019;9(1):1–10. doi:10.1038/s41598-019-50188-y
34. Zhang Y, Wang G, Xie M, et al. Piezo1 mediates inflammation in balloon-inflated rat brain and its bidirectional mechanosensitivity. *Curr Mol Med*. 2022. doi:10.2174/1566524023666221222111934
35. Ayata P, Schaefer A. Innate sensing of mechanical properties of brain tissue by microglia. *Curr Opin Immunol*. 2020;62:123–130. doi:10.1016/j.coi.2020.01.003
36. Wu C, Yan X, Liao Y, et al. Increased perihematomal neuron autophagy and plasma thrombin-antithrombin levels in patients with intracerebral hemorrhage: an observational study. *Medicine*. 2019;98(39):e17130. doi:10.1097/MD.0000000000017130
37. Krenzlin H, Gresser E, Jussen D, et al. The cerebral thrombin system is activated after intracerebral hemorrhage and contributes to secondary lesion growth and poor neurological outcome in C57Bl/6 mice. *J Neurotraum*. 2020;37(12):1481–1490. doi:10.1089/neu.2019.6582
38. Ye F, Garton HJL, Hua Y, Keep RF, Xi G. The role of thrombin in brain injury after hemorrhagic and ischemic stroke. *Transl Stroke Res*. 2021;12(3):496–511. doi:10.1007/s12975-020-00855-4
39. Xi G, Reiser G, Keep RF. The role of thrombin and thrombin receptors in ischemic, hemorrhagic and traumatic brain injury: deleterious or protective?. *J Neurochem*. 2003;84(1):3–9. doi:10.1046/j.1471-4159.2003.01268.x
40. Shlobin NA, Har-Even M, Itsekson-Hayosh Z, Harnof S, Pick CG. Role of thrombin in central nervous system injury and disease. *Biomolecules*. 2021;11(4):562. doi:10.3390/biom11040562
41. Iannucci J, Grammas P. Thrombin, a key driver of pathological inflammation in the brain. *Cells*. 2023;12(9):1222. doi:10.3390/cells12091222
42. Krenzlin H, Frenz C, Schmitt J, et al. High CSF thrombin concentration and activity is associated with an unfavorable outcome in patients with intracerebral hemorrhage. *PLoS One*. 2020;15(11):e0241565. doi:10.1371/journal.pone.0241565
43. Babu R, Bagley JH, Di C, Friedman AH, Adamson C. Thrombin and hemin as central factors in the mechanisms of intracerebral hemorrhage-induced secondary brain injury and as potential targets for intervention. *Neurosurg Focus*. 2012;32(4):E8. doi:10.3171/2012.1.FOCUS11366
44. Schlunk F, Bohm M, Boulouis G, et al. Secondary bleeding during acute experimental intracerebral hemorrhage. *Stroke*. 2019;50(5):1210–1215. doi:10.1161/STROKEAHA.118.021732
45. Kitaoka T, Hua Y, Xi G, Hoff JT, Keep RF. Delayed argatroban treatment reduces edema in a rat model of intracerebral hemorrhage. *Stroke*. 2002;33(12):3012–3018. doi:10.1161/01.str.0000037673.17260.1b
46. Masada T, Hua Y, Xi G, Yang GY, Hoff JT, Keep RF. Attenuation of intracerebral hemorrhage and thrombin-induced brain edema by overexpression of interleukin-1 receptor antagonist. *J Neurosurg*. 2001;95(4):680–686. doi:10.3171/jns.2001.95.4.0680
47. Rodriguez-Gomez JA, Kavanagh E, Engskog-Vlachos P, et al. Microglia: agents of the CNS pro-inflammatory response. *Cells*. 2020;9(7). doi:10.3390/cells9071717
48. Shao L, Chen S, Ma L. Secondary brain injury by oxidative stress after cerebral hemorrhage: recent advances. *Front Cell Neurosci*. 2022;16:853589. doi:10.3389/fncel.2022.853589
49. Kirshner H, Schrag M. Management of intracerebral hemorrhage: update and future therapies. *Curr Neurol Neurosci Rep*. 2021;21(10):57. doi:10.1007/s11910-021-01144-9
50. Keep RF, Zhou N, Xiang J, Andjelkovic AV, Hua Y, Xi G. Vascular disruption and blood-brain barrier dysfunction in intracerebral hemorrhage. *Fluids Barriers CNS*. 2014;11:18. doi:10.1186/2045-8118-11-18
