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*Review*

# Potential Therapeutic Targets and Emerging Strategies to Promote Hematoma Resolution in Intracerebral Hemorrhage

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**Abstract**

Intracerebral hemorrhage (ICH) is a devastating stroke subtype with high morbidity and mortality. Beyond primary injury from blood extravasation, secondary injury driven by erythrocyte lysis and its toxic degradation products exacerbates inflammation, oxidative stress, and neuronal damage. Accelerating endogenous hematoma resolution, including the removal of erythrocytes and their byproducts, represents a promising therapeutic strategy. This review systematically delineates three key mechanisms of hematoma resolution post-ICH: (1) erythrophagocytosis by microglia/macrophages through Tyro3, Axl, and Mertk (TAM) receptors, the cluster of differentiation (CD) 36 receptor, the triggering receptor expressed on myeloid cells 2, and the signal regulatory protein α receptor; (2) clearance of hemolytic products through the hemoglobin-haptoglobin-CD163 and hemin-hemopexin-CD91 axes; and (3) glymphatic and meningeal lymphatic drainage. Pharmacological, genetic, and physical interventions targeting these pathways have demonstrated potential to enhance phagocytosis, promote glymphatic and meningeal lymphatic function, accelerate hematoma resolution, and improve neurological outcomes in ICH models. By leveraging the intrinsic clearance mechanisms of the intracerebral hematoma, this review highlights promising therapeutic targets and strategies to overcome current clinical limitations and demonstrates significant translational potential.

**Keywords:** intracerebral hemorrhage; hematoma absorption; novel therapy; phagocytosis; glymphatic system; meningeal lymphatic vessels

**Posibles Objetivos Terapéuticos y Estrategias Emergentes Para favorecer la Resolución del Hematoma en las Hemorragias Intracerebrales**

**Resumen**

La hemorragia intracerebral (ICH, intracerebral hemorrhage) es un subtipo de accidente cerebrovascular devastador con una alta morbilidad y mortalidad. Más allá de la lesión primaria causada por la extravasación de sangre, la lesión secundaria provocada por la lisis de los eritrocitos y sus productos de degradación tóxicos exacerba la inflamación, el estrés oxidativo y el daño neuronal. Por ello, acelerar la resolución endógena del hematoma, que incluye eliminar los eritrocitos y sus subproductos, representa una estrategia terapéutica prometedora. Esta revisión describe sistemáticamente tres mecanismos clave de resolución del hematoma tras una ICH: (1) la eritrofagocitosis por parte de la microglía/macrófagos a través de los receptores TAM (Tyro3, Axl y Mertk), el grupo de diferenciación (CD, cluster of differentiation) 36, el receptor activador expresado en células mieloides 2 y el receptor de la proteína reguladora de señales α; (2) la eliminación de productos hemolíticos a través de los ejes hemoglobina-haptoglobina-CD163 y hemina-hemopexina-CD91; y (3) el drenaje glinfático y linfático meníngeo. Las intervenciones farmacológicas, genéticas y físicas dirigidas a estas vías han demostrado su potencial para mejorar la fagocitosis, favorecer la función glinfática y linfática meníngea, acelerar la resolución del hematoma y mejorar los resultados neurológicos en modelos de ICH. Al hacer uso de los mecanismos de eliminación intrínsecos del hematoma intracerebral, esta revisión destaca objetivos y estrategias terapéuticas prometedoras para superar las limitaciones clínicas actuales y demuestra un importante potencial traslacional.

**Palabras Claves:** hemorragia intracerebral; absorción de hematomas; terapia novedosa; fagocitosis; sistema glinfático; vasos linfáticos meníngeos

## 1. Introduction

Intracerebral hemorrhage (ICH), a non-traumatic focal hemorrhage within the brain parenchyma, is the most devastating stroke subtype [1,2]. Although it represents approximately 20% of all strokes, it accounts for 49.6% of stroke-related disability-adjusted life years [1,3]. Prognosis of ICH is poor, with a 1-year survival rate of 46%, which declines to 29% at 5 years, and only 33.2% achieving functional independence at 3 months [4,5].

Brain injury after ICH involves primary and secondary mechanisms. Primary injury arises from tissue damage and mass effect due to blood extravasation. Hematoma expansion, seen in 70% of patients during the acute phase, worsens intracranial pressure and is a strong predictor of poor outcome [6]. Secondary injury is triggered by hemoglobin (Hb) from lysed erythrocytes and its breakdown products (hemin, iron), which drive immune-inflammatory reactions, oxidative stress, blood-brain barrier (BBB) disruption, cerebral edema, and neuronal death [7,8]. Accelerating hematoma clearance may therefore improve recovery.

Therapeutic options for ICH remain limited to supportive and surgical hematoma evacuation, as emphasized in the latest American Heart Association (AHA)/American Stroke Association (ASA) and European Stroke Organization (ESO) clinical guidelines [9,10]. In MISTIE III trial, exploratory analysis found better outcomes in patients with post-evacuation hematoma volumes $<$15 mL [11]. The ENRICH trial showed that minimally invasive surgery within 24 hours improved 180-day outcomes in ICH [12]. However, complications such as rebleeding, tissue injury, infection, and incomplete evacuation have spurred interest in enhancing endogenous hematoma clearance as a potential alternative or adjunctive therapeutic strategy. Moreover, in patient ineligible for surgery, early enhancement of hematoma absorption to alleviate mass effect may promote functional recovery.

This review summarizes therapeutic strategies to enhance endogenous hematoma clearance after ICH, focusing on promoting erythrocyte phagocytosis via the activation of TAM (Tyro3, Axl and Mertk) receptors, cluster of differentiation (CD) 36, and triggering receptor expressed on myeloid cells 2 (TREM2), and the inhibition of signal regulatory protein $\alpha$ (SIRP$\alpha$)-CD47 pathway; accelerating hemolytic product removal through the Hb-haptoglobin (Hp)-CD163 and hemin-hemopexin (Hx)-CD91 pathways; and enhancing glymphatic and meningeal lymphatic clearance.

## 2. Phagocytosis of Erythrocyte

A critical step in hematoma clearance involves the phagocytosis of extravasated erythrocytes by brain-resident microglia and infiltrating macrophages [13]. Erythrocytes exhibit both pro-phagocytic and anti-phagocytic signals on surface. The phagocytic clearance of erythrocytes by microglia/macrophages is regulated through four main pathways: the TAM receptor-growth arrest-specific protein 6 (Gas6)/protein S (Pros1)-phosphatidylserine (PtdSer) pathway, the CD36-oxidized PtdSer pathway, the TREM2-PtdSer pathway, and the SIRP$\alpha$-CD47 pathway (Fig. 1).

### *2.1 TAM Receptors-Gas6/Pros1-PtdSer Pathway*

Following ICH, the hypoxic, oxidative, and pro-inflammatory microenvironment induces erythrocyte apoptosis. PtdSer exposed on the surface of apoptotic erythrocytes acts as a pro-phagocytic signal [14]. The TAM receptor family on microglia/macrophages recognizes PtdSer through the bridging ligands Gas6 and Pros1, thereby triggering apoptotic cell clearance [15]. Post-ICH, Axl and Mertk are upregulated in microglia/macrophages [16–18]. Axl/Mertk double knockout markedly reduces macrophage erythrophagocytosis in ICH mice, resulting in larger hematomas, greater iron deposition, and worse neurological deficits [18]. Conversely, recombinant Gas6 promotes hematoma resolution, attenuates edema, and improves neurological function via Axl activation [16,17].

TAM signaling can be inhibited by a disintegrin and metalloproteinase (ADAM)10 and ADAM17, which cleave the extracellular domain of TAM receptors to generate soluble ligand-binding fragments that competitively bind to Gas6 [19,20]. Inhibition of ADAM10/ADAM17 enhances microglial/macrophage clearance of apoptotic cells [20]. Fan *et al*. [21] developed a pH-responsive neutrophil membrane-based nanoplatform carrying the ADAM17 inhibitor GW280264X and the liver X receptor agonist desmosterol. This platform enables targeted delivery to injury sites, promoting erythrophagocytosis, accelerating hematoma clearance, and improving functional recovery [21]. Taken together, activation of the TAM receptors-Gas6/Pros1-PtdSer pathway may provide a viable therapeutic approach to accelerate hematoma resolution and promote neurological recovery after ICH.

### *2.2 CD36-oxidized PtdSer Pathway*

CD36, a class B scavenger receptor, is critical for phagocytosis [22]. Its ectopic expression endows non-phagocytic cells with phagocytic capability, whereas genetic deletion or antibody-mediated blockade significantly impairs phagocyte activity [23–25]. In phagocytes, CD36 primarily recognizes oxidized PtdSer exposed on apoptotic cells, thereby triggering phagocytosis [26]. Deficiency of CD36 in patients or animal models leads to delayed hematoma clearance and worsened neurological outcomes due to impaired erythrophagocytosis of microglia/macrophages [27].

