Review article

Mechanisms and therapeutic targets of mitophagy after intracerebral hemorrhage

Qinghua Huang [a,b,1], Xiaoqin Yu [a,1], Peijie Fu [a,b], Moxin Wu [b,d], Xiaoping Yin [a,b], Zhiying Chen [a,b,*], Manqing Zhang [c,**]

[a] Department of Neurology, Affiliated Hospital of Jiujiang University, Jiujiang, Jiangxi 332000, China
[b] Jiujiang Clinical Precision Medicine Research Center, Jiujiang, Jiangxi, 332000, China
[c] School of Basic Medicine, Jiujiang University, Jiujiang, Jiangxi, 332000, China
[d] Department of Medical Laboratory, Affiliated Hospital of Jiujiang University, Jiujiang, Jiangxi, 332000, China

ARTICLE INFO

ABSTRACT

Mitochondria are dynamic organelles responsible for cellular energy production. In addition to regulating energy homeostasis, mitochondria are responsible for calcium homeostasis, clearance of damaged organelles, signaling, and cell survival in the context of injury and pathology. In stroke, the mechanisms underlying brain injury secondary to intracerebral hemorrhage are complex and involve cellular hypoxia, oxidative stress, inflammatory responses, and apoptosis. Recent studies have shown that mitochondrial damage and autophagy are essential for neuronal metabolism and functional recovery after intracerebral hemorrhage, and are closely related to inflammatory responses, oxidative stress, apoptosis, and other pathological processes. Because hypoxia and inflammatory responses can cause secondary damage after intracerebral hemorrhage, the restoration of mitochondrial function and timely clearance of damaged mitochondria have neuroprotective effects. Based on studies on mitochondrial autophagy (mitophagy), cellular inflammation, apoptosis, ferroptosis, the BNIP3 autophagy gene, pharmacological and other regulatory approaches, and normobaric oxygen (NBO) therapy, this article further explores the neuroprotective role of mitophagy after intracerebral hemorrhage.

1. Introduction

Intracerebral hemorrhage (ICH) is a common stroke disorder that accounts for approximately 15 % of strokes and 50 % of stroke-related mortalities, with an estimated 2.8 million deaths worldwide each year [1]. It involves vascular malformations (e.g., arteriovenous and venomal malformations and dural arteriovenous fistulas) and mass lesions (e.g., metastatic tumors) that can cause blood vessel rupture and ICH [2]. Secondary brain injury after ICH is caused by physiological and pathological hematomas and substances that can result in brain edema, blood-brain barrier injury, inflammatory response, membrane attack complex formation, oxidative stress reactions, mitochondrial dysfunction, apoptosis, and activation of cytotoxicity [3,4]. During the removal of damaged organelles and toxic substances, mitophagy can be used as an efficient mechanism to restore the function of damaged nerve cells and brain tissue

homeostasis by timely self-phagocytosis to remove damaged organelles and toxic substances, and has become a new research hotspot [5]. However, research and exploration of mitophagy after intracerebral hemorrhage is in its infancy. The protective or damaging role of mitophagy remains controversial, and the role of related gene proteins remains to be further studied. In this study, we investigated the effects of mitophagy after ICH.

2. Secondary brain injury after ICH

Hematoma and edema caused by blood vessel rupture after ICH leads to secondary brain injury, leading to severe neurological deficits, activation of pro-apoptotic proteins and inflammatory factors, leading to delayed nerve cell death, and then degradation of red blood cells results in iron accumulation, ferroptosis, and aggravates neuronal toxicity, which can cause secondary brain injury [6]. Although it can be treated with surgery and drugs, disability and death rates remain high. Therefore, this review focuses on the causes of injury after ICH as well as the cell types and pathway regulation involved in mitophagy to control secondary brain injury, with the hope of finding new therapeutic targets to reduce the disability rate and mortality of ICH. Currently, the main focus of autophagy research is neurogenesis and nutrition. Here, we discuss the effects of autophagy and mitophagy on microglial cells and neurons.