51. Zhang Y, Khan S, Liu Y, Wu G, Yong VW, Xue M. Oxidative stress following intracerebral hemorrhage: from molecular mechanisms to therapeutic targets. *Front Immunol*. 2022;13:847246. doi:10.3389/fimmu.2022.847246
52. Yao Z, Bai Q, Wang G. Mechanisms of oxidative stress and therapeutic targets following intracerebral hemorrhage. *Oxid Med Cell Longev*. 2021;2021:8815441. doi:10.1155/2021/8815441

53. Duan X, Wen Z, Shen H, Shen M, Chen G. Intracerebral hemorrhage, oxidative stress, and antioxidant therapy. *Oxid Med Cell Longev*. 2016;2016:1203285. doi:10.1155/2016/1203285
54. Bai Q, Xue M, Yong VW. Microglia and macrophage phenotypes in intracerebral haemorrhage injury: therapeutic opportunities. *Brain*. 2020;143(5):1297–1314. doi:10.1093/brain/awz393
55. Haslund-Vinding J, McBean G, Jaquet V, Vilhardt F. NADPH oxidases in oxidant production by microglia: activating receptors, pharmacology and association with disease. *Br J Pharmacol*. 2017;174(12):1733–1749. doi:10.1111/bph.13425
56. Yauger YJ, Bermudez S, Moritz KE, Glaser E, Stoica B, Byrnes KR. Iron accentuated reactive oxygen species release by NADPH oxidase in activated microglia contributes to oxidative stress in vitro. *J Neuroinflammation*. 2019;16(1):41. doi:10.1186/s12974-019-1430-7
57. Lan X, Han X, Li Q, Yang QW, Wang J. Modulators of microglial activation and polarization after intracerebral haemorrhage. *Nat Rev Neurol*. 2017;13(7):420–433. doi:10.1038/nrneurol.2017.69
58. Brown GC, Vilalta A. How microglia kill neurons. *Brain Res*. 2015;1628(Pt B):288–297. doi:10.1016/j.brainres.2015.08.031
59. Rendevski V, Aleksovski B, Mihajlovska Rendevska A, et al. Inflammatory and oxidative stress markers in intracerebral hemorrhage: relevance as prognostic markers for quantification of the edema volume. *Brain Pathol*. 2023;33(2):e13106. doi:10.1111/bpa.13106
60. Jiang C, Guo H, Zhang Z, et al. Molecular, Pathological, Clinical, and Therapeutic Aspects of Perihematomal Edema in Different Stages of Intracerebral Hemorrhage. *Oxid Med Cell Longev*. 2022;2022:1–38. doi:10.1155/2022/3948921
61. Fukuda AM, Badaut J. Aquaporin 4: a player in cerebral edema and neuroinflammation. *J Neuroinflammation*. 2012;9:279. doi:10.1186/1742-2094-9-279
62. Wan Y, Holste KG, Hua Y, Keep RF, Xi G. Brain edema formation and therapy after intracerebral hemorrhage. *Neurobiol Dis*. 2023;176:105948. doi:10.1016/j.nbd.2022.105948
63. Chen Y, Chen S, Chang J, Wei J, Feng M, Wang R. Perihematomal edema after intracerebral hemorrhage: an update on pathogenesis, risk factors, and therapeutic advances. *Front Immunol*. 2021;12:740632. doi:10.3389/fimmu.2021.740632
64. Del Zoppo GJ, Frankowski H, Gu YH, et al. Microglial cell activation is a source of metalloproteinase generation during hemorrhagic transformation. *J Cerebr Blood F Met*. 2012;32(5):919–932. doi:10.1038/jcbfm.2012.11
65. Ruan Z, Zhang D, Huang R, et al. Microglial activation damages dopaminergic neurons through MMP-2/-9-mediated increase of blood-brain barrier permeability in a parkinson's disease mouse model. *Int J mol Sci*. 2022;23(5):2793. doi:10.3390/ijms23052793
66. Lu H, Ashiqueali R, Lin CI, et al. Histone deacetylase 3 inhibition decreases cerebral edema and protects the blood-brain barrier after stroke. *mol Neurobiol*. 2023;60(1):235–246. doi:10.1007/s12035-022-03083-z
67. Liao Y, Cheng J, Kong X, et al. HDAC3 inhibition ameliorates ischemia/reperfusion-induced brain injury by regulating the microglial cGAS-STING pathway. *Theranostics*. 2020;10(21):9644–9662. doi:10.7150/thno.47651