At transcriptional level, CD36 expression is regulated by peroxisome proliferator-activated receptor $\gamma$ (PPAR$\gamma$) and nuclear factor erythroid 2-related factor 2 (Nrf2) [28]. Activation of PPAR$\gamma$ or Nrf2 enhances CD36 expression and erythrophagocytosis of microglia/macrophages, thereby promoting hematoma resolution and neurological

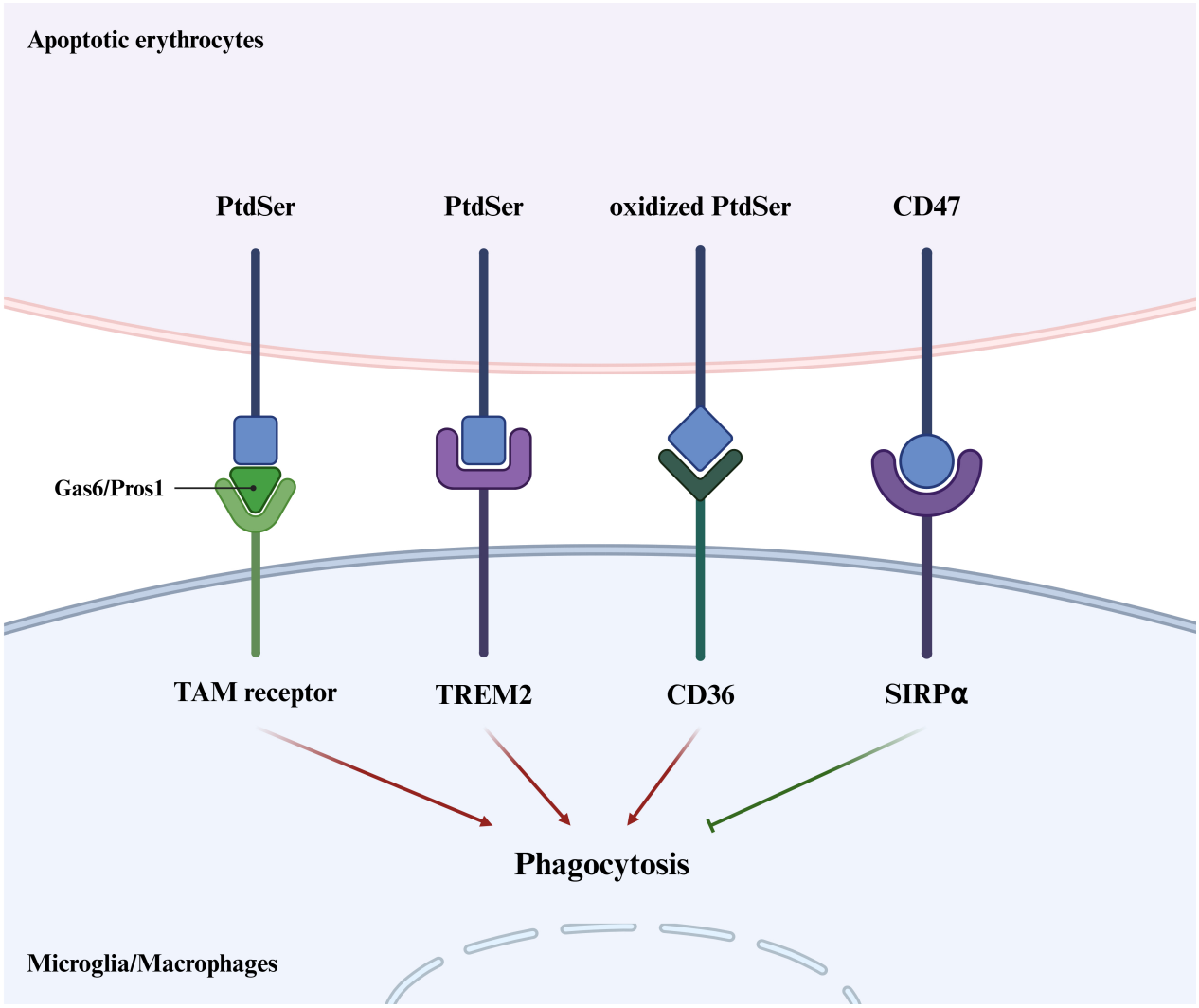


**Fig. 1. Erythrophagocytosis of microglia/macrophages.** Microglia/macrophages initiate phagocytosis of apoptotic erythrocytes by recognizing pro-phagocytic signals, phosphatidylserine (PtdSer) or oxidized PtdSer, through TAM (Tyro3, Axl and Mertk) receptors via the bridging ligands growth arrest-specific protein 6 (Gas6)/protein S (Pros1), triggering receptor expressed on myeloid cells 2 (TREM2) and cluster of differentiation (CD) 36. Conversely, CD47 on erythrocytes serves as an anti-phagocytic signal that inhibits phagocytic activity by binding to signal regulatory protein $\alpha$ (SIRP$\alpha$) on the microglia/macrophages. Created with BioRender.com.

recovery after ICH [29–31]. Pharmacological activation of PPAR$\gamma$ by thiazolidinediones such as pioglitazone and rosiglitazone has demonstrated pro-phagocytic effects in atherosclerosis, underscoring the translational potential of targeting this pathway in ICH models [32]. In 2013, Gonzales *et al*. [33] initiated a randomized controlled trial to investigate the PPAR$\gamma$ agonist pioglitazone for the treatment of spontaneous ICH (NCT00827892), but the final results have yet to be reported. Post-translational modifications, such as SUMOylation, can also enhance microglial CD36 expression and erythrophagocytosis, promote hematoma absorption and alleviate neurological deficits [34].

Moreover, CD36-mediated phagocytosis is modulated by inflammatory signals: pro-inflammatory cytokines such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and interleukin (IL)-1$\beta$ suppress CD36 expression, delaying hematoma resolution and exacerbating neurological deficits, whereas the anti-inflammatory cytokine IL-10 enhances CD36 expression, accelerating hematoma clearance and functional recovery [27]. Furthermore, the soluble extracellular domain of TREM2 impairs microglial/macrophage erythrophagocytosis by inhibiting vacuolar protein sorting 35-mediated CD36 recycling and promoting lysosomal degradation of non-recycled CD36, ultimately delaying hematoma clearance and worsening neurological deficits [35]. Non-pharmacological interventions, including pulsed electromagnetic field therapy and remote ischemic conditioning (RIC), similarly promote hematoma resolution via CD36 modulation [36,37]. These findings suggest that activating the CD36-oxidized PtdSer pathway could provide a therapeutic strategy to enhance hematoma resolution after ICH.

### 2.3 TREM2-PtdSer Pathway

TREM2, a type I immunoglobulin superfamily cell-surface receptor comprising a variable immunoglobulin domain, a transmembrane region, and a short cytoplasmic tail, is primarily expressed on microglia, macrophages, and dendritic cells [38]. Similarly, TREM2 is critical for phagocytic function. Transfection of the *TREM2* gene confers phagocytic activity to Chinese hamster ovary cells that natively lack known phagocytic receptors [39]. In addition, TREM2 has been demonstrated to regulate phagocytosis in both microglia and macrophages [39,40]. The TREM2 receptor on the surface of microglia/macrophages can be activated by binding to PtdSer exposed on apoptotic cells [41]. In ICH models, TREM2 knockout impairs hematoma clearance and worsens neurological deficits, whereas microglia-specific overexpression of TREM2 accelerates hematoma resolution and neurobehavioral recovery [35]. Furthermore, TREM2 agonistic antibody AL002, have been investigated for the treatment of Alzheimer's disease and have demonstrated favorable safety and tolerability profiles in phase I clinical trials, suggesting that pharmacological modulation of the TREM2-PtdSer pathway could potentially be repurposed to promote hematoma resolution following ICH [42].

### 2.4 SIRP$\alpha$-CD47 Pathway

CD47, an integrin-associated protein on erythrocytes, functions as an anti-phagocytic signal by binding the inhibitory receptor SIRP$\alpha$ on microglia/macrophages, thereby suppressing phagocytosis [43]. In a porcine ICH model, CD47 expression in white and gray matter increased within 4 hours and remained elevated for up to 14 days [44]. Erythrocytes lacking CD47 are more readily phagocytosed than wild-type cells [45]. Compared with wild-type erythrocytes, nude mice injected with CD47 knockout erythrocytes exhibited faster hematoma resolution, reduced brain edema, and fewer neurological deficits [46]. Similarly, anti-CD47 antibodies enhances hematoma clearance, attenuates brain injury and reduces neurological deficits in ICH models [47–50]. However, it is particularly noteworthy that CD47 is expressed not only on erythrocytes but also on neurons [44]. Non-specific CD47 blockade may lead to unintended phagocytosis of neurons. Developing strategies to specifically target erythrocyte CD47 may be essential for minimizing off-target effects [51].

Furthermore, strategies that inhibit SIRP$\alpha$ on microglia and macrophages offer an alternative approach to promote hematoma clearance. Yu *et al.* [52] developed a pH-responsive nano-regulator composed of $Mg^{2+}$ and a SIRP$\alpha$ DNAzyme, which releases its components in acidic environments. $Mg^{2+}$ activates the SIRP$\alpha$ DNAzyme, disrupting CD47-SIRP$\alpha$ signaling pathway and thereby enhancing erythrophagocytosis and accelerating hematoma clearance. Collectively, approaches that disrupt CD47-SIRP$\alpha$ pathway represent a promising strategy to facilitate hematoma resolution. Anti-CD47 antibodies such as magrolimab have advanced to phase III clinical trials for myelodysplastic syndrome and acute myeloid leukemia, providing a conceptual framework for application in ICH [53,54].

## 3. Clearance of Hemolytic Product

Within 24 hours post-ICH, erythrocytes in the hematoma core undergo complement-mediated lysis and release Hb, which is subsequently degraded into neurotoxic hemin and iron ions [55]. Resident microglia and infiltrating macrophages uptake free Hb and hemin through the Hb-haptoglobin (Hp)-CD163 and hemin-hemopexin (Hx)-CD91 pathways [56,57]. After internalization, Hb is degraded in lysosomes to release hemin, which is subsequently metabolized into $Fe^{2+}$, biliverdin, and carbon monoxide by heme oxygenase (HO)-1 in the cytosol. The $Fe^{2+}$ is then captured by ferritin and stored as $Fe^{3+}$, or transported extracellularly via ferroportin [58] (Fig. 2).

### 3.1 Erythrocyte Lysis

As the main cellular component of hematoma after ICH, erythrocytes begin to lysis within 24 hours [55]. The complement cascade plays a crucial role, activated via classical, alternative, and lectin pathways, all converging to generate C3 convertase [59]. RNA sequencing shows increased expression of classical and alternative pathway components post-ICH, while lectin pathway changes are minimal [60].

C3 is cleaved into C3a and C3b, leading to C5 convertase formation, cleavage of C5, and subsequent assembly of membrane attack complex (MAC, C5b-C9) that disrupts cell membranes and induces lysis [59]. RNA sequencing shows that *C3* mRNA is primarily expressed in microglia. A study incorporating both clinical and murine data demonstrates that plasma C3 levels are elevated following ICH and correlate with hematoma volume and disease severity [61]. C3-deficient mice exhibit reduced erythrocyte lysis, less brain injury, and improved neurological recovery, indicating that targeting C3 may mitigate erythrocyte lysis post-ICH [62]. CR2-Crry, a recombinant fusion protein inhibiting C3 activation, offers neuroprotection in murine hemorrhagic models [63]. Additionally, normobaric hyperoxia has been shown to reduce C3 levels, promote neurological recovery, and enhance hematoma resolution following ICH [61].