2.1. Hypoxia, inflammation, OS after ICH

Hypoxia, oxidative stress, and inflammatory response injury occur after ICH. Hypoxia caused by temporarily reduced blood flow in turn induces hypoxia and the generation of the inflammatory transcription factor SP3, which participates in platelet activation and inflammation regulation after ICH [7]. The accumulation of oxidative stressors leads to secondary injury after ICH (cerebral edema, inflammation, neuronal apoptosis, and mitochondrial toxicity), red blood cell lysis, and heme expression [8]. Hemoglobin-activated NADPH oxidase and nitric oxide synthase are involved in the synthesis of reactive oxygen species (ROS), sustaining the opening of the mitochondrial permeability transition pore (mPTP) and decreasing the levels of adenosine triphosphate (ATP), which leads to the downregulation of growth differentiation factor 11 and aggravation of brain injury [9].

Hypoxia following ICH is a major factor that aggravates brain damage. According to a study on sleep apnea syndrome with ICH, hypoxia disrupts the blood-brain barrier and induces ROS production via activating the transcription factor 4/C/Ebp-Homologous Protein signaling pathway, and this pathway can release inflammatory factors interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, NF-κB, and pro-apoptotic proteins (caspase-3, Bax, and Beclin-2 (Bcl-2)) to mediate apoptosis [10].

To repair the damage caused by ICH, specific immune and inflammatory cells in the hematoma area function effectively in immunosuppression and phagocytosis. The fragments caused by blood vessel rupture activate microglia and macrophages in the brain and recruit white blood cells to the areas around the hematoma; for example, neutrophils and leukocytes infiltrate the brain, aggravating inflammatory injury. Activated microglia/macrophages and peripheral blood leukocytes release pro-inflammatory cytokines, including TNF-α, IL-1β, chemokines, free radicals, and other toxic chemicals, ultimately leading to cerebral edema, blood-brain barrier breakdown, and neuronal death [11]. This inflammatory response is closely related to the two phenotypic states of microglia, M1 and M2, where M1 plays a pro-inflammatory role in immune surveillance and M2 plays an anti-inflammatory role in regulating the recovery from intracerebral hemorrhage [12]. The M1 pro-inflammatory phenotype is induced mainly by immune cells, related kinases, and inflammatory cytokines. T-cell immunoglobulin and mucin structural domain-containing molecule 3 (Tim-3) and TonEBP can block nuclear factor erythroid 2 like 1 (Nrf2) bind to the HO-2 promoter and suppress its expression and transformation to the M2 subtype, thus inducing macrophages to polarize into the M1 phenotype, releasing inflammatory signals [13,14]. NOD-, LRR- and pyrin domain-containing 3 (NLRP3), which induces inflammation in microglia, can be activated after ICH to induce IL-1α, TNF-α and caspase-1 apoptotic pathways, leading to an inflammatory cascade reaction and aggravating brain injury. NLRP3 inhibition promotes the transformation of M1 to M2 and reduces ROS accumulation resulting from oxidative stress damage [15]. In addition, miRNAs are potential biomarkers of inflammatory diseases and participate in immune regulation. The upregulated expression of miR-34a-5p and miR-494 after ICH can inhibit M1 polarization of microglia into M2, exacerbating cerebral edema and damage to neurological functions. Whereas inhibiting the expression of inflammatory mediators can promote the transformation of microglia into M2 anti-inflammatory phenotype, for example, downregulation of neuregulin receptor degradation protein-1 in macrophages significantly promotes the polarization of M2 macrophages by activating transcription factor C/EBP-β and playing an anti-inflammatory role [16,17]. miR-146a-5p expression in bone marrow mesenchymal stem cells can reduce inducible nitric synthase (iNOS) released by M1 microglia, cyclooxygenase-2, monocyte chemoattractant protein-1, interleukin-1 receptor-associated kinase1, and nuclear factor of activated T cells 5 to protect neural function [18]. Relevant studies have found that the janus kinase 1 (JNK1)/signal transducer and activator of transcription 6 (STAT6) pathway can also activate the M2 phenotype. IL-4 converts microglia to the anti-inflammatory phenotype through JAK1/STAT6, and a study on ferrostatin 1 (Fer-1) also affirmed that Fer-1 can promote phagocytosis of damaged red blood cells in M2-polarized microglia and inhibit inflammation by activating the JAK1/STAT6 pathway to clear hematomas and mitigate neurologic defects [19,20]. In addition to microglia participating in autophagy and inflammation, the aquaporins of astrocytes play a role in the formation of edema after ICH, astrocyte migration, and inflammation. Aquaporin 2 can promote the activation of astrocytes by regulating the toll-like receptor 4 (TLR4)/NF-κB-p65 pathway after ICH, and indirectly promote the polarization of microglia towards M1 phenotype to mediate heme-induced inflammatory response [21]. Therefore, timely conversion of the microglia to the M2 phenotype can significantly reduce damage, by inhibiting mammalian target of rapamycin (mTOR) and the TLR4/NF-κβ pathway in macrophages, and promoting the adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) pathway to relieve inflammatory response [22,23]. In addition, monocytes and multinucleated giant cells can activate the expression of M1 and M2 phenotypes for further degradation of hemoglobin and removal of hematomas [24].

