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Inflammation and Autophagy in Cerebral Hemorrhage: A Microglial Perspective

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Abstract: *Intracerebral hemorrhage (ICH) remains a devastating global health issue with high mortality and disability. Despite current supportive management strategies, there is a critical lack of treatments targeting the molecular pathways of neuronal death. The neurological injury post-ICH involves both primary damage from the hematoma and complex secondary injuries, where microglia play a central role. The polarization of activated microglia into pro-inflammatory M1 or anti-inflammatory/reparative M2 phenotypes is crucial; an imbalance towards sustained M1 activation exacerbates injury, while an M2 shift promotes repair. Emerging evidence highlights a critical crosstalk between inflammation and autophagy in regulating microglial function. Key signaling pathways, including the NLRP3 inflammasome and HMGB1/TLR4 axis, serve as molecular bridges in this dialogue. The outcome of this interaction significantly influences disease progression, where balanced autophagy can suppress excessive inflammation, but dysregulated autophagy can worsen damage. Therefore, elucidating and therapeutically targeting the key nodes within the microglial inflammation-autophagy crosstalk represents a highly promising avenue for developing novel neuroprotective strategies for ICH.*

Keywords: *Intracerebral Hemorrhage; Autophagy; Secondary Brain Injury; Neuroinflammatory; Microglia; Mitophagy*

1. Introduction

Intracerebral hemorrhage (ICH), one of the most devastating subtypes of stroke, poses a major global public health challenge due to its high mortality and disability rates [1,2]. Although age-standardized stroke mortality has declined, the absolute disease burden of ICH continues to increase owing to population aging [3]. Furthermore, its incidence shows a trend towards affecting younger individuals, posing a growing threat to the health of the working-age population [4]. Current clinical management primarily relies on supportive measures such as acute-phase blood pressure control [5], complication management, and early rehabilitation. While these strategies can improve outcomes to some extent, they fail to fundamentally intervene in the molecular pathways leading to neuronal cell death, highlighting the urgent need for specific neuroprotective agents.

Neurological injury following ICH stems from primary damage caused by hematoma formation and a cascade of complex secondary injuries. Within this pathological process, microglia, the resident immune cells of the central nervous system, play a central role [6]. Activated microglia can polarize into either a pro-inflammatory M1 phenotype or an anti-inflammatory/reparative M2 phenotype. The dynamic balance between these phenotypes profoundly influences the outcomes of the inflammatory response, hematoma clearance, and tissue repair [7]. Excessive and sustained M1 polarization drives an "inflammatory storm," exacerbating blood-brain barrier disruption, cerebral edema, and neuronal death [8,9]. Conversely, a timely shift towards the M2 phenotype is crucial for controlling inflammation and promoting repair [10,11].

Recent research further reveals that microglial functional states are precisely regulated by their autophagic activity, and there exists a close crosstalk between inflammation and autophagy. Evidence indicates that key signaling nodes, such as the NLRP3 inflammasome and the HMGB1/TLR4 axis, constitute molecular bridges for this bidirectional crosstalk [12,13]. The outcome of this dialogue determines disease progression: appropriate autophagy can provide negative feedback to suppress excessive inflammation, exerting neuroprotective effects, whereas dysregulated autophagy can form a vicious cycle with inflammatory responses, aggravating secondary injury [14]. Therefore, in-depth elucidation and precise targeting of the key nodes in the inflammation-autophagy crosstalk within

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microglia present a highly promising direction for developing novel therapeutic strategies for ICH.

2. ICH

2.1 Overview of ICH

Intracerebral hemorrhage (ICH), the second most devastating subtype of stroke, poses a major global public health challenge due to its extremely high mortality and disability rates. According to the Global Burden of Disease (GBD) study data, stroke (including ICH) was the leading neurological disorder contributing to disability-adjusted life years (DALYs) in Asia in 2019 and remains one of the leading causes of death and long-term disability worldwide [1,2]. Although age-standardized stroke mortality has declined in recent years, the absolute disease burden of ICH continues to rise due to population aging [3]. It is particularly noteworthy that the incidence of ICH is showing a trend towards affecting younger individuals, with a significant increase in incidence among the 18-64 age group, making its threat to the health of the working-age population especially prominent [4].