MAC, the terminal product of the complement cascade, directly mediates erythrocyte lysis and Hb release [64]. Animal studies demonstrate that MAC accumulates within hematomas and colocalizes with erythrocytes [63,65]. Inhibitors such as N-acetylheparin and aurintricarboxylic acid block MAC formation, thereby reducing erythrocyte lysis and brain injury in models of ICH [64]. Depletion of the gut microbiota upregulates regulatory T cells,

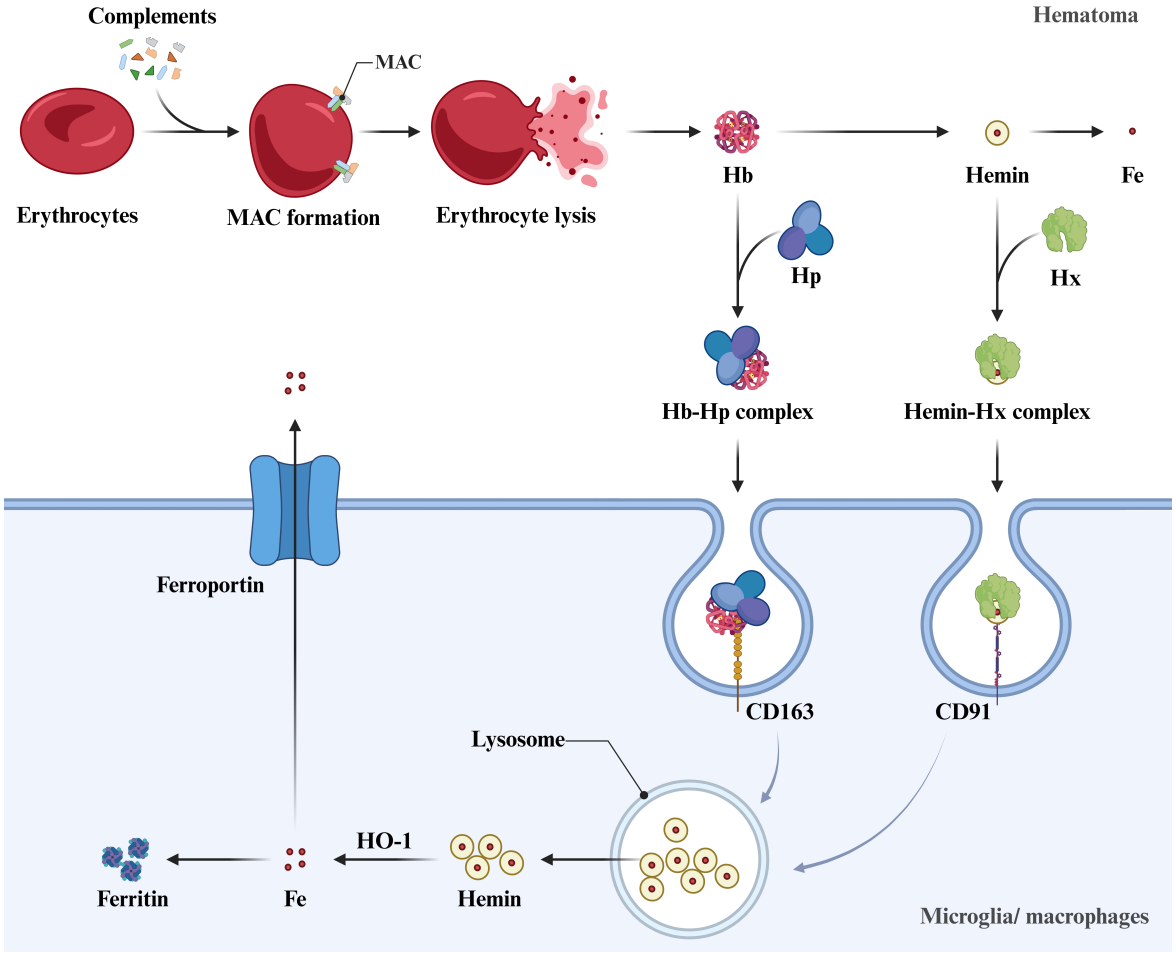


**Fig. 2. Complement-mediated erythrocyte lysis and microglial/macrophage clearance of hemolytic products.** Following intracerebral hemorrhage, complement system activation and membrane attack complex (MAC) formation induces erythrocyte lysis within the hematoma, releasing hemoglobin (Hb) which is subsequently metabolized into hemin and iron ions. Microglia/macrophages phagocytose Hb and hemin through the Hb-haptoglobin (Hp)-CD163 pathway and the hemin-hemopexin (Hx)-CD91 pathway. Then, Hb is degraded in lysosomes to release hemin, which is metabolized in the cytosol by heme oxygenase-1 (HO-1) into $Fe^{2+}$, biliverdin, and carbon monoxide. $Fe^{2+}$ is captured by ferritin or transported extracellularly via ferroportin. Created with BioRender.com.

which in turn reduces MAC formation, facilitates neurological recovery, and accelerates hematoma resolution [66].

### *3.2 Hb Clearance*

Hb and its degradation products induce neurotoxicity via multiple pathways, making extracellular Hb clearance a key therapeutic target after ICH. The Hb-Hp-CD163 axis is the primary pathway for this process. Hp is an acute-phase $\alpha_2$-glycoprotein that binds free Hb with exceptionally high affinity to form Hb–Hp complexes. These complexes inhibit Hb-induced oxidative damage and facilitate Hb clearance via the CD163-mediated endocytic pathway [67,68]. Following ICH, oligodendrocytes can synthesize and secrete Hp to promote Hb clearance [69]. The neuroprotective effects of Hp in both *in vivo* and *in vitro* ICH models are highly complex. They appear to depend on factors such as age, disease stage, and the local microenvironment [69–71].

CD163 is a scavenger receptor highly expressed on microglia/macrophages. It mediates the endocytosis of Hb-Hp complexes and free Hb in Hp deficiency [56]. CD163-positive microglia/macrophages accumulate in perihematomal regions after ICH [65]. Studies indicate that upregulating CD163 expression in microglia/macrophages after ICH through activation of the PPAR-$\gamma$ pathway (via PPAR-$\gamma$ agonist monascin and chemokine fractalkine) or the Nrf2 pathway (via C-C motif chemokine ligand 17) promotes hematoma clearance [72–74]. However, Leclerc *et al.* [75] revealed a biphasic role of CD163 deficiency in ICH, with early protective effects shifting to later detrimental consequences.

Notably, neuronal CD163 expression is also upregulated following ICH or Hb stimulation [70,76]. However, neurons express very low levels of ferritin, which limits the degradation of heme products and ultimately leads to neuronal injury or death [70]. Selectively upregulating CD163

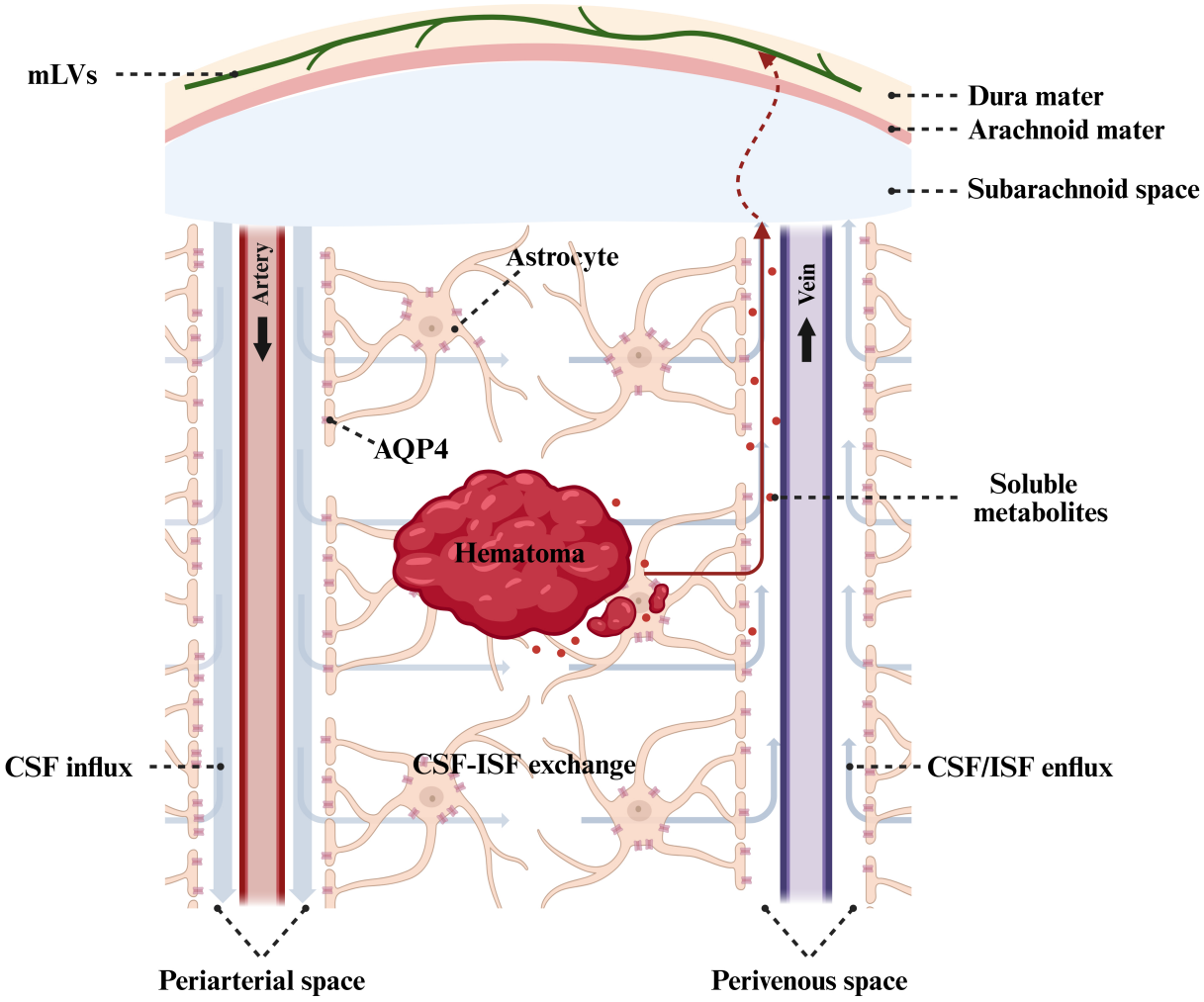


**Fig. 3. Endogenous hematoma clearance mediated by the glymphatic system and meningeal lymphatic vessels.** Cerebrospinal fluid (CSF) in the subarachnoid space flows into the periarterial spaces, enters the interstitial space via aquaporin-4 (AQP4) channels on astrocytic endfeet, mixes with interstitial fluid (ISF) containing soluble hematoma metabolites, subsequently refluxes along the perivenous spaces back to the subarachnoid space, and ultimately drains to the cervical lymph nodes via meningeal lymphatic vessels (mLVs), thereby promoting hematoma clearance. Created with BioRender.com.