68. Ronaldson PT, Davis TP. Regulation of blood-brain barrier integrity by microglia in health and disease: a therapeutic opportunity. *J Cerebr Blood F Met*. 2020;40(1_suppl):S6–S24. doi:10.1177/0271678X20951995
69. Versele R, Sevin E, Gosselet F, Fenart L, Candela P. TNF-α and IL-1β modulate blood-brain barrier permeability and decrease amyloid-β peptide efflux in a human blood-brain barrier model. *Int J mol Sci*. 2022;23(18):10235. doi:10.3390/ijms231810235
70. Michael BD, Griffiths MJ, Granerod J, et al. The interleukin-1 balance during encephalitis is associated with clinical severity, blood-brain barrier permeability, neuroimaging changes, and disease outcome. *J Infect Dis*. 2016;213(10):1651–1660. doi:10.1093/infdis/jiv771
71. Chen AQ, Fang Z, Chen XL, et al. Microglia-derived TNF-alpha mediates endothelial necroptosis aggravating blood brain-barrier disruption after ischemic stroke. *Cell Death Dis*. 2019;10(7):487. doi:10.1038/s41419-019-1716-9
72. Wong R, Lénárt N, Hill L, et al. Interleukin-1 mediates ischaemic brain injury via distinct actions on endothelial cells and cholinergic neurons. *Brain Behav Immun*. 2019;76:126–138. doi:10.1016/j.bbi.2018.11.012
73. Guo H, Zhang W, Wang Z, Li Z, Zhou J, Yang Z. Dexmedetomidine post-conditioning protects blood-brain barrier integrity by modulating microglia/macrophage polarization via inhibiting NF-κB signaling pathway in intracerebral hemorrhage. *Front Mol Neurosci*. 2022;15:977941. doi:10.3389/fnmol.2022.977941
74. Wang M, Xia F, Wan S, Hua Y, Keep RF, Xi G. Role of complement component 3 in early erythrolysis in the hematoma after experimental intracerebral hemorrhage. *Stroke*. 2021;52(8):2649–2660. doi:10.1161/strokeaha.121.034372
75. Gong Y, Ren P, Deng J, et al. Role of mass effect and trehalose on early erythrolysis after experimental intracerebral hemorrhage. *J Neurochem*. 2022;160(1):88–99. doi:10.1111/jnc.15361
76. Wang G, Wang L, Sun XG, Tang J. Haematoma scavenging in intracerebral haemorrhage: from mechanisms to the clinic. *J Cell Mol Med*. 2018;22(2):768–777. doi:10.1111/jcmm.13441
77. Chang CF, Massey J, Osherov A, Angenendt da Costa LH, Sansing LH. Bexarotene enhances macrophage erythrophagocytosis and hematoma clearance in experimental intracerebral hemorrhage. *Stroke*. 2020;51(2):612–618. doi:10.1161/STROKEAHA.119.027037
78. Wang Y, Chen Q, Tan Q, et al. Simvastatin accelerates hematoma resolution after intracerebral hemorrhage in a PPARγ-dependent manner. *Neuropharmacology*. 2018;128:244–254. doi:10.1016/j.neuropharm.2017.10.021
79. Zhuang J, Peng Y, Gu C, et al. Wogonin accelerates hematoma clearance and improves neurological outcome via the PPAR-γ pathway after intracerebral hemorrhage. *Transl Stroke Res*. 2021;12(4):660–675. doi:10.1007/s12975-020-00842-9
80. Zhou H, Li J, Hu L, et al. Soluble Trem2 is a negative regulator of erythrophagocytosis after intracerebral hemorrhage in a CD36 receptor recycling manner. *J Adv Res*. 2023;44:185–199. doi:10.1016/j.jare.2022.03.011
81. Leclerc JL, Lampert AS, Loyola Amador C, et al. The absence of the CD163 receptor has distinct temporal influences on intracerebral hemorrhage outcomes. *J Cerebr Blood F Met*. 2018;38(2):262–273. doi:10.1177/0271678X17701459
82. Ni W, Mao S, Xi G, Keep RF, Hua Y. Role of erythrocyte CD47 in intracerebral hematoma clearance. *Stroke*. 2016;47(2):505–511. doi:10.1161/STROKEAHA.115.010920