The poor prognosis of ICH is closely related to its unique pathophysiological processes. The rapid formation of a hematoma within the brain parenchyma causes not only direct neuronal damage through mass effect but also triggers a cascade of complex secondary injuries. These injury mechanisms include inflammatory responses (microglial activation, inflammatory cell infiltration, and pyroptosis) [15,16], blood-brain barrier disruption [17], neurotoxicity induced by the release of hemoglobin and iron ions leading to ferroptosis [18], and the formation of cerebral edema [8]. These processes collectively result in severe neurological deficits, with recovery trajectories often being slow and incomplete; survivors are frequently left with significant motor and cognitive impairments [19].

Current clinical management strategies for ICH are primarily limited to supportive and symptomatic treatments, such as strict acute-phase blood pressure control to limit hematoma expansion [5,20], management of complications, and early rehabilitation interventions. While these measures can help improve outcomes to some extent, they fail to fundamentally intervene in the molecular pathways leading to neuronal cell death described above. Consequently, the effectiveness of current treatment regimens in improving long-term functional outcomes for patients remains very limited, highlighting the urgent clinical need for specific neuroprotective agents. However, to date, no specific drug that definitively blocks secondary injury and promotes neural repair has been approved for clinical use [15,19]. Given the limitations of existing treatments, in-depth investigation into the mechanisms of ICH is of critical necessity.We strongly encourage authors to use this document for the preparation of the camera-ready.

2.2 Pathophysiology of ICH

Spontaneous intracerebral hemorrhage (ICH) typically occurs in the deep regions of the brain, such as the basal ganglia and thalamus [12]. The most common etiologies are hypertensive small vessel disease (leading to deep hemorrhages) and cerebral amyloid angiopathy (CAA) (leading to lobar hemorrhages). Other causes include vascular malformations, anticoagulant or antiplatelet therapy, and tumors [21,22]. Hematoma formation is primarily caused by vessel rupture, and the initial mechanical damage it inflicts on brain tissue constitutes the primary injury, involving direct compression and tearing of brain tissue [23]. Secondary injury occurs hours to days after the hemorrhage and involves a series of complex pathophysiological processes, with changes in the perihematomal region (PHR) being particularly critical. These changes include blood-brain barrier (BBB) disruption, edema formation, inflammatory responses, toxicity from iron ions released from red blood cell degradation products, oxidative stress, and neuronal death [24,25]. For instance, studies have found BBB disruption in areas distant from the hematoma in ICH patients, evidenced by contrast agent leakage, which is associated with lobar microbleeds (suggesting CAA) [26]. Perihematomal edema (PHE) is a significant marker of secondary injury and is associated with inflammatory cell infiltration and iron overload [27]. Furthermore, spreading depolarization (SD), a pathophysiological event, can be triggered during rapid hematoma expansion and may, in turn, affect hematoma growth and perfusion in the surrounding brain tissue [28].

Following ICH, microglia, as the primary immune cells of the central nervous system, are rapidly activated. Their pathophysiological changes play a dual role (both detrimental and potentially reparative) in secondary brain injury [15]. Markers of activated microglia/macrophages (such as Iba1 and CD68) are significantly increased in brain tissue after ICH. Research suggests an innate immune anti-inflammatory response exists post-ICH, where anti-inflammatory (reparative) phenotype microglia/macrophages (e.g., expressing CD163 and CD206) are activated alongside the pro-inflammatory phenotype, dynamically

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changing at different time points; for example, CD163 shows a continuous increase 7-12 days after ICH [29]. These anti-inflammatory phenotype cells may originate from resident brain microglia and peripherally infiltrating monocytes. Microglial activation drives neuroinflammation, releasing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) [30]. For instance, TREM2 (triggering receptor expressed on myeloid cells 2) activation (e.g., using its ligand apoE mimetic peptide COG1410) can attenuate neuroinflammation and neuronal apoptosis after ICH, a process involving the PI3K/Akt signaling pathway. Conversely, suppressing excessive microglia-mediated inflammation, for example, through immunomodulation with the sphingosine-1-phosphate receptor (S1PR) modulator siponimod (BAF-312), can reduce perihematomal edema and improve neurological function after ICH [27]. Additionally, microglia are involved in clearing hematoma components (like red blood cells and their degradation products), but sustained overactivation exacerbates tissue damage. Therefore, modulating the phenotypic shift of microglia is a potential therapeutic target for ICH.