We assume that the M1 in response to inflammation, presenting inflammatory signals in the process of inflammatory factors, can aggravate brain damage, and then the M2 anti-inflammatory phenotypic transformation is not responsive in time, which fails to eliminate damaged neuronal poison, severe inflammatory lesions, and further damage to mitochondrial functions. Mitochondria-targeted protein kinases such as PTEN-induced kinase 1 (PINK) in microglial cells are inhibited and unable to provide protective mitophagy functions [25]. Hence, the timely restoration of mitochondrial functions can exert mitophagy and inhibit the damage of inflammation and oxidative stress caused by the early stage of glial cells in the neuronal system (Fig. 1).

2.2. Mitochondrial dysfunction after ICH

Mitochondrial dysfunction caused by hypoxia, oxidative stress, inflammation, and apoptosis after intracerebral hemorrhage plays a critical role in brain injury [26]. Mitochondrial dysfunction is mainly reflected in three ways: decreased mitochondrial respiratory chain oxidative phosphorylation (OXPHOS) activity [27], increased mitochondrial ROS (mtROS) production, and increased mitochondrial DNA damage. Knockdown of Nrf2 and optineurin (OPTN) inhibits mitophagy, resulting in the accumulation of NLRP3, aggravating inflammatory damage, and causing secondary brain injury [28].

2.2.1. Damages caused by accumulation of mtROS

A large accumulation of ROS destroys the inner mitochondrial membrane, leading to mitochondrial damage. The mitochondrial calcium uniporter (MCU) contributes to Ca2+ accumulation in the cytoplasm after ICH, resulting in membrane potential disturbance and mitochondrial swelling. Calcium overload and oxidative stress lead to mPTP opening and rapid loss of energy, which further causes microtubule disassembly and subsequent mitochondrial dysfunction, with eventual axonal degeneration within 24 h. MCU knockout can restore the mitochondrial membrane and structure, reduce ROS accumulation, and protect mitochondrial function [29, 30].

To alleviate mitochondrial damage and reverse this situation, mitochondrial protein MIC60, a key component of the mitochondrial contact site and cristae connective organizing system (MICOS), is a potential target in ICH and facilitates the interaction between the
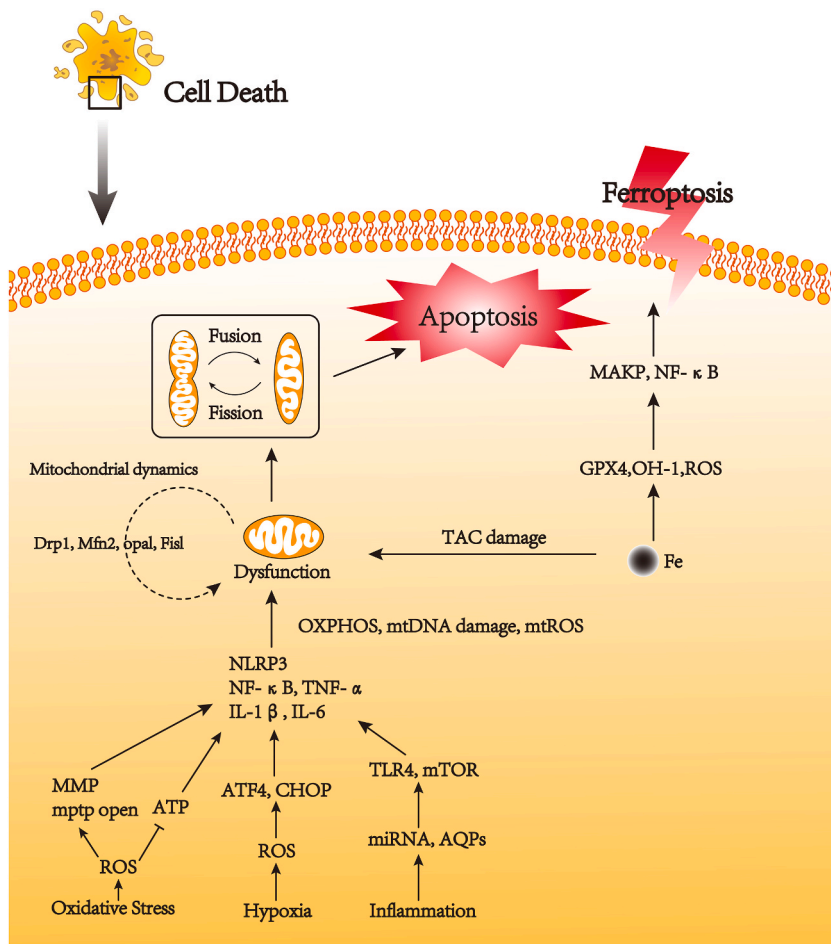