expression in microglia/macrophages while suppressing its expression in neurons may be a potential therapeutic strategy to mitigate brain injury following ICH. 5$\alpha$-androst-3$\beta$,5$\alpha$,6$\beta$-triol (TRIOL), selectively increases CD163 expression in microglia/macrophages without affecting neuronal CD163 levels [77]. Moreover, deferoxamine attenuates ICH- and Hb-induced neuronal CD163 upregulation and associated neuronal damage both *in vitro* and *in vivo* [76].

### *3.3 Hemin Clearance*

Following ICH, the released Hb is subsequently degraded to hemin, which contributes to oxidative stress, inflammation, and neuronal injury [78]. In porcine autologous blood injection models, hemin levels in the hematoma and perihematomal tissue rise sharply within 24 hours, peak at day 3, and remain elevated through day 7, exceeding *in vitro* thresholds for neuronal death [79]. The Hb-Hx-CD91 axis is the primary pathway for hemin clearance.

Hx is a 60 kDa glycoprotein normally present at very low levels in the brain. After ICH, the level of Hx in the brain increases markedly due to the entry of peripheral Hx into the brain tissue through the hemorrhage or the disrupted blood-brain barrier, as well as increased local secretion of Hx [80]. Hx binds free heme with high affinity, and the resulting complex can be endocytosed via CD91/low-density lipoprotein receptor-related protein 1 [57]. Perihematomal microglia/macrophages upregulate both Hx and CD91 to facilitate hemin clearance [79,81]. Microglia/macrophage-specific CD91 knockout impairs hematoma resolution, exacerbates oxidative stress, and worsens neurological deficits following ICH [81].

Therapeutically, cerebral Hx overexpression via recombinant adeno-associated virus vectors reduces lesion volume and alleviates neurological deficits in ICH models. However, systemic administration of exogenous Hx fails to improve neurological function [80,82]. Administration of exogenous CD91 promotes hemin clearance, reduces oxidative stress and neuronal damage, and markedly decreases hematoma volume and neurological deficits, while these neuroprotective effects are partially reversed by CD91 siRNA. Additionally, rosuvastatin upregulates CD91 expression and diminishes neuropathological damage in ICH mice [83].

Hemin is degraded into $Fe^{2+}$ by HO in the cytosol [58]. Among the three isoforms (HO-1, HO-2, and HO-3), HO-1 and HO-2 play major roles in hemin degradation after ICH [77,84]. Increased expression of HO-1 in microglia/macrophages and HO-2 in neurons is observed in the perihematomal region [77,84]. The role of HO-1 appears to be phase-dependent. Pharmacologically induced HO-1 upregulation exacerbates brain injury in the early phase (day 1–3) of ICH but promotes hematoma resolution and neurological recovery in the late phase (day 28) [85,86]. The optimal timing and extent of HO-1 activation required for therapeutic benefit remain to be further elucidated. Astrocytic HO-1 overexpression reduces cell death, BBB disruption, and neurological deficits in ICH models [87,88]. The role of HO-2 remains controversial. *In vitro* studies by Rogers *et al*. [89] and Regan *et al*. [90] found that HO-2 knockout reduces neuronal sensitivity to Hb and hemin toxicity, whereas Wang *et al*. [91] reported opposite conclusions. *In vivo* studies of HO-2 knockout exhibited significant model-dependent variations [91–97].

## 4. Glymphatic and Meningeal Lymphatic Clearance

### *4.1 Glymphatic Clearance*

The glymphatic system is a perivascular network formed by astrocytic endfeet [98]. Cerebrospinal fluid (CSF) in the subarachnoid space flows along the periarterial spaces, then enters the brain parenchyma through aquaporin-4 (AQP4) channels on astrocytic endfeet. Here it exchanges with interstitial fluid, subsequently drains along perivenous spaces back to the subarachnoid space, and is ultimately transported to cervical lymph nodes (CLNs) via meningeal lymphatic vessels (mLVs), thereby achieving the clearance of metabolic waste from the parenchyma (Fig. 3) [99,100]. An experimental study indicates that the AQP4-dependent glymphatic pathway contributes to hematoma clearance. The AQP4 activator mifepristone enhances AQP4 expression and polarization after ICH, improves glymphatic function and lymphatic drainage, thereby accelerating hematoma clearance, reducing neuronal injury, and improving neurological outcomes. Conversely, AQP4 inhibition or knockout produced opposite effects [101]. Melatonin treatment similarly improved AQP4 polarization, glymphatic function, lymphatic drainage, and hematoma resolution, while its effects were blocked by the receptor antagonist luzindole [98]. Collectively, these findings highlight the therapeutic potential of targeting the AQP4-glymphatic pathway in ICH.

Various drugs and interventions, including the transient receptor potential vanilloid 4 inhibitor HC-067047, $\beta$-hydroxybutyrate, nimodipine, oxytocin, fingolimod, IL-33, the small molecule OAB-14, the matrix metalloproteinase-9 inhibitor GM6001, traditional Chinese medicines Xuefu Zhuyu Decoction and Yuanzhi Powder, RIC, very low-intensity ultrasound, and repetitive transcranial magnetic stimulation (rTMS) have been shown to improve glymphatic function in different disease models [102–114]. However, their efficacy in ICH models has not yet been verified and requires further investigation.

### *4.2 Meningeal Lymphatic Clearance*

Current studies indicate that erythrocytes and solutes in the brain parenchyma can be drained to CLNs via mLVs after ICH (Fig. 3) [115,116]. During the acute phase of ICH (within 3 days), mLV function is impaired, whereas during the recovery phase (days 10–14), lymphatic drainage and lymphangiogenesis are enhanced and can persist for months [115,117]. In ICH models, cilostazol, panax notoginseng saponins and simvastatin enhance meningeal lymphatic function, promotes erythrocyte drainage to CLNs, enhances hematoma clearance, reduces neuronal damage, and improves neurological function [115,118,119]. As these medications may increase the risk of bleeding, their use should be exercised with caution. Conversely, mLV ablation or functional inhibition impairs hematoma clearance [115]. Overall, enhancing meningeal lymphatic clearance represents a promising strategy for hematoma resolution and functional recovery after ICH.

Vascular endothelial growth factor-C, ketoprofen, 9-cis retinoic acid, Yoda1, down syndrome critical region 1, transcranial photobiomodulation, and rTMS have also been shown to promote meningeal lymphatic drainage [114,120–123]; however, their efficacy in ICH remains unverified, and further studies are needed to clarify clinical applicability.

## 5. Discussion

Although erythrophagocytosis, hemolytic product clearance, and lymphatic drainage have been described as distinct mechanisms, they operate in a tightly coordinated and temporally ordered manner during hematoma resolution. In the acute phase, microglial and macrophage erythrophagocytosis initiates the removal of intact erythrocytes, thereby limiting erythrolysis and the release of toxic hemolytic products. Subsequently, the Hb-Hp-CD163 and Hemin-Hx-CD91 pathways become predominant, facilitating detoxification and iron sequestration within phagocytes. As debris and soluble metabolites accumulate, the glym-

phatic and meningeal lymphatic systems gradually assume a dominant role, draining residual byproducts and inflammatory mediators from the parenchyma to peripheral lymph nodes. Spatially, these processes are interlinked, as phagocytes near the hematoma core mediate local degradation, while the glymphatic and meningeal lymphatic networks provide distal clearance routes.

Although numerous preclinical studies have demonstrated the efficacy of interventions that enhance hematoma clearance, translation to clinical application remains challenging. Interspecies differences in immune responses, erythrophagocytic capacity, and glymphatic-lymphatic anatomy limit the extrapolation of animal data to humans. Rodent models often exhibit faster hematoma resolution and milder inflammation than observed clinically, highlighting the need for large-animal or humanized models to validate therapeutic mechanisms [124].

Therapeutic timing is a critical factor. Interventions targeting HO-1 show phase-dependent effects, being detrimental in the early phase but neuroprotective in the late phase. Similarly, the functional capacity of meningeal lymphatic vessels (mLVs) changes over time after hemorrhage, affecting hematoma clearance efficiency. Understanding the temporal dynamics of both HO-1 regulation and mLV function is therefore essential for optimizing therapeutic strategies, as appropriately timed interventions may enhance hematoma resolution while minimizing adverse effects.

The safety of immune modulation therapies also warrants careful consideration. Enhancing microglial or macrophage phagocytosis can accelerate hematoma absorption, but excessive activation may induce secondary inflammation [125]. Likewise, approaches such as CD47 blockade, PPAR$\gamma$ agonists, or HO-1 inducers require precise dose titration to balance efficacy and safety, as off-target effects may further complicate therapeutic outcomes. Emerging nanotherapeutic platforms offer improved brain targeting and sustained drug release, although their biocompatibility, clearance, and long-term toxicity remain insufficiently characterized [126,127]. Therefore, comprehensive pharmacokinetic and biosafety evaluations are essential before clinical translation.