3. Microglia

As the immune sentinels within the brain, microglia are core participants in the inflammatory response following ICH, and their functional state is profoundly influenced by their autophagic activity. Current research strongly suggests the existence of close crosstalk between inflammation and autophagy within microglia, which influences the disease outcome of ICH through various molecular mechanisms.

Under physiological conditions, microglia, as the brain's resident immune cells, primarily function to dynamically monitor the intracranial environment and maintain the stability of the central nervous system. When brain tissue is damaged or abnormal, they are rapidly activated to perform functions such as clearing cellular debris and harmful substances, playing a crucial homeostatic role [6]. For instance, under physiological conditions, microglia/macrophages can effectively clear apoptotic cells via scavenger receptors like CD91, limiting potential damage [31].

Under pathological conditions such as ICH, microglia are massively activated and undergo phenotypic polarization, primarily into the classically activated M1 pro-inflammatory phenotype and the alternatively activated M2 anti-inflammatory/reparative phenotype [7]. M1 phenotype microglia release large amounts of pro-inflammatory cytokines (such as TNF-α, IL-1β) and toxic substances, exacerbating neuroinflammation and driving secondary brain injury [9,16]. Conversely, the M2 phenotype exerts anti-inflammatory effects and participates in beneficial processes such as hematoma clearance, tissue repair, and neurogenesis [10,11]. Studies indicate that various interventions, such as activating TREM2 [30], intermittent fasting [32], or administering Fractalkine [10], can exert neuroprotective effects in ICH models by promoting the polarization of microglia towards the M2 phenotype.

Microglia occupy a central position in the pathological process following ICH. On one hand, their excessive activation leading to M1 polarization is a key factor driving the "inflammatory storm," resulting in blood-brain barrier disruption, brain edema, and neuronal apoptosis/pyroptosis [33,34]. On the other hand, their timely switch to the M2 phenotype is crucial for controlling inflammation, clearing hematoma debris (e.g., via receptors like CD36, CD163), and initiating repair processes, representing a core link in limiting brain injury and promoting functional recovery [35-37]. Therefore, regulating the activation state and polarization direction of microglia is considered a highly promising strategy for ICH treatment [6].

4. Inflammation and Autophagy

The pathological process following Intracerebral Hemorrhage (ICH) is intricate, wherein the inflammatory response and autophagy, as two core mechanisms, play dynamic and dualistic key roles. The inflammatory response post-ICH is a "double-edged sword": moderate inflammation is a necessary defensive reaction for hematoma clearance and initiating repair; however, excessive, uncontrolled neuroinflammation is a primary driver of Secondary Brain Injury (SBI), exacerbating neuronal death and neurological deficits [12,38]. This detrimental inflammation is often driven by the activation of inflammasomes (such as NLRP3 and NLRP6), leading to the maturation and release of pro-inflammatory factors like Interleukin-1β (IL-1β) [38,39].

Concurrently, autophagy—a "self-digestion" process used by cells to maintain homeostasis under stress—also exhibits distinct dual potential in ICH. On one hand, autophagy can exert neuroprotective and anti-inflammatory effects by clearing damaged organelles (e.g., mitochondria) and misfolded

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proteins, as well as directly degrading key inflammasome components like ASC specks [12,14]. For instance, the mitophagy receptor FUNDC1 promotes mitophagy to clear damaged mitochondria, thereby inhibiting NLRP3 inflammasome activation and alleviating inflammatory injury after ICH [14]. On the other hand, under specific conditions, autophagy can be "hijacked" to participate in damaging processes. For example, upregulation of autophagy levels facilitated by the activation of the HMGB1/TLR4 signaling axis can promote neuroinflammation and apoptosis [13]. Furthermore, NLRP6 has been shown to activate autophagy in an inflammasome-dependent manner, thereby exacerbating the inflammatory response after ICH, revealing a pathway through which autophagy contributes to harmful processes [38]. Therefore, the balance of inflammation and the appropriate activation of autophagy collectively determine the fate of brain tissue after ICH.