Fig. 1. Damage pathways after intracerebral hemorrhage.

inner and outer membranes of mitochondria. After intracranial hemorrhage, mitochondrial damage leads to the remodeling of the mitochondrial cristae structure, and MIC60 is reduced due to PINK downregulation. Recovery of MIC60 expression can close mPTP and reduce matrix metalloproteinase (MMP) levels, maintain mitochondrial ridge structure to protect mitochondrial structure, promote mitophagy to reduce neuronal death, and improve cognitive function after ICH [31].

2.2.2. Mitochondrial oxidative phosphorylation, dynamic Abnormality and dysfunction

Stabilization of mitochondrial membrane potential is closely related to mitochondrial fusion and fission mechanisms and is important in energy synthesis. The decrease of Notch1, WNT family member 1, and Peroxisome proliferator-activated receptor-γ coactivator-1alpha (PGC-1α) signal transduction will damage the blood-brain barrier and aggravate ICH pathological injury. Increased levels of mitochondrial dynamin-related protein 1 (Drp1) interfere with mitochondrial fusion and fission. Drp1 inhibition inhibits heme-induced hippocampal neuronal death and exacerbates synaptic damage. After ICH, decreased expression of OXPHOS complexes in mitochondria leads to decreased Notch1 signaling and expression, and changes in the direction of electron transfer, inducing ROS accumulation to disrupt the mitochondrial function of endothelial cells and the blood-brain barrier [32,33].

Excessive mitochondrial fission and fusion aggravate cell death. Drp1 and its receptor mitochondrial fission 1 are important proteins for mitochondrial fission, leading to mitochondrial fragmentation. Mitofusin 2 (Mfn2) and optic atrophy 1 can promote fusion. Excessive mitochondrial fission damages the mitochondrial structure, resulting in impaired oxidative phosphorylation, increased mROS production, ATP shortage, MMP damage, and the release of cytochrome-inducing apoptosis, which interferes with mitophagy [34]. The application of mitochondrial division inhibitor 1, a small-molecule inhibitor of Drp1, can alleviate Drp1-mediated mitochondrial fission after traumatic brain injury and inhibit autophagy and mitophagy in some regions of cortical neurons, thereby protecting the blood-brain barrier [35]. In subarachnoid hemorrhage, activation of AMPK not only promotes mitophagy to protect the blood-brain barrier, but also inhibits the damage caused by Drp1-and Mfn2-induced fission [36].

2.3. Ferroptosis in ICH

Ferroptosis is a pathway that does not depend on caspase (a mediator of apoptosis and pyroptosis), ATP depletion, Bax/Bak (an important mediator of mitochondrial membrane transmutation), or intracellular $Ca2+$ elevation to cause neuronal death. Instead, it occurs via the accumulation of ROS produced by NAPDH oxidase, leading to glutamate-induced organotypic hippocampal slice culture cell death [37]. Accumulation of iron-dependent toxic lipid ROS aggravates lipid damage and irreversible damage to membrane permeability, eventually resulting in membrane disturbance, non-specific membrane perforation, and mitochondrial ridge fracture injury. ROS are produced by the tricarboxylic acid cycle and the activity of electron transfer chain, which aggravate the destruction of mitochondrial membrane potential [38,39]. After blood vessel rupture in brain tissue, the neurotoxin hemoglobin/heme is released from lysed red blood cells, and free iron ions lead to the accumulation of intracellular lipid ROS and ultimately lipid oxidation [40]. Mitogen-activated protein kinase (MAPK) and NF-κB pathways are activated after iron accumulation, resulting in cell membrane damage and neuronal death [41].