Finally, integrating these biological insights into the current clinical framework according to the AHA/ASA 2022 and ESO 2023 guidelines will be crucial to achieve therapeutic synergy. The clearance-promoting strategies discussed herein may complement guideline-based management to enhance neurological recovery after ICH.

## 6. Conclusions

Endogenous hematoma resolution after ICH involves coordinated processes of erythrophagocytosis, clearance of hemolytic products, and glymphatic-meningeal lymphatic drainage. Enhancing microglial/macrophage erythrophagocytosis through activation of TAM receptors, CD36, and TREM2 or inhibition of the SIRP$\alpha$-CD47 pathway plays a central role in promoting hematoma clearance and mitigating secondary brain injury. Inhibiting erythrocyte lysis while facilitating the clearance of hemolytic products via the Hb-Hp-CD163 and Hemin-Hx-CD91 pathways constitutes another critical mechanism. In parallel, enhancement of glymphatic and meningeal lymphatic drainage contributes to the efficient removal of erythrocytes and hemolytic products. Further research is needed to determine the optimal timing, efficacy, and safety of interventions targeting these pathways for potential clinical application.

## Author Contributions

SW and ML were responsible for literature search and manuscript drafting. RM and XJ contributed to the study conception and manuscript revision. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

## References


[1] Hao Y, Xia X, Zhu J, Yang W, Zhao X, Wang A. Temporal trends in the incidence of intracerebral hemorrhage from 1992 to 2021: An age-period-cohort analysis based on the global burden of disease study 2021. Ageing Research Reviews. 2025; 110: 102789. https://doi.org/10.1016/j.arr.2025.102789.

[2] Zheng J, Zou W, Yu X. Autophagy in Intracerebral Hemorrhage: From Mechanism to Regulation. Journal of Integrative Neuroscience. 2023; 22: 134. https://doi.org/10.31083/j.jin2205134.

[3] Irimia-Sieira P, Moya-Molina M, Martínez-Vila E. Clinical aspects and prognostic factors of intracerebral hemorrhage. Revista De Neurologia. 2000; 31: 192–198.

[4] Poon MTC, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. Journal of Neurology, Neurosurgery, and Psychiatry. 2014; 85: 660–667. https://doi.org/10.1136/jnnp-2013-306476.

[5] Goeldlin MB, Mueller A, Siepen BM, Mueller M, Strambo D, Michel P, *et al*. Etiology, 3-Month Functional Outcome and Recurrent Events in Non-Traumatic Intracerebral Hemorrhage. Journal of Stroke. 2022; 24: 266–277. https://doi.org/10.5853/jos.2021.01823.

[6] Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, *et al*. Hematoma growth is a determinant of mor-

tality and poor outcome after intracerebral hemorrhage. Neurology. 2006; 66: 1175–1181. https://doi.org/10.1212/01.wnl.0000208408.98482.99.

[7] Vasconcellos LRDC, Pimentel-Coelho PM. Heme as an inducer of cerebral damage in hemorrhagic stroke: potential therapeutic implications. Neural Regeneration Research. 2022; 17: 1961–1962. https://doi.org/10.4103/1673-5374.335148.

[8] Bulters D, Gaastra B, Zolnourian A, Alexander S, Ren D, Blackburn SL, *et al*. Haemoglobin scavenging in intracranial bleeding: biology and clinical implications. Nature Reviews. Neurology. 2018; 14: 416–432. https://doi.org/10.1038/s41582-018-0020-0.

[9] Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, *et al*. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2022; 53: e282–e361. https://doi.org/10.1161/STR.0000000000000407.

[10] Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, *et al*. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. International Journal of Stroke: Official Journal of the International Stroke Society. 2014; 9: 840–855. https://doi.org/10.1111/ijs.12309.

[11] Hanley DF, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, *et al*. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. Lancet (London, England). 2019; 393: 1021–1032. https://doi.org/10.1016/S0140-6736(19)30195-3.

[12] Pradilla G, Ratcliff JJ, Hall AJ, Saville BR, Allen JW, Paulon G, *et al*. Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage. The New England Journal of Medicine. 2024; 390: 1277–1289. https://doi.org/10.1056/NEJMoa2308440.

[13] Xu J, Chen Z, Yu F, Liu H, Ma C, Xie D, *et al*. IL-4/STAT6 signaling facilitates innate hematoma resolution and neurological recovery after hemorrhagic stroke in mice. Proceedings of the National Academy of Sciences of the United States of America. 2020; 117: 32679–32690. https://doi.org/10.1073/pnas.2018497117.

[14] Fang M, Xia F, Chen Y, Shen Y, Ma L, You C, *et al*. Role of Eryptosis in Hemorrhagic Stroke. Frontiers in Molecular Neuroscience. 2022; 15: 932931. https://doi.org/10.3389/fnmol.2022.932931.

[15] Lemke G. Phosphatidylserine Is the Signal for TAM Receptors and Their Ligands. Trends in Biochemical Sciences. 2017; 42: 738–748. https://doi.org/10.1016/j.tibs.2017.06.004.

[16] Tong LS, Shao AW, Ou YB, Guo ZN, Manaenko A, Dixon BJ, *et al*. Recombinant Gas6 augments Axl and facilitates immune restoration in an intracerebral hemorrhage mouse model. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2017; 37: 1971–1981. https://doi.org/10.1177/0271678X16658490.

[17] Ye XH, Xu ZM, Shen D, Jin YJ, Li JW, Xu XH, *et al*. Gas6/Axl signaling promotes hematoma resolution and motivates protective microglial responses after intracerebral hemorrhage in mice. Experimental Neurology. 2024; 382: 114964. https://doi.org/10.1016/j.expneurol.2024.114964.

[18] Chang CF, Goods BA, Askenase MH, Hammond MD, Renfroe SC, Steinschneider AF, *et al*. Erythrocyte efferocytosis modulates macrophages towards recovery after intracerebral hemorrhage. The Journal of Clinical Investigation. 2018; 128: 607–624. https://doi.org/10.1172/JCI95612.

[19] Orme JJ, Du Y, Vanarsa K, Mayeux J, Li L, Mutwally A, *et al*. Heightened cleavage of Axl receptor tyrosine kinase by ADAM metalloproteases may contribute to disease pathogenesis in SLE. Clinical Immunology (Orlando, Fla.). 2016; 169: 58–68. https://doi.org/10.1016/j.clim.2016.05.011.

[20] Sather S, Kenyon KD, Lefkowitz JB, Liang X, Varnum BC, Henson PM, *et al*. A soluble form of the Mer receptor tyrosine kinase inhibits macrophage clearance of apoptotic cells and platelet aggregation. Blood. 2007; 109: 1026–1033. https://doi.org/10.1182/blood-2006-05-021634.

[21] Fan L, Jin L, Tang T, Zheng Y, Chen Z, Lin H, *et al*. Neutrophil-like pH-responsive pro-efferocytic nanoparticles improve neurological recovery by promoting erythrophagocytosis after intracerebral hemorrhage. Theranostics. 2024; 14: 283–303. https://doi.org/10.7150/thno.90370.

[22] Fadok VA, Warner ML, Bratton DL, Henson PM. CD36 is required for phagocytosis of apoptotic cells by human macrophages that use either a phosphatidylserine receptor or the vitronectin receptor (alpha v beta 3). Journal of Immunology (Baltimore, Md.: 1950). 1998; 161: 6250–6257.

[23] Ren Y, Silverstein RL, Allen J, Savill J. CD36 gene transfer confers capacity for phagocytosis of cells undergoing apoptosis. The Journal of Experimental Medicine. 1995; 181: 1857–1862. https://doi.org/10.1084/jem.181.5.1857.

[24] Patel SN, Serghides L, Smith TG, Febbraio M, Silverstein RL, Kurtz TW, *et al*. CD36 mediates the phagocytosis of Plasmodium falciparum-infected erythrocytes by rodent macrophages. The Journal of Infectious Diseases. 2004; 189: 204–213. https://doi.org/10.1086/380764.

[25] Stolzing A, Grune T. Neuronal apoptotic bodies: phagocytosis and degradation by primary microglial cells. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2004; 18: 743–745. https://doi.org/10.1096/fj.03-0374fje.

[26] Greenberg ME, Sun M, Zhang R, Febbraio M, Silverstein R, Hazen SL. Oxidized phosphatidylserine-CD36 interactions play an essential role in macrophage-dependent phagocytosis of apoptotic cells. The Journal of Experimental Medicine. 2006; 203: 2613–2625. https://doi.org/10.1084/jem.20060370.

[27] Fang H, Chen J, Lin S, Wang P, Wang Y, Xiong X, *et al*. CD36-mediated hematoma absorption following intracerebral hemorrhage: negative regulation by TLR4 signaling. Journal of Immunology (Baltimore, Md.: 1950). 2014; 192: 5984–5992. https://doi.org/10.4049/jimmunol.1400054.

[28] Olagnier D, Lavergne RA, Meunier E, Lefèvre L, Dardenne C, Aubouy A, *et al*. Nrf2, a PPARγ alternative pathway to promote CD36 expression on inflammatory macrophages: implication for malaria. PLoS Pathogens. 2011; 7: e1002254. https://doi.org/10.1371/journal.ppat.1002254.

[29] Luo Z, Sheng Z, Hu L, Shi L, Tian Y, Zhao X, *et al*. Targeted macrophage phagocytosis by Irg1/itaconate axis improves the prognosis of intracerebral hemorrhagic stroke and peritonitis. EBioMedicine. 2024; 101: 104993. https://doi.org/10.1016/j.ebiom.2024.104993.

[30] Wang Y, Chen Q, Tan Q, Feng Z, He Z, Tang J, *et al*. Simvastatin accelerates hematoma resolution after intracerebral hemorrhage in a PPARγ-dependent manner. Neuropharmacology. 2018; 128: 244–254. https://doi.org/10.1016/j.neuropharm.2017.10.021.