Within the complex microenvironment of ICH, the "crosstalk" between inflammatory and autophagic pathways occurring within microglia, the resident immune cells of the central nervous system, is a core link influencing disease outcome. Microglia are the primary source of the inflammatory storm after ICH, and their functional state is profoundly regulated by autophagic activity. This interactive dialogue is bidirectional: on one hand, autophagy acts as a negative regulatory mechanism to restrain excessive microglial activation. For example, besides FUNDC1-mediated mitophagy [14], a functional autophagy-lysosome pathway regulated by the transcription factor EB (TFEB) is crucial for maintaining microglial homeostasis [40]. On the other hand, inflammatory signals can also significantly influence autophagic activity. The activation of the NLRP6 inflammasome is a typical example of promoting autophagy and exacerbating inflammation [38]. This complex interaction determines the phenotype of microglia and their phagocytic function (i.e., the ability to clear cellular debris). Dysfunctional phagocytosis can further lead to the accumulation of apoptotic cells, which continuously release Damage-Associated Molecular Patterns (DAMPs), perpetuating the inflammatory cycle [41]. Studies indicate that microRNAs (such as miR-210) can inhibit excessive autophagy through the AMPK/mTOR pathway, thereby alleviating the inflammatory response and cell death, and promoting functional recovery [42]. Additionally, significant changes in autophagy-related genes (such as Pik3c3, Akt1, Ulk2) in astrocytes after ICH suggest that the interaction between autophagy and inflammation in non-immune cells is also significant and cannot be ignored [39].

In summary, the intricate network of inflammation and autophagy within microglia and other glial cells constitutes a key signaling hub affecting the balance between injury and repair after ICH. Interventions targeting specific nodes in this crosstalk (such as specific inflammasomes, autophagy receptors, or signaling pathways) hold promise for opening new avenues in ICH treatment.

4.1 Activation Signals of Microglia Following Intracerebral Hemorrhage

Following intracerebral hemorrhage (ICH), microglia are rapidly activated by a series of "Danger Signals" originating from the blood and damaged brain cells [6,7]. These signals primarily include erythrocyte lysate products (such as hemoglobin, heme, and iron ions) [43,44], thrombin [44,45], damage-associated molecular patterns (DAMPs) [34,46], and a complex network of chemokines and cytokines [47,48]. For instance, the interaction between oxidatively stressed erythrocytes and brain endothelial cells can induce microglial responses and cerebral microhemorrhages [43], while direct intracerebral injection of iron or thrombin triggers microglial death or proliferation, respectively [44]. Complement system activation exacerbates early erythrolysis and iron deposition, further driving microglial activation [49]. Additionally, DAMPs such as High Mobility Group Box 1 protein (HMGB1) interact with receptors like TREM-1 [33], hypoxia-induced HIF-1α crosstalks with the NLRP3 inflammasome [46], and signaling pathways such as NOD1/RIP2 [50] collectively form a complex early alarm network that continually activates microglia and initiates neuroinflammatory responses.

In the subsequent inflammatory cascade, specific receptors and signaling pathways finely regulate the phenotypic and functional polarization of microglia [30,51]. Certain signals, such as CCR5 activation, promote neuronal pyroptosis via the PKA/CREB pathway, exacerbating injury [16]. In contrast, the activation of other signals, such as TREM2 [30], CX3CR1 agonism [10], CCR4 activation [48], or GPR40 activation [52], exert anti-inflammatory effects, promote hematoma resolution, and provide neuroprotection through the PI3K/Akt, AMPK/PPARγ, PI3K/AKT/Foxo1, and PAK4/CREB/KDM6B pathways, respectively. Orexin-A also alleviates neuroinflammation via the OXR2/CaMKKβ/AMPK pathway [52]. These activating signals not only originate from the hemorrhage itself but are also amplified during secondary injury processes [11,53]. They intertwine to form a dense signaling network that collectively determines the fate of microglia and their dual role in inflammation [7,36]. Therefore, a deep understanding of these signals is crucial for developing novel therapies that target the modulation of microglia to mitigate neurological damage [6,37].