Microglia and infiltrating macrophages in the pericerebral hematoma area phagocytose damaged erythrocytes; autophagosome formation is observed, as well as swollen mitochondria in axon dendrites [42]. The production of free iron ions can affect microglia polarization, ROS-induced NF-κB-p65 translocates in microglia, and astrocytes are expressed as M1 microglia and A1 astrocytes, inducing inflammatory damage [43]. Inhibition of microglial and macrophage activation and neutrophil infiltration can reduce ferroptotic damage and increase the level of Bclin-2 protein, which can inhibit Bax-induced apoptosis. Hence, the timely transformation of microglia from the M1 to the M2 phenotype can enhance phagocytosis, prevent hemoglobin-induced inflammatory damage in the hippocampal layer, and enhance mitophagy to alleviate injury after ICH [20,44].

Mitophagy promotion can enhance ICH recovery and inhibit the oxidative stress response and ferroptosis caused by heme accumulation. In a study on traumatic brain injury, mitophagy mediated by the PINK1/Parkin pathway was found to protect neurons from iron-induced death [45]. Nrf2 participates in this protective mechanism when mitophagy is activated. Nrf2 can also activate the antioxidant pathway p62/kelch-like ECH-associated protein 1 (Keap1), upregulation of ferritin heavy chain 1 and GPX4, and promote the expression of HO-1 to decrease neuronal death [46–48].

2.4. Autophagy in ICH

Autophagy is an intracellular lysosome-mediated catabolic mechanism that forms bilayer vesicle structures to remove damaged or dysfunctional cytoplasmic components and degrade intracellular organelles for transport to lysosomes for recycling [49]. Autophagy can occur in the area around the hematoma after ICH, usually induced by thrombin accumulation, to maintain material and energy stability, ensure cell survival in the face of starvation or other types of damage, and maintain cell homeostasis, which is sensitive to anoxic environments [50]. Mesenchymal stem cells can activate autophagy after hypoxic preconditioning and promote autophagy through the polypyrimidine tract-binding protein 1/phosphoinositide 3-kinase (PTBP1/PI3K) signaling pathway, miR-326 plays a protective role in alleviating cell senescence [51]. In certain situations, excessive autophagy may lead to inflammation, induce apoptosis, or destroy the blood-brain barrier. The activation of microglial autophagy and high mobility group box-1 transferred from the nucleus to the cytoplasm play a destructive role in neurological deficiency [52]. Upregulation of TLR4 and myeloid differentiation factor 88 induces neurological impairment, during which Beclin1 can be discovered. Combination of autophagy related 5 and light chain 3 (LC3) can induce IL-1β and TNF-α-induced inflammatory damage induced by microglial autophagy [53]. Red blood cell lysate can induce TLR4 to produce inflammatory factors and caspase-3 cell apoptosis pathway, and IL-17 can promote microglia autophagy to

activate the p38 via extracellular signal-regulated kinases (ERK) and phosphoinositide 3-kinase (PI3K) pathways, which significantly increase the levels of TNF-α, iNOS, and IL-6 proteins, exacerbating neurological impairment and brain edema [54,55].

In addition, expression of the inflammatory factor NLRP6 is upregulated after ICH, which induces autophagy and brain injury [56]. Activation of NLRP3 in microglia/macrophages promotes the extracellular release of IL-1β, leading to excessive autophagy and neuron binding through AMPK/Beclin-1 pathway to induce apoptosis in vivo and in vitro, and inhibition of the NLRP3 inflammasome reduces subependymal edema after ICH [57]. PI3K/protein kinase B) signaling and phosphorylation of the downstream effector forkhead box O3 (FOXO3a) subsequently enhance FOXO3a nuclear translocation, which induces excessive autophagy of hippocampal neurons, resulting in apoptotic damage [58].