83. Jing C, Bian L, Wang M, Keep RF, Xi G, Hua Y. Enhancement of hematoma clearance with CD47 blocking antibody in experimental intracerebral hemorrhage. *Stroke*. 2019;50(6):1539–1547. doi:10.1161/STROKEAHA.118.024578
84. Ye F, Hua Y, Keep RF, Xi G, Garton HJL. CD47 blocking antibody accelerates hematoma clearance and alleviates hydrocephalus after experimental intraventricular hemorrhage. *Neurobiol Dis*. 2021;155:105384. doi:10.1016/j.nbd.2021.105384
85. Gao X, Yang H, Xiao W, et al. Modified exosomal SIRPα variants alleviate white matter injury after intracerebral hemorrhage via microglia/macrophages. *Biomater Res*. 2022;26(1). doi:10.1186/s40824-022-00311-4

86. Buzzi RM, Akeret K, Schwendinger N, et al. Spatial transcriptome analysis defines heme as a hemopexin-targetable inflammatoxin in the brain. *Free Radic Biol Med*. 2022;179:277–287. doi:10.1016/j.freeradbiomed.2021.11.011
87. Ardic AF, Ardic N. Role of neutrophils as therapeutic targets in intracerebral hemorrhage. *Ther Innov Regul Sci*. 2024;58(5):807–816. doi:10.1007/s43441-024-00668-9
88. Shi M, Li XF, Zhang TB, Tang QW, Peng M, Zhao WY. Prognostic role of the neutrophil-to-lymphocyte ratio in intracerebral hemorrhage: a systematic review and meta-analysis. *Front Neurosci*. 2022;16:825859. doi:10.3389/fnins.2022.825859
89. Moxon-Emre I, Schlichter LC. Neutrophil depletion reduces blood-brain barrier breakdown, axon injury, and inflammation after intracerebral hemorrhage. *J Neuropathol Exp Neurol*. 2011;70(3):218–235. doi:10.1097/NEN.0b013e31820d94a5
90. Hijioka M, Futokoro R, Ohto-Nakanishi T, Nakanishi H, Katsuki H, Kitamura Y. Microglia-released leukotriene B(4) promotes neutrophil infiltration and microglial activation following intracerebral hemorrhage. *Int Immunopharmacol*. 2020;85:106678. doi:10.1016/j.intimp.2020.106678
91. Hermann DM, Kleinschnitz C, Gunzer M. Implications of polymorphonuclear neutrophils for ischemic stroke and intracerebral hemorrhage: predictive value, pathophysiological consequences and utility as therapeutic target. *J Neuroimmunol*. 2018;321:138–143. doi:10.1016/j.jneuroim.2018.04.015
92. Zhao X, Ting SM, Liu CH, et al. Neutrophil polarization by IL-27 as a therapeutic target for intracerebral hemorrhage. *Nat Commun*. 2017;8(1):602. doi:10.1038/s41467-017-00770-7
93. Zheng J, Wu H, Wang X, et al. Temporal dynamics of microglia-astrocyte interaction in neuroprotective glial scar formation after intracerebral hemorrhage. *J Pharm Anal*. 2023;13(8):862–879. doi:10.1016/j.jpha.2023.02.007
94. Fei X, Dou YN, Wang L, et al. Homer1 promotes the conversion of A1 astrocytes to A2 astrocytes and improves the recovery of transgenic mice after intracerebral hemorrhage. *J Neuroinflammation*. 2022;19(1):67. doi:10.1186/s12974-022-02428-8
95. Shi SX, Li YJ, Shi K, Wood K, Ducruet AF, Liu Q. IL (Interleukin)-15 bridges astrocyte-microglia crosstalk and exacerbates brain injury following intracerebral hemorrhage. *Stroke*. 2020;51(3):967–974. doi:10.1161/strokeaha.119.028638
96. Butler CA, Popescu AS, Kitchener EJA, Allendorf DH, Puigdellivol M, Brown GC. Microglial phagocytosis of neurons in neurodegeneration, and its regulation. *J Neurochem*. 2021;158(3):621–639. doi:10.1111/jnc.15327
97. You M, Long C, Wan Y, et al. Neuron derived fractalkine promotes microglia to absorb hematoma via CD163/HO-1 after intracerebral hemorrhage. *Cell mol Life Sci*. 2022;79(5):224. doi:10.1007/s00018-022-04212-6
98. Dienel GA. Brain glucose metabolism: integration of energetics with function. *Physiol Rev*. 2019;99(1):949–1045. doi:10.1152/physrev.00062.2017