[31] Zhuang J, Peng Y, Gu C, Chen H, Lin Z, Zhou H, *et al*. Wogonin Accelerates Hematoma Clearance and Improves Neurological Outcome via the PPAR-γ Pathway After Intracerebral Hemorrhage. Translational Stroke Research. 2021; 12: 660–675. https://doi.org/10.1007/s12975-020-00842-9.

[32] Chawla A, Barak Y, Nagy L, Liao D, Tontonoz P, Evans RM. PPAR-gamma dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. Nature Medicine. 2001; 7: 48–52. https://doi.org/10.1038/83336.

[33] Gonzales NR, Shah J, Sangha N, Sosa L, Martinez R, Shen L, *et al*. Design of a prospective, dose-escalation study evaluating the Safety of Pioglitazone for Hematoma Resolution in Intracerebral Hemorrhage (SHRINC). International Journal of Stroke: Official Journal of the International Stroke Society. 2013; 8: 388–396. https://doi.org/10.1111/j.1747-4949.2011.00761.x.

[34] Kinoshita K, Ushida K, Hirata Y, Tsujita S, Hitora-Imamura N, Kurauchi Y, *et al*. Inhibition of SUMOylation exacerbates neurological dysfunction and delays hematoma clearance after intracerebral hemorrhage in mice. Neuroscience. 2025; 568: 433–443. https://doi.org/10.1016/j.neuroscience.2025.01.062.

[35] Zhou H, Li J, Hu L, Yu J, Fu X, Liang F, *et al*. Soluble Trem2 is a negative regulator of erythrophagocytosis after intracerebral hemorrhage in a CD36 receptor recycling manner. Journal of Advanced Research. 2023; 44: 185–199. https://doi.org/10.1016/j.jare.2022.03.011.

[36] Yang Y, Wang P, Liu A, Wu X, Yan Z, Dai S, *et al*. Pulsed Electromagnetic Field Protects Against Brain Injury After Intracerebral Hemorrhage: Involvement of Anti-Inflammatory Processes and Hematoma Clearance via CD36. Journal of Molecular Neuroscience: MN. 2022; 72: 2150–2161. https://doi.org/10.1007/s12031-022-02063-1.

[37] Vaibhav K, Braun M, Khan MB, Fatima S, Saad N, Shankar A, *et al*. Remote ischemic post-conditioning promotes hematoma resolution via AMPK-dependent immune regulation. The Journal of Experimental Medicine. 2018; 215: 2636–2654. https://doi.org/10.1084/jem.20171905.

[38] Yi F, Wu H, Zhao HK. Role of triggering receptor expressed on myeloid cells 1/2 in secondary injury after cerebral hemorrhage. World Journal of Clinical Cases. 2025; 13: 100312. https://doi.org/10.12998/wjcc.v13.i9.100312.

[39] Hsieh CL, Koike M, Spusta SC, Niemi EC, Yenari M, Nakamura MC, *et al*. A role for TREM2 ligands in the phagocytosis of apoptotic neuronal cells by microglia. Journal of Neurochemistry. 2009; 109: 1144–1156. https://doi.org/10.1111/j.1471-4159.2009.06042.x.

[40] Kawabori M, Kacimi R, Kauppinen T, Calosing C, Kim JY, Hsieh CL, *et al*. Triggering receptor expressed on myeloid cells 2 (TREM2) deficiency attenuates phagocytic activities of microglia and exacerbates ischemic damage in experimental stroke. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2015; 35: 3384–3396. https://doi.org/10.1523/JNEUROSCI.2620-14.2015.

[41] Pocock J, Vasilopoulou F, Svensson E, Cosker K. Microglia and TREM2. Neuropharmacology. 2024; 257: 110020. https://doi.org/10.1016/j.neuropharm.2024.110020.

[42] Wang S, Mustafa M, Yuede CM, Salazar SV, Kong P, Long H, *et al*. Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. The Journal of Experimental Medicine. 2020; 217: e20200785. https://doi.org/10.1084/jem.20200785.

[43] Olsson M, Nilsson A, Oldenborg PA. Target cell CD47 regulates macrophage activation and erythrophagocytosis. Transfusion Clinique et Biologique: Journal De La Societe Francaise De Transfusion Sanguine. 2006; 13: 39–43. https://doi.org/10.1016/j.tracli.2006.02.013.

[44] Zhou X, Xie Q, Xi G, Keep RF, Hua Y. Brain CD47 expression in a swine model of intracerebral hemorrhage. Brain Research. 2014; 1574: 70–76. https://doi.org/10.1016/j.brainres.2014.06.003.

[45] Oldenborg PA, Zheleznyak A, Fang YF, Lagenaur CF, Gresham HD, Lindberg FP. Role of CD47 as a marker of self on red blood cells. Science (New York, N.Y.). 2000; 288: 2051–2054. https://doi.org/10.1126/science.288.5473.2051.

[46] Ni W, Mao S, Xi G, Keep RF, Hua Y. Role of Erythrocyte CD47 in Intracerebral Hematoma Clearance. Stroke. 2016; 47: 505–511. https://doi.org/10.1161/STROKEAHA.115.010920.

[47] 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: 1539–1547. https://doi.org/10.1161/STROKEAHA.118.024578.

[48] Tao C, Keep RF, Xi G, Hua Y. CD47 Blocking Antibody Accelerates Hematoma Clearance After Intracerebral Hemorrhage in Aged Rats. Translational Stroke Research. 2020; 11: 541–551. https://doi.org/10.1007/s12975-019-00745-4.

[49] Song Y, Wang H, Li F, Huang Q, Zhang Z. Anti-CD47 antibody administration via cisterna magna in proper dosage can reduce perihematomal cell death following intracerebral hemorrhage in rats. Brain Research Bulletin. 2021; 174: 359–365. https://doi.org/10.1016/j.brainresbull.2021.07.003.

[50] Wang P, Yang X, Yang F, Cardiff K, Houchins M, Carballo N, *et al*. Intravenous Administration of Anti-CD47 Antibody Augments Hematoma Clearance, Mitigates Acute Neuropathology, and Improves Cognitive Function in a Rat Model of Penetrating Traumatic Brain Injury. Journal of Neurotrauma. 2024; 41: 2413–2427. https://doi.org/10.1089/neu.2024.0047.

[51] Hua Y, Keep RF, Xi G. Response by Hua et al to Letter Regarding Article, "Enhancement of Hematoma Clearance With CD47 Blocking Antibody in Experimental Intracerebral Hemorrhage". Stroke. 2019; 50: e266. https://doi.org/10.1161/STROKEAHA.119.026620.

[52] Yu W, Che C, Yang Y, Zhao Y, Liu J, Chen A, *et al*. Bioactive Self-Assembled Nanoregulator Enhances Hematoma Resolution and Inhibits Neuroinflammation in the Treatment of Intracerebral Hemorrhage. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2025; 12: e2408647. https://doi.org/10.1002/advs.202408647.

[53] Sallman DA, Al Malki MM, Asch AS, Wang ES, Jurcic JG, Bradley TJ, *et al*. Magrolimab in Combination With Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes: Final Results of a Phase Ib Study. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2023; 41: 2815–2826. https://doi.org/10.1200/JCO.22.01794.

[54] Zeidner JF, Sallman DA, Récher C, Daver NG, Leung AYH, Hiwase DK, *et al*. Magrolimab plus azacitidine vs physician's choice for untreated TP53-mutated acute myeloid leukemia: the ENHANCE-2 study. Blood. 2025; 146: 590–600. https://doi.org/10.1182/blood.2024027408.

[55] Dang G, Yang Y, Wu G, Hua Y, Keep RF, Xi G. Early Erythrolysis in the Hematoma After Experimental Intracerebral Hemorrhage. Translational Stroke Research. 2017; 8: 174–182. https://doi.org/10.1007/s12975-016-0505-3.

[56] Etzerodt A, Kjolby M, Nielsen MJ, Maniecki M, Svendsen P, Moestrup SK. Plasma clearance of hemoglobin and haptoglobin in mice and effect of CD163 gene targeting disruption. Antioxidants & Redox Signaling. 2013; 18: 2254–2263. https://doi.org/10.1089/ars.2012.4605.

[57] Hvidberg V, Maniecki MB, Jacobsen C, Højrup P, Møller HJ, Moestrup SK. Identification of the receptor scavenging hemopexin-heme complexes. Blood. 2005; 106: 2572–2579. https://doi.org/10.1182/blood-2005-03-1185.

[58] de Oliveira J, Denadai MB, Costa DL. Crosstalk between Heme Oxygenase-1 and Iron Metabolism in Macrophages: Implications for the Modulation of Inflammation and Immunity. Antioxidants (Basel, Switzerland). 2022; 11: 861. https://doi.org/10.3390/antiox11050861.

[59] Li Y, Tao C, An N, Liu H, Liu Z, Zhang H, *et al*. Revisiting the role of the complement system in intracerebral hemorrhage and therapeutic prospects. International Immunopharmacology. 2023; 123: 110744. https://doi.org/10.1016/j.intimp.2023.110744.

[60] Zheng Y, Fan L, Xia S, Yang Q, Zhang Z, Chen H, *et al*. Role

of complement C1q/C3-CR3 signaling in brain injury after experimental intracerebral hemorrhage and the effect of minocycline treatment. Frontiers in Immunology. 2022; 13: 919444. https://doi.org/10.3389/fimmu.2022.919444.

[61] Wu M, Chen K, Zhao Y, Jiang M, Bao B, Yu W, *et al*. Normobaric hyperoxia alleviates complement C3-mediated synaptic pruning and brain injury after intracerebral hemorrhage. CNS Neuroscience & Therapeutics. 2024; 30: e14694. https://doi.org/10.1111/cns.14694.

[62] 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: 2649–2660. https://doi.org/10.1161/STROKEAHA.121.034372.

[63] Alshareef M, Hatchell D, Vasas T, Mallah K, Shingala A, Cutrone J, *et al*. Complement Drives Chronic Inflammation and Progressive Hydrocephalus in Murine Neonatal Germinal Matrix Hemorrhage. International Journal of Molecular Sciences. 2023; 24: 10171. https://doi.org/10.3390/ijms241210171.