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4.2 M1 Polarization and the Pro-inflammatory Storm

Following intracerebral hemorrhage (ICH), the polarization of microglia towards the M1 phenotype is a central event driving the "pro-inflammatory storm." Activated M1 microglia markedly upregulate characteristic markers such as CD86 and inducible nitric oxide synthase (iNOS). iNOS catalyzes the production of large amounts of nitric oxide, initiating neurotoxic cascades [37,46]. More critically, these cells release a storm of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which directly attack and compromise the integrity of the blood-brain barrier (BBB), leading to severe vasogenic brain edema [33,54]. Concurrently, M1 microglia generate substantial amounts of reactive oxygen species (ROS), triggering intense oxidative stress that acts synergistically with pro-inflammatory cytokines to exacerbate BBB damage [16,55].

This M1 microglia-dominated pro-inflammatory milieu significantly aggravates secondary brain injury. On one hand, pro-inflammatory cytokines and ROS can directly induce programmed neuronal death pathways, including apoptosis and pyroptosis. For instance, CCR5 activation has been shown to promote neuronal pyroptosis via the NLRP1 pathway [54]. On the other hand, persistent inflammation and oxidative stress impede intrinsic brain repair processes. For example, excessive ROS accumulation inhibits the maturation of oligodendrocyte progenitor cells (OPCs) and hampers remyelination, leading to difficult-to-repair white matter injury [51]. Furthermore, pro-inflammatory signals like IL-15 can establish a vicious cycle between astrocytes and microglia, further amplifying neuroinflammation and ultimately resulting in irreversible neurological deficits [51]. Therefore, suppressing excessive M1 polarization is a crucial therapeutic strategy for mitigating injury after ICH.

4.3 M2 Polarization and Inflammation Resolution

Following intracerebral hemorrhage (ICH), the polarization of microglia/macrophages towards the M2 phenotype is a critical process that drives inflammation resolution and initiates repair. M2 cells are characterized by specific markers such as the mannose receptor (CD206) and arginase-1 (Arg-1), and the upregulation of these markers signifies a transition to an anti-inflammatory, reparative state. Studies confirm that interventions promoting M2 polarization significantly improve outcomes. For instance, intermittent fasting was found to increase the number of "Iba-1+ microglia mainly expressing Arg1" on day 7 after ICH, which coincided with a decrease in pro-inflammatory cytokine levels [32]. More importantly, M2 cells actively terminate harmful neuroinflammation by releasing key anti-inflammatory mediators like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). For example, TREM2 activation not only "inhibited microglia/macrophage activation and neutrophil infiltration" but was also associated with the upregulation of the anti-inflammatory cytokine IL-10, thereby reducing neuronal apoptosis [30]. Functionally, cells with an M2 phenotype exhibit potent phagocytic capacity and are the primary effectors of hematoma clearance. Bexarotene treatment accelerates hematoma resolution by "enhancing macrophage phagocytic receptors and erythrophagocytosis" [35]. Similarly, CD47 blocking antibodies, which target the "don't eat me" signal, can "accelerate hematoma/iron clearance by macrophages/microglia," leading to significant neurological improvement [37]. Therefore, through their specific markers and anti-inflammatory factors, M2 polarization establishes a microenvironment conducive to inflammation resolution and hematoma clearance.

Building upon successful hematoma clearance and inflammation suppression, the microenvironment fostered by M2 microglia further provides the necessary conditions for tissue repair and neuroregeneration. This reparative function stems not only from their anti-inflammatory properties but also from their secretion of neurotrophic factors and synergistic interactions with other brain cells. For instance, research shows that pharmacologically reducing the inhibitory molecule neurite outgrowth inhibitor A (Nogo-A) in the ICH lesion can "promote oligodendrogenesis and functional recovery" while shifting microglia/macrophage function towards a beneficial regulatory phenotype [56]. This directly demonstrates the support provided by an M2-type environment for remyelination, a key repair process. Furthermore, the repair process involves precise intercellular collaboration. Mitochondria derived from astrocytes or the astrocyte-derived peptide Humanin can be taken up by microglia, "promoting their reparative/phagocytic phenotype," thereby collectively "facilitating hematoma clearance and neurological recovery after ICH" [57]. This indicates that M2 microglia act as central coordinators within the neurovascular unit's repair network. In summary, from clearing damage products to actively constructing a regenerative microenvironment, M2 microglia play an indispensable and driving role in tissue repair and neuroregeneration after ICH through multidimensional, multicellular cooperative mechanisms.