99. Steiner P. Brain fuel utilization in the developing brain. *Ann Nutr Metab*. 2019;75(Suppl 1):8–18. doi:10.1159/000508054
100. Meierhans R, Béchir M, Ludwig S, et al. Brain metabolism is significantly impaired at blood glucose below 6 mm and brain glucose below 1 mm in patients with severe traumatic brain injury. *Crit Care*. 2010;14(1):R13. doi:10.1186/cc8869
101. An Y, Varma VR, Varma S, et al. Evidence for brain glucose dysregulation in Alzheimer's disease. *Alzheimer's Dementia*. 2018;14(3):318–329. doi:10.1016/j.jalz.2017.09.011
102. Snowden SG, Ebshiana AA, Hye A, et al. Association between fatty acid metabolism in the brain and Alzheimer's disease neuropathology and cognitive performance: a nontargeted metabolomic study. *PLoS Med*. 2017;14(3):e1002266. doi:10.1371/journal.pmed.1002266
103. Wang Y, Hou Z, Gong Y, Hao S, Wang B. Proteomic analysis of rat brain related to mass effect after experimental intracerebral hemorrhage. *Brain Hemorrhages*. 2021;2(3):101–105. doi:10.1016/j.hest.2021.01.001
104. Liu T, Zhou J, Cui H, et al. Quantitative proteomic analysis of intracerebral hemorrhage in rats with a focus on brain energy metabolism. *Brain Behav*. 2018;8(11). doi:10.1002/brb3.1130
105. Askenase MH, Goods BA, Beatty HE, et al. Longitudinal transcriptomics define the stages of myeloid activation in the living human brain after intracerebral hemorrhage. *Scie immunol*. 2021;6(56). doi:10.1126/sciimmunol.abd6279
106. Wang Q, Lu M, Zhu X, et al. The role of microglia immunometabolism in neurodegeneration: focus on molecular determinants and metabolic intermediates of metabolic reprogramming. *Biomed Pharmacother*. 2022;153:113412. doi:10.1016/j.biopha.2022.113412
107. Korshoj LE, Kielian T. Neuroimmune metabolism: uncovering the role of metabolic reprogramming in central nervous system disease. *J Neurochem*. 2021;158(1):8–13. doi:10.1111/jnc.15376
108. Bernier LP, York EM, MacVicar BA. Immunometabolism in the brain: how metabolism shapes microglial function. *Trends Neurosci*. 2020;43(11):854–869. doi:10.1016/j.tins.2020.08.008
109. Yang S, Qin C, Hu ZW, et al. Microglia reprogram metabolic profiles for phenotype and function changes in central nervous system. *Neurobiol Dis*. 2021;152:105290. doi:10.1016/j.nbd.2021.105290
110. Han X, Ren H, Nandi A, Fan X, Koehler RC. Analysis of glucose metabolism by (18)F-FDG-PET imaging and glucose transporter expression in a mouse model of intracerebral hemorrhage. *Sci Rep*. 2021;11(1):10885. doi:10.1038/s41598-021-90216-4
111. Zhao Y, Xu H. Microglial lactate metabolism as a potential therapeutic target for Alzheimer's disease. *Mol Neurodegener*. 2022;17(1):36. doi:10.1186/s13024-022-00541-z
112. Zhang L, Zhang Y, Wang X, Zhao Y, Li Y, Gu L. Correlation of levels of lactic acid and glucose in cerebrospinal fluid of cerebral hemorrhage patients with the occurrence of postoperative intracranial infection and clinical prognosis. *J Med Biochem*. 2023;42(2):282–288. doi:10.5937/jomb0-44058
113. Lehmann F, Schenk LM, Schneider M, et al. Predictive relevance of baseline lactate and glucose levels in patients with spontaneous deep-seated intracerebral hemorrhage. *Brain Sci*. 2021;11(5):633. doi:10.3390/brainsci11050633
114. Zheng X, Boyer L, Jin M, et al.. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. *eLife*. 2016:5. doi:10.7554/eLife.13374
115. Abdel-Haq R, Schlachetzki JCM, Glass CK, Mazmanian SK. Microbiome-microglia connections via the gut-brain axis. *J Exp Med*. 2019;216(1):41–59. doi:10.1084/jem.20180794