[64] Wang M, Hua Y, Keep RF, Wan S, Novakovic N, Xi G. Complement Inhibition Attenuates Early Erythrolysis in the Hematoma and Brain Injury in Aged Rats. Stroke. 2019; 50: 1859–1868. https://doi.org/10.1161/STROKEAHA.119.025170.

[65] Cao S, Zheng M, Hua Y, Chen G, Keep RF, Xi G. Hematoma Changes During Clot Resolution After Experimental Intracerebral Hemorrhage. Stroke. 2016; 47: 1626–1631. https://doi.org/10.1161/STROKEAHA.116.013146.

[66] Zheng Y, Li Y, He X, Zhu Y, Xu S, Feng Y, *et al*. Gut microbiota depletion accelerates hematoma resolution and neurological recovery after intracerebral hemorrhage via p-coumaric acid-promoted Treg differentiation. Theranostics. 2025; 15: 6628–6650. https://doi.org/10.7150/thno.113764.

[67] Cooper CE, Schaer DJ, Buehler PW, Wilson MT, Reeder BJ, Silkstone G, *et al*. Haptoglobin binding stabilizes hemoglobin ferryl iron and the globin radical on tyrosine $\beta$145. Antioxidants & Redox Signaling. 2013; 18: 2264–2273. https://doi.org/10.1089/ars.2012.4547.

[68] Kristiansen M, Graversen JH, Jacobsen C, Sonne O, Hoffman HJ, Law SK, *et al*. Identification of the haemoglobin scavenger receptor. Nature. 2001; 409: 198–201. https://doi.org/10.1038/35051594.

[69] Zhao X, Song S, Sun G, Strong R, Zhang J, Grotta JC, *et al*. Neuroprotective role of haptoglobin after intracerebral hemorrhage. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2009; 29: 15819–15827. https://doi.org/10.1523/JNEUROSCI.3776-09.2009.

[70] Chen-Roetling J, Regan RF. Haptoglobin increases the vulnerability of CD163-expressing neurons to hemoglobin. Journal of Neurochemistry. 2016; 139: 586–595. https://doi.org/10.1111/jnc.13720.

[71] Leclerc JL, Li C, Jean S, Lampert AS, Amador CL, Diller MA, *et al*. Temporal and age-dependent effects of haptoglobin deletion on intracerebral hemorrhage-induced brain damage and neurobehavioral outcomes. Experimental Neurology. 2019; 317: 22–33. https://doi.org/10.1016/j.expneurol.2019.01.011.

[72] Wang G, Li T, Duan SN, Dong L, Sun XG, Xue F. PPAR-$\gamma$ Promotes Hematoma Clearance through Haptoglobin-Hemoglobin-CD163 in a Rat Model of Intracerebral Hemorrhage. Behavioural Neurology. 2018; 2018: 7646104. https://doi.org/10.1155/2018/7646104.

[73] You M, Long C, Wan Y, Guo H, Shen J, Li M, *et al*. Neuron derived fractalkine promotes microglia to absorb hematoma via CD163/HO-1 after intracerebral hemorrhage. Cellular and Molecular Life Sciences: CMLS. 2022; 79: 224. https://doi.org/10.1007/s00018-022-04212-6.

[74] Deng S, Sherchan P, Jin P, Huang L, Travis Z, Zhang JH, *et al*. Recombinant CCL17 Enhances Hematoma Resolution and Activation of CCR4/ERK/Nrf2/CD163 Signaling Pathway After Intracerebral Hemorrhage in Mice. Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics. 2020; 17: 1940–1953. https://doi.org/10.1007/s13311-020-00908-4.

[75] Leclerc JL, Lampert AS, Loyola Amador C, Schlakman B, Vasilopoulos T, Svendsen P, *et al*. The absence of the CD163 receptor has distinct temporal influences on intracerebral hemorrhage outcomes. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2018; 38: 262–273. https://doi.org/10.1177/0271678X17701459.

[76] Liu R, Cao S, Hua Y, Keep RF, Huang Y, Xi G. CD163 Expression in Neurons After Experimental Intracerebral Hemorrhage. Stroke. 2017; 48: 1369–1375. https://doi.org/10.1161/STROKEAHA.117.016850.

[77] Wei C, Chen C, Li S, Ding Y, Zhou Y, Mai F, *et al*. TRIOL attenuates intracerebral hemorrhage injury by bidirectionally modulating microglia- and neuron-mediated hematoma clearance. Redox Biology. 2025; 80: 103487. https://doi.org/10.1016/j.redox.2024.103487.

[78] Vasconcellos LRC, Martimiano L, Dantas DP, Fonseca FM, Mata-Santos H, Travassos L, *et al*. Intracerebral Injection of Heme Induces Lipid Peroxidation, Neuroinflammation, and Sensorimotor Deficits. Stroke. 2021; 52: 1788–1797. https://doi.org/10.1161/STROKEAHA.120.031911.

[79] Hu S, Hua Y, Keep RF, Feng H, Xi G. Deferoxamine therapy reduces brain hemin accumulation after intracerebral hemorrhage in piglets. Experimental Neurology. 2019; 318: 244–250. https://doi.org/10.1016/j.expneurol.2019.05.003.

[80] Leclerc JL, Santiago-Moreno J, Dang A, Lampert AS, Cruz PE, Rosario AM, *et al*. Increased brain hemopexin levels improve outcomes after intracerebral hemorrhage. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2018; 38: 1032–1046. https://doi.org/10.1177/0271678X16679170.

[81] Zhao X, Ting SM, Sun G, Bautista Garrido J, Obertas L, Aronowski J. Clearance of Neutrophils From ICH-Affected Brain by Macrophages Is Beneficial and Is Assisted by Lactoferrin and CD91. Stroke. 2024; 55: 166–176. https://doi.org/10.1161/STROKEAHA.123.045194.

[82] Chen-Roetling J, Li Y, Cao Y, Yan Z, Lu X, Regan RF. Effect of hemopexin treatment on outcome after intracerebral hemorrhage in mice. Brain Research. 2021; 1765: 147507. https://doi.org/10.1016/j.brainres.2021.147507.

[83] Guo T, Wang Y, Hayat MA, Si Y, Ni Y, Zhang J, *et al*. Recombinant human heavy-chain ferritin nanoparticles loaded with rosuvastatin attenuates secondary brain injury in intracerebral hemorrhage. International Journal of Biological Macromolecules. 2025; 302: 140542. https://doi.org/10.1016/j.ijbiomac.2025.140542.

[84] Wang J, Doré S. Heme oxygenase-1 exacerbates early brain injury after intracerebral haemorrhage. Brain: a Journal of Neurology. 2007; 130: 1643–1652. https://doi.org/10.1093/brain/awm095.

[85] Liu Q, Han Z, Li T, Meng J, Zhu C, Wang J, *et al*. Microglial HO-1 aggravates neuronal ferroptosis via regulating iron metabolism and inflammation in the early stage after intracerebral hemorrhage. International Immunopharmacology. 2025; 147: 113942. https://doi.org/10.1016/j.intimp.2024.113942.

[86] Zhang Z, Song Y, Zhang Z, Li D, Zhu H, Liang R, *et al*. Distinct role of heme oxygenase-1 in early- and late-stage intracerebral hemorrhage in 12-month-old mice. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2017; 37: 25–38.