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4.4 The core pathways of microglial inflammatory response

After intracerebral hemorrhage (ICH), the activation state of microglia is a key determinant of the neuroinflammatory process and the extent of secondary brain injury. Their inflammatory response is tightly coupled with autophagic activity through several core signaling pathways, forming a complex regulatory network(Table 1). The PI3K/Akt/mTOR pathway is an important regulatory axis. When specific receptors on the microglial surface, such as TREM2 or CCR4, are activated, they can positively regulate this pathway. Activated Akt inhibits autophagy initiation by activating mTOR, while simultaneously favoring the polarization of microglia towards the anti-inflammatory M2 phenotype, thereby alleviating neuroinflammation and neuronal apoptosis, as demonstrated by the TREM2 activator COG1410 and recombinant CCL17 [30,48]. In contrast, the AMPK/mTOR pathway is activated during energy stress. Fractalkine, through its receptor CX3CR1, or Orexin A, through the OXR2 receptor, can activate AMPK, which in turn inhibits mTOR and promotes autophagy. This process is also associated with M2 polarization and anti-inflammatory effects, for example, by inhibiting the NF-κB pathway to mitigate inflammation [32,58]. Furthermore, the Nrf2/HO-1 pathway plays a crucial role in antioxidant stress. Its activation not only directly exerts anti-inflammatory effects but also indirectly inhibits NLRP3 inflammasome activation by promoting autophagy, particularly mitophagy that clears damaged mitochondria. The protective effect of intermittent fasting is partly attributed to the upregulation of the Sirt3/Nrf2/HO-1 axis [14].

Table 1: Core Pathways Linking Microglial Inflammation and Autophag.

Core Pathways	Upstream Signals/ Triggers	Key Molecular Events	Effect on Autophagy	Effect on Microglial Inflammation/ Polarization	Main Functional Outcome
PI3K/Akt/mTOR	TREM2 activation	PI3K/Akt activation → mTOR activation	Typically inhibits autophagy initiation	Promotes M2 polarization; inhibits pro-inflammatory factors	Alleviates neuroinflammation and neuronal apoptosis; improves neurological function
PI3K/Akt/mTOR	CCR4 activation	PI3K/Akt/Foxo 1 activation → mTOR activation	Typically inhibits autophagy initiation	Promotes M2 polarization; inhibits pro-inflammatory factors	Alleviates neuroinflammation and neuronal apoptosis; improves neurological function
AMPK/mTOR	Fractalkine/C X3CR1	AMPK activation → mTOR inhibition	Promotes autophagy initiation	Promotes M2 polarization; inhibits NF-κB pathway	Reduces brain edema and inflammation; promotes hematoma clearance
AMPK/mTOR	Orexin A/OXR2	AMPK activation → mTOR inhibition	Promotes autophagy initiation	Promotes M2 polarization; inhibits NF-κB pathway	Alleviates neuroinflammation
Nrf2/HO-1	Intermittent fasting/Sirt3	Nrf2 nuclear translocation → upregulation of HO-1, etc.	Promotes autophagy/mi tophagy	Potent antioxidant and anti-inflammatory effects; inhibits NLRP3	Reduces oxidative stress and neuroinflammation; improves neurological function
TFEB/ Lysosome	Lysosomal stress, calcium signaling	TFEB nuclear translocation → transcription of autophagy/lysos ome genes	Enhances autophagic flux and degradation capacity	Indirectly anti-inflammatory by clearing DAMPs	Maintains proteostasis; reduces cellular damage
NLRP3 Inflammasome	Hematoma components (Hb, iron), mtROS, DAMPs	NLRP3-ASC-pro-caspase-1 assembly → caspase-1 activation → IL-1β/IL-18 maturation	Autophagy negatively regulates NLRP3 (clears components/ activators)	Drives strong pro-inflammatory response (M1 phenotype)	Exacerbates brain edema and neuronal death; pathway inhibition alleviates injury
Mitophagy	PINK1/Parkin , Receptors (e.g., FUNDC1)	Damaged mitochondria are labeled and engulfed	Specifically clears damaged mitochondria	Inhibits NLRP3 activation by reducing mtROS	FUNDC1-promoted mitophagy can inhibit the NLRP3 inflammasome