116. Bauer KC, York EM, Cirstea MS, et al. Gut microbes shape microglia and cognitive function during malnutrition. *Glia*. 2022;70(5):820–841. doi:10.1002/glia.24139
117. Donoso F, Cryan JF, Olavarría-Ramírez L, Nolan YM, Clarke G. Inflammation, lifestyle factors, and the microbiome-gut-brain axis: relevance to depression and antidepressant action. *Clin Pharmacol Ther*. 2023;113(2):246–259. doi:10.1002/cpt.2581

118. Zhao L, Xiao J, Li S, et al. The interaction between intestinal microenvironment and stroke. *CNS Neurosci Ther*. 2023;29(Suppl 1):185–199. doi:10.1111/cns.14275
119. Chen L, Wang S, Zhang Y, et al. Multi-omics reveals specific host metabolism-microbiome associations in intracerebral hemorrhage. *Front Cell Infect Microbiol*. 2022;12:999627. doi:10.3389/fcimb.2022.999627
120. Yu X, Zhou G, Shao B, et al. Gut microbiota dysbiosis induced by intracerebral hemorrhage aggravates neuroinflammation in mice. *Front Microbiol*. 2021;12:647304. doi:10.3389/fmicb.2021.647304
121. Wang H, Zhang M, Li J, et al. Gut microbiota is causally associated with poststroke cognitive impairment through lipopolysaccharide and butyrate. *J Neuroinflammation*. 2022;19(1):76. doi:10.1186/s12974-022-02435-9
122. Bostick JW, Mazmanian SK. Impaired gut barrier affects microglia health. *Nat Neurosci*. 2022;25(3):268–270. doi:10.1038/s41593-022-01028-2
123. Zhang Y, Yu W, Flynn C, et al. Interplay between gut microbiota and NLRP3 inflammasome in intracerebral hemorrhage. *Nutrients*. 2022;14 (24):5251. doi:10.3390/nu14245251
124. Liu J, Chen H, Yu T, Fu X, Qian C, Feng X. Berberine mitigates intracerebral hemorrhage-induced neuroinflammation in a gut microbiota-dependent manner in mice. *Aging*. 2023;15(7):2705–2720. doi:10.18632/aging.204642
125. Huang Y, Wu J, Zhang H, et al. The gut microbiome modulates the transformation of microglial subtypes. *mol Psychiatry*. 2023;28 (4):1611–1621. doi:10.1038/s41380-023-02017-y
126. Bulters D, Gaastra B, Zolnourian A, et al. Haemoglobin scavenging in intracranial bleeding: biology and clinical implications. *Nat Rev Neurol*. 2018;14(7):416–432. doi:10.1038/s41582-018-0020-0
127. Yu F, Wang Y, Stetler AR, Leak RK, Hu X, Chen J. Phagocytic microglia and macrophages in brain injury and repair. *CNS Neurosci Ther*. 2022;28(9):1279–1293. doi:10.1111/cns.13899
128. Liu YJ, Spangenberg EE, Tang B, Holmes TC, Green KN, Xu X. Microglia elimination increases neural circuit connectivity and activity in adult mouse cortex. *J Neurosci*. 2021;41(6):1274–1287. doi:10.1523/JNEUROSCI.2140-20.2020
129. Chen Z, Jalabi W, Hu W, et al. Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain. *Nat Commun*. 2014;5:4486. doi:10.1038/ncomms5486
130. Wu G, Sun S, Sheng F, Wang L, Wang F. Perihematomal glutamate level is associated with the blood-brain barrier disruption in a rabbit model of intracerebral hemorrhage. *SpringerPlus*. 2013;2:358. doi:10.1186/2193-1801-2-358
131. Li Q, Weiland A, Chen X, et al. Ultrastructural characteristics of neuronal death and white matter injury in mouse brain tissues after intracerebral hemorrhage: coexistence of ferroptosis, autophagy, and necrosis. *Front Neurol*. 2018;9:581. doi:10.3389/fneur.2018.00581
132. Puigdellívol M, Milde S, Vilalta A, et al. The microglial P2Y6 receptor mediates neuronal loss and memory deficits in neurodegeneration. *Cell Rep*. 2021;37(13):110148. doi:10.1016/j.celrep.2021.110148