https://doi.org/10.1177/0271678X16655814.
[87] Chen-Roetling J, Kamalapathy P, Cao Y, Song W, Schipper HM, Regan RF. Astrocyte heme oxygenase-1 reduces mortality and improves outcome after collagenase-induced intracerebral hemorrhage. Neurobiology of Disease. 2017; 102: 140–146. https://doi.org/10.1016/j.nbd.2017.03.008.
[88] Li X, Li C, Hou L, He M, Song G, Ren S, *et al*. Higher Level of Serum Heme Oxygenase-1 in Patients With Intracerebral Hemorrhage. International Surgery. 2015; 100: 1220–1224. https://doi.org/10.9738/INTSURG-D-14-00086.1.
[89] Rogers B, Yakopson V, Teng ZP, Guo Y, Regan RF. Heme oxygenase-2 knockout neurons are less vulnerable to hemoglobin toxicity. Free Radical Biology & Medicine. 2003; 35: 872–881. https://doi.org/10.1016/s0891-5849(03)00431-3.
[90] Regan RF, Chen J, Benvenisti-Zarom L. Heme oxygenase-2 gene deletion attenuates oxidative stress in neurons exposed to extracellular hemin. BMC Neuroscience. 2004; 5: 34. https://doi.org/10.1186/1471-2202-5-34.
[91] Wang J, Zhuang H, Doré S. Heme oxygenase 2 is neuroprotective against intracerebral hemorrhage. Neurobiology of Disease. 2006; 22: 473–476. https://doi.org/10.1016/j.nbd.2005.12.009.
[92] Qu Y, Chen-Roetling J, Benvenisti-Zarom L, Regan RF. Attenuation of oxidative injury after induction of experimental intracerebral hemorrhage in heme oxygenase-2 knockout mice. Journal of Neurosurgery. 2007; 106: 428–435. https://doi.org/10.3171/jns.2007.106.3.428.
[93] Chen-Roetling J, Cai Y, Regan RF. Neuroprotective effect of heme oxygenase-2 knockout in the blood injection model of intracerebral hemorrhage. BMC Research Notes. 2014; 7: 561. https://doi.org/10.1186/1756-0500-7-561.
[94] Qu Y, Chen J, Benvenisti-Zarom L, Ma X, Regan RF. Effect of targeted deletion of the heme oxygenase-2 gene on hemoglobin toxicity in the striatum. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2005; 25: 1466–1475. https://doi.org/10.1038/sj.jcbfm.9600143.
[95] Wang J, Doré S. Heme oxygenase 2 deficiency increases brain swelling and inflammation after intracerebral hemorrhage. Neuroscience. 2008; 155: 1133–1141. https://doi.org/10.1016/j.neuroscience.2008.07.004.
[96] Zhang Z, Pang Y, Wang W, Zhu H, Jin S, Yu Z, *et al*. Neuroprotection of Heme Oxygenase-2 in Mice AfterIntracerebral Hemorrhage. Journal of Neuropathology and Experimental Neurology. 2021; 80: 457–466. https://doi.org/10.1093/jnen/nlab025.
[97] Chen-Roetling J, Lu X, Regan KA, Regan RF. A rapid fluorescent method to quantify neuronal loss after experimental intracerebral hemorrhage. Journal of Neuroscience Methods. 2013; 216: 128–136. https://doi.org/10.1016/j.jneumeth.2013.03.025.
[98] Chen Y, Guo H, Sun X, Wang S, Zhao M, Gong J, *et al*. Melatonin Regulates Glymphatic Function to Affect Cognitive Deficits, Behavioral Issues, and Blood-Brain Barrier Damage in Mice After Intracerebral Hemorrhage: Potential Links to Circadian Rhythms. CNS Neuroscience & Therapeutics. 2025; 31: e70289. https://doi.org/10.1111/cns.70289.
[99] Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, *et al*. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid $\beta$. Science Translational Medicine. 2012; 4: 147ra111. https://doi.org/10.1126/scitranslmed.3003748.
[100] Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, *et al*. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. The Journal of Experimental Medicine. 2015; 212: 991–999. https://doi.org/10.1084/jem.20142290.
[101] Chen W, Liang C, Peng S, Bao S, Xue F, Lian X, *et al*. Aquaporin-4 activation facilitates glymphatic system function and hematoma clearance post-intracerebral hemorrhage. Glia. 2025; 73: 368–380. https://doi.org/10.1002/glia.24639.
[102] Li Y, Zhou H, Xie J, Yu M, Ye G, Zhang Y, *et al*. Targeting TRPV4 to restore glymphatic system function and alleviate cerebral edema in ischemic stroke. Brain Pathology (Zurich, Switzerland). 2025; 35: e70022. https://doi.org/10.1111/bpa.70022.
[103] Yi T, Gao P, Hou M, Lv H, Huang M, Gao S, *et al*. The mechanisms underlying the actions of Xuefu Zhuyu decoction pretreatment against neurological deficits after ischemic stroke in mice: The mediation of glymphatic function by aquaporin-4 and its anchoring proteins. Frontiers in Pharmacology. 2022; 13: 1053253. https://doi.org/10.3389/fphar.2022.1053253.
[104] Tan X, Li X, Li R, Meng W, Xie Z, Li J, *et al*. $\beta$-hydroxybutyrate alleviates neurological deficits by restoring glymphatic and inflammation after subarachnoid hemorrhage in mice. Experimental Neurology. 2024; 378: 114819. https://doi.org/10.1016/j.expneurol.2024.114819.
[105] Hou C, Liu Q, Zhang H, Wang W, Wang B, Cui X, *et al*. Nimodipine Attenuates Early Brain Injury by Protecting the Glymphatic System After Subarachnoid Hemorrhage in Mice. Neurochemical Research. 2022; 47: 701–712. https://doi.org/10.1007/s11064-021-03478-9.
[106] Liu M, Huang J, Liu T, Yuan J, Lv C, Sha Z, *et al*. Exogenous interleukin 33 enhances the brain's lymphatic drainage and toxic protein clearance in acute traumatic brain injury mice. Acta Neuropathologica Communications. 2023; 11: 61. https://doi.org/10.1186/s40478-023-01555-4.
[107] Feng D, Liu T, Zhang X, Xiang T, Su W, Quan W, *et al*. Fingolimod improves diffuse brain injury by promoting AQP4 polarization and functional recovery of the glymphatic system. CNS Neuroscience & Therapeutics. 2024; 30: e14669. https://doi.org/10.1111/cns.14669.
[108] Zhang X, Cao R, Zhu C, Yang L, Zheng N, Ji W, *et al*. Mechanism of anti-AD action of OAB-14 by enhancing the function of glymphatic system. Neurochemistry International. 2023; 105633. https://doi.org/10.1016/j.neuint.2023.105633.
[109] Ye C, Wang S, Niu L, Yang F, Wang G, Wang S, *et al*. Unlocking potential of oxytocin: improving intracranial lymphatic drainage for Alzheimer's disease treatment. Theranostics. 2024; 14: 4331–4351. https://doi.org/10.7150/thno.98587.
[110] Li J, Hao Y, Wang S, Li W, Yue S, Duan X, *et al*. Yuanzhi powder facilitated A$\beta$ clearance in APP/PS1 mice: Target to the drainage of glymphatic system and meningeal lymphatic vessels. Journal of Ethnopharmacology. 2024; 319: 117195. https://doi.org/10.1016/j.jep.2023.117195.
[111] Si X, Dai S, Fang Y, Tang J, Wang Z, Li Y, *et al*. Matrix metalloproteinase-9 inhibition prevents aquaporin-4 depolarization-mediated glymphatic dysfunction in Parkinson's disease. Journal of Advanced Research. 2024; 56: 125–136. https://doi.org/10.1016/j.jare.2023.03.004.
[112] Li X, Tan X, Zhou Q, Xie Z, Meng W, Pang Y, *et al*. Limb Remote Ischemic Postconditioning Improves Glymphatic Dysfunction After Cerebral Ischemia-Reperfusion Injury. Neuroscience. 2023; 521: 20–30. https://doi.org/10.1016/j.neuroscience.2023.04.017.
[113] Wu CH, Liao WH, Chu YC, Hsiao MY, Kung Y, Wang JL, *et al*. Very Low-Intensity Ultrasound Facilitates Glymphatic Influx and Clearance via Modulation of the TRPV4-AQP4 Pathway. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2024; 11: e2401039. https://doi.org/10.1002/advs.202401039.
[114] Lin Y, Jin J, Lv R, Luo Y, Dai W, Li W, et al. Repetitive transcranial magnetic stimulation increases the brain's drainage efficiency in a mouse model of Alzheimer's disease. Acta Neuropathol Commun. 2021; 9: 102. https://doi.org/10.1186/s40478-021-01198-3.

[115] Tsai HH, Hsieh YC, Lin JS, Kuo ZT, Ho CY, Chen CH, *et al*. Functional Investigation of Meningeal Lymphatic System in Experimental Intracerebral Hemorrhage. Stroke. 2022; 53: 987–998. https://doi.org/10.1161/STROKEAHA.121.037834.

[116] Virenque A, Balin R, Noe FM. Dorsal skull meningeal lymphatic vessels drain blood-solutes after intracerebral hemorrhage. bioRxiv. 2021. https://doi.org/10.1101/2021.03.09.434530. (preprint)

[117] Liu Y, Liu X, Sun P, Li J, Nie M, Gong J, *et al*. rTMS treatment for abrogating intracerebral hemorrhage-induced brain parenchymal metabolite clearance dysfunction in male mice by regulating intracranial lymphatic drainage. Brain and Behavior. 2023; 13: e3062. https://doi.org/10.1002/brb3.3062.

[118] Yu Z, Yang XY, Cai YQ, Hu E, Li T, Zhu WX, *et al*. Panax Notoginseng Saponins promotes the meningeal lymphatic system-mediated hematoma absorption in intracerebral hemorrhage. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2024; 135: 156149. https://doi.org/10.1016/j.phymed.2024.156149.

[119] Liao J, Duan Y, Liu Y, Chen H, An Z, Chen Y, *et al*. Simvastatin alleviates glymphatic system damage via the VEGF-C/VEGFR3/PI3K-Akt pathway after experimental intracerebral hemorrhage. Brain Research Bulletin. 2024; 216: 111045. https://doi.org/10.1016/j.brainresbull.2024.111045.

[120] Liao J, Zhang M, Shi Z, Lu H, Wang L, Fan W, *et al*. Improving the Function of Meningeal Lymphatic Vessels to Promote Brain Edema Absorption after Traumatic Brain Injury. Journal of Neurotrauma. 2023; 40: 383–394. https://doi.org/10.1089/neu.2022.0150.

[121] Matrongolo MJ, Ang PS, Wu J, Jain A, Thackray JK, Reddy A, *et al*. Piezo1 agonist restores meningeal lymphatic vessels, drainage, and brain-CSF perfusion in craniosynostosis and aged mice. The Journal of Clinical Investigation. 2023; 134: e171468. https://doi.org/10.1172/JCI171468.

[122] Choi C, Park J, Kim H, Chang KT, Park J, Min KT. DSCR1 upregulation enhances dural meningeal lymphatic drainage to attenuate amyloid pathology of Alzheimer's disease. The Journal of Pathology. 2021; 255: 296–310. https://doi.org/10.1002/path.5767.

[123] Semyachkina-Glushkovskaya O, Abdurashitov A, Dubrovsky A, Klimova M, Agranovich I, Terskov A, *et al*. Photobiomodulation of lymphatic drainage and clearance: perspective strategy for augmentation of meningeal lymphatic functions. Biomedical Optics Express. 2020; 11: 725–734. https://doi.org/10.1364/BOE.383390.

[124] Bai Q, Sheng Z, Liu Y, Zhang R, Yong VW, Xue M. Intracerebral haemorrhage: from clinical settings to animal models. Stroke and Vascular Neurology. 2020; 5: 388–395. https://doi.org/10.1136/svn-2020-000334.

[125] Tseng KY, Stratoulias V, Hu WF, Wu JS, Wang V, Chen YH, *et al*. Augmenting hematoma-scavenging capacity of innate immune cells by CDNF reduces brain injury and promotes functional recovery after intracerebral hemorrhage. Cell Death & Disease. 2023; 14: 128. https://doi.org/10.1038/s41419-022-05520-2.

[126] You ZQ, Wu Q, Zhou XM, Zhang XS, Yuan B, Wen LL, *et al*. Receptor-Mediated Delivery of Astaxanthin-Loaded Nanoparticles to Neurons: An Enhanced Potential for Subarachnoid Hemorrhage Treatment. Frontiers in Neuroscience. 2019; 13: 989. https://doi.org/10.3389/fnins.2019.00989.

[127] Li M, Liu G, Wang K, Wang L, Fu X, Lim LY, *et al*. Metal ion-responsive nanocarrier derived from phosphonated calix[4]arenes for delivering dauricine specifically to sites of brain injury in a mouse model of intracerebral hemorrhage. Journal of Nanobiotechnology. 2020; 18: 61. https://doi.org/10.1186/s12951-020-00616-3.