Downstream of these pathways, several key effector mechanisms directly determine the inflammatory output of microglia. The activation of the NLRP3 inflammasome is a core driver of the strong pro-inflammatory response after ICH. Autophagy, especially mitophagy, can negatively regulate NLRP3 by clearing damaged mitochondria (reducing activators like mtROS) or directly degrading inflammasome components. For instance, FUNDC1-mediated mitophagy has been shown to effectively inhibit NLRP3-

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mediated inflammation [14]. On the other hand, the transcription factor EB (TFEB), as the master regulator of the autophagy-lysosome pathway, enhances the flux and degradation capacity of the entire autophagic process upon activation. This helps clear damage-associated molecular patterns (DAMPs) and maintain intracellular homeostasis, thereby indirectly suppressing excessive inflammation [59]. It is noteworthy that these pathways do not operate in isolation but engage in extensive crosstalk. For example, AMPK activation can both inhibit mTOR and upregulate Nrf2; effective mitophagy can feedback to inhibit NLRP3. However, the role of autophagy is context-dependent and can be double-edged; under certain conditions (e.g., excessive activation of the HMGB1/TLR4 axis), it may also promote inflammation [13]. Therefore, the key to future therapeutic strategies lies in precisely targeting the core nodes of these pathways, aiming to synergistically promote protective autophagy and M2 polarization in microglia while inhibiting their harmful overactive inflammatory response. This provides a broad prospect for developing new approaches to improve outcomes after ICH.

5. Conclusion

The neurological injury following intracerebral hemorrhage (ICH) is a dynamically evolving pathological process. The core driving force has shifted from the static mechanical compression of the hematoma to the highly complex remodeling of the immune-metabolic microenvironment mediated by microglia. This review elucidates that the functional state and ultimate fate of microglia—the balance between pro-inflammatory M1 and reparative M2 phenotypes, which are precisely regulated by a sophisticated bidirectional crosstalk between intracellular autophagy pathways and inflammatory signaling. Specifically, protective autophagy pathways, such as FUNDC1-mediated mitophagy, can negatively regulate the activation of the NLRP3 inflammasome by clearing damaged mitochondria and reducing mtROS. Conversely, the activation of the AMPK/mTOR pathway (e.g., triggered by Fractalkine/CX3CR1) not only promotes autophagy initiation but also drives M2 polarization and suppresses the NF-κB inflammatory pathway. In contrast, detrimental autophagy activation driven by signaling axes such as HMGB1/TLR4 or the NLRP6 inflammasome can form a vicious cycle with inflammation, exacerbating injury. Therefore, key pathways including PI3K/Akt/mTOR, AMPK/mTOR, Nrf2/HO-1, and TFEB constitute critical signaling hubs that determine the fate of the neurovascular unit.

Looking ahead, the therapeutic paradigm for ICH must evolve from generalized anti-inflammatory and pro-survival strategies towards mechanism-based, specific immunometabolic modulation. The forefront of research points to two promising directions: First, spatiotemporally precise targeting, it involves using nanotechnology or cell-specific carriers to accurately intervene in the key nodes mentioned above during different time windows of the disease. For instance, in the acute phase, activating the TREM2/PI3K/Akt axis or administering rCCL17/CCR4 agonists could suppress excessive inflammation while guiding M2 polarization; in the subacute phase, activating the AMPK/Sirt3/Nrf2 axis via Orexin A/OXR2 signaling or intermittent fasting mimetics could synergistically enhance antioxidant and mitophagy capacity. Second, reprogramming cellular fate, it shifts the strategic core from "inhibiting microglia" to "guiding their functional regeneration." This can be achieved by synergistically upregulating FUNDC1 and activating the TFEB-driven autophagy-lysosomal pathway to actively reshape their phenotype, transforming them into endogenous engines for repair. Ultimately, by deciphering and harnessing the core inflammation-autophagy dialogue network centered on specific autophagy pathways, we can anticipate the development of novel therapies capable of fundamentally improving the long-term neurological outcomes of ICH patients.

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