133. Zhang Y, Li H, Li X, et al. TMEM16F aggravates neuronal loss by mediating microglial phagocytosis of neurons in a rat experimental cerebral ischemia and reperfusion model. *Front Immunol*. 2020;11:1144. doi:10.3389/fimmu.2020.01144
134. Brown GC. Neuronal loss after stroke due to microglial phagocytosis of stressed neurons. *Int J mol Sci*. 2021;22(24):13442. doi:10.3390/ijms222413442
135. Wilkinson DA, Keep RF, Hua Y, Xi G. Hematoma clearance as a therapeutic target in intracerebral hemorrhage: from macro to micro. *J Cerebr Blood F Met*. 2018;38(4):741–745. doi:10.1177/0271678x17753590
136. Fu P, Zhang M, Wu M, et al. Research progress of endogenous hematoma absorption after intracerebral hemorrhage. *Front Neurol*. 2023;14:1115726. doi:10.3389/fneur.2023.1115726
137. Chen S, Li L, Peng C, et al. Targeting oxidative stress and inflammatory response for blood-brain barrier protection in intracerebral hemorrhage. *Antioxid Redox Sign*. 2022;37(1–3):115–134. doi:10.1089/ars.2021.0072
138. Zhang R, Xue M, Yong VW. Central nervous system tissue regeneration after intracerebral hemorrhage: the next frontier. *Cells*. 2021;10 (10):2513. doi:10.3390/cells10102513
139. Lei X, Hu Q, Ge H, et al. A redox-reactive delivery system via neural stem cell nanoencapsulation enhances white matter regeneration in intracerebral hemorrhage mice. *Bioeng Transl Med*. 2023;8(2):e10451. doi:10.1002/btm2.10451
140. Zhao X, Sun G, Zhang J, et al. Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor gamma in microglia/macrophages. *Ann Neurol*. 2007;61(4):352–362. doi:10.1002/ana.21097
141. Fu X, Zeng H, Zhao J, et al. Inhibition of dectin-1 ameliorates neuroinflammation by regulating microglia/macrophage phenotype after intracerebral hemorrhage in mice. *Transl Stroke Res*. 2021;12(6):1018–1034. doi:10.1007/s12975-021-00889-2
142. Li Q, Lan X, Han X, et al. Microglia-derived interleukin-10 accelerates post-intracerebral hemorrhage hematoma clearance by regulating CD36. *Brain Behav Immun*. 2021;94:437–457. doi:10.1016/j.bbi.2021.02.001
143. Xu J, Chen Z, Yu F, et al. IL-4/STAT6 signaling facilitates innate hematoma resolution and neurological recovery after hemorrhagic stroke in mice. *Proc Natl Acad Sci USA*. 2020;117(51):32679–32690. doi:10.1073/pnas.2018497117
144. Liu J, Li N, Zhu Z, et al. Vitamin D enhances hematoma clearance and neurologic recovery in intracerebral hemorrhage. *Stroke*. 2022;53 (6):2058–2068. doi:10.1161/strokeaha.121.037769
145. Tseng KY, Stratoulias V, Hu WF, et al. Augmenting hematoma-scavenging capacity of innate immune cells by CDNF reduces brain injury and promotes functional recovery after intracerebral hemorrhage. *Cell Death Dis*. 2023;14(2):128. doi:10.1038/s41419-022-05520-2
146. Yan X, He M, Huang H, et al. Endogenous H(2)S targets mitochondria to promote continual phagocytosis of erythrocytes by microglia after intracerebral hemorrhage. *Redox Biol*. 2022;56:102442. doi:10.1016/j.redox.2022.102442
147. Zheng J, Lu J, Mei S, et al. Ceria nanoparticles ameliorate white matter injury after intracerebral hemorrhage: microglia-astrocyte involvement in remyelination. *J Neuroinflammation*. 2021;18(1):43. doi:10.1186/s12974-021-02101-6
148. Jin WN, Shi SX, Li Z, et al. Depletion of microglia exacerbates postischemic inflammation and brain injury. *J Cerebr Blood F Met*. 2017;37 (6):2224–2236. doi:10.1177/0271678x17694185
149. Zhang R, Yong VW, Xue M. Revisiting minocycline in intracerebral hemorrhage: mechanisms and clinical translation. *Front Immunol*. 2022;13:844163. doi:10.3389/fimmu.2022.844163
150. Cheng F, Wang C, Yan B, et al. CSF1R blockade slows progression of cerebral hemorrhage by reducing microglial proliferation and increasing infiltration of CD8 + CD122+ T cells into the brain. *Int Immunopharmacol*. 2024;133:112071. doi:10.1016/j.intimp.2024.112071

151. Wylot B, Mieczkowski J, Niedziolka S, Kaminska B, Zawadzka M. Csf1 deficiency dysregulates glial responses to demyelination and disturbs CNS white matter remyelination. *Cells*. 2019;9(1):99. doi:10.3390/cells9010099
152. Chen S, Peng J, Sherchan P, et al. TREM2 activation attenuates neuroinflammation and neuronal apoptosis via PI3K/Akt pathway after intracerebral hemorrhage in mice. *J Neuroinflammation*. 2020;17(1):168. doi:10.1186/s12974-020-01853-x
153. Wang Y, Tian M, Tan J, et al. Irisin ameliorates neuroinflammation and neuronal apoptosis through integrin αVβ5/AMPK signaling pathway after intracerebral hemorrhage in mice. *J Neuroinflammation*. 2022;19(1):82. doi:10.1186/s12974-022-02438-6
154. Dai S, Wei J, Zhang H, et al. Intermittent fasting reduces neuroinflammation in intracerebral hemorrhage through the Sirt3/Nrf2/HO-1 pathway. *J Neuroinflammation*. 2022;19(1):122. doi:10.1186/s12974-022-02474-2
155. Kucic N, Racki V, Sverko R, Vidovic T, Grahovac I, Mrsic-Pelcic J. Immunometabolic modulatory role of naltrexone in bv-2 microglia cells. *Int J mol Sci*. 2021;22(16). doi:10.3390/ijms22168429
156. Xie WJ, Yu HQ, Zhang Y, Liu Q, Meng HM. CD163 promotes hematoma absorption and improves neurological functions in patients with intracerebral hemorrhage. *Neural Regen Res*. 2016;11(7):1122–1127. doi:10.4103/1673-5374.187047
157. Han R, Lan X, Han Z, et al. Improving outcomes in intracerebral hemorrhage through microglia/macrophage-targeted IL-10 delivery with phosphatidylserine liposomes. *Biomaterials*. 2023;301:122277. doi:10.1016/j.biomaterials.2023.122277
158. Tao C, Keep RF, Xi G, Hua Y. CD47 blocking antibody accelerates hematoma clearance after intracerebral hemorrhage in aged rats. *Transl Stroke Res*. 2020;11(3):541–551. doi:10.1007/s12975-019-00745-4
159. Yong HYF, Rawji KS, Ghorbani S, Xue M, Yong VW. The benefits of neuroinflammation for the repair of the injured central nervous system. *Cell mol Immunol*. 2019;16(6):540–546. doi:10.1038/s41423-019-0223-3
160. Wang Y, Wernersbach I, Strehle J, et al. Early posttraumatic CSF1R inhibition via PLX3397 leads to time- and sex-dependent effects on inflammation and neuronal maintenance after traumatic brain injury in mice. *Brain Behav Immun*. 2022;106:49–66. doi:10.1016/j.bbi.2022.07.164
161. Ding X, Gu R, Zhang M, et al. Microglia enhanced the angiogenesis, migration and proliferation of co-cultured RMECs. *BMC Ophthalmol*. 2018;18(1):249. doi:10.1186/s12886-018-0886-z
162. Dudvarski Stankovic N, Teodorczyk M, Ploen R, Zipp F, Schmidt MHH. Microglia-blood vessel interactions: a double-edged sword in brain pathologies. *Acta Neuropathol*. 2016;131(3):347–363. doi:10.1007/s00401-015-1524-y
163. Zhu X, Xu Z, Liu Y, et al. Unveiling microglia heterogeneity in intracerebral hemorrhage. *Neuroscience*. 2024;555:167–177. doi:10.1016/j.neuroscience.2024.07.039
164. Li R, Liu Z, Wu X, Yu Z, Zhao S, Tang X. Lithium chloride promoted hematoma resolution after intracerebral hemorrhage through GSK-3β-mediated pathways-dependent microglia phagocytosis and M2-phenotype differentiation, angiogenesis and neurogenesis in a rat model. *Brain Res Bull*. 2019;152:117–127. doi:10.1016/j.brainresbull.2019.07.019