We speculated that mitophagy may balance the damage caused by microglial autophagy, inhibit inflammation, and play a protective role. After ICH, the expression of the mitophagy proteins PINK-Parkin and LC3II decreased in microglial cells. Increasing the level of PINK-Parkin can increase the density and length of mitochondria in motor neurons and neuromuscular joints and protect the nervous system [59]. Timely and appropriate expression of mitophagy proteins is beneficial for the recovery of mitochondrial functions [25]. It is of great importance to inhibit the inflammatory injury caused by autophagy induced by microglial cells and the healing of ICH.

3. Mitophagy

Mitochondria are dynamic two-membrane organelles involved in the regulation of cellular health and energy supply during respiration. In addition to ATP production, mitochondria play a central role in shaping cellular signaling characteristics by mediating cell death, calcium balance, immune signaling, neuroplasticity, neurotransmission, and monitoring neural health [60]. Autophagy forms dissociation membranes that expand spherically to phagocytose and degrade organelles, resulting in double-membrane vesicles called autophagosomes that transport these phagocytic substances to lysosomes for later degradation [61]. Mitophagy is a selective autophagy that plays an important role in removing dysfunctional or damaged mitochondria to maintain mitochondrial dynamics, thus alleviating damage and cell dysfunction and enabling organelles to restore energy metabolism and maintain cell homeostasis [62]. At present, studies on the role and protective mechanism of mitophagy after ICH are relatively limited, and the effects of mitophagy and related targets are still controversial, such as Bcl-2/adenovirus E1B 19-kDa interacting proteins (BNIP3/BNIP3L) playing both positive and negative roles in different stroke disorders [63–65]. We will further explore the roles of the different targets in mitophagy and their functions under hypoxic conditions.

3.1. Mitophagy's functions in ischemic stroke

In studies of ischemic stroke and post-ischemic reperfusion diseases, prostaglandin C-1α promotes mitophagy through unc-51-like kinase 1, reduces the activation of NLRP3, and alleviates brain injury caused by NLRP3 inflammatory factor [66,67]. By increasing AMPK, FUN14 domain-containing 1 (FUNDC1), and PINK/Parkin protein binding to LC3 receptors, mitophagy can clear damaged mitochondria, restore the number of lysosomes, close ROS accumulation to induce the opening of mPTP channels in the mitochondrial membrane, improve the low-energy state of ATP, and remove damaged mitochondria [68,69]. In an anoxic environment during ischemic stroke, the expression of BNIP3 causes demyelination and death of oligodendrocytes, and the ectopic position with EndoG causes neuronal cell death [70,71]. According to a study on MAPK's regulation of proliferation, survival, and differentiation of neural stem cells, it has been found that mitogen-activated protein kinase phosphatase 1 (MKP-1) participates in mitophagy, whereas a lack of MKP-1 enhances BNIP3-induced autophagy and promotes apoptosis of neuronal stem cells [72]. We speculate that the different roles of mitophagy in stroke are closely related to neurons and glial cells, the location of occurrence, and the active targets of autophagy genes and proteins. Some active-related genes and proteins can be helpful in the recovery of mitochondrial functions, protection of neurons and glial cells, and maintenance of homeostasis.

3.2. 3.2 mitophagy in ICH

After ICH, mitophagy plays a role in reducing apoptosis caused by the inflammatory response and in restoring mitochondrial and nervous system functions. Activating the p62/Keap1/Nrf2 pathway using drugs to promote mitophagy can improve the level of LC3II receptors and avoid damage induced by oxygenated hemoglobin. Nrf2 can also promote optineurin-mediated mitophagy. LC3 II/I, Beclin1, Parkin, PINK1, and other proteins can be found around the brain tissue to inhibit the NLRP3 inflammasome and secondary brain injury [46,73]. When Nrf2 is deficient, the mitophagy protein levels of LC3 II/I, OPTN, Beclin1, Parkin, and PINK1 are relatively reduced, the endogenous antioxidant capacity is weakened, leaving the blood-brain barrier damaged, brain edema is aggravated after ICH, and the inflammatory response is activated to aggravate the apoptosis of neuronal cells. Therefore, enhanced mitophagy can restore mitochondrial function [46]. MiR-146a expression can activate mitophagy by increasing Beclin1, Beclin2, and LC3 II protein, reducing brain edema and hippocampal neuronal apoptosis induced by NF-κB, Bax, and caspase3 [74]. PINK/Parkin plays a powerful protective role in microglial cells and neurons, promotes autophagy, and reduces oxidative stress damage caused by ROS accumulation. In a study on GV20-GB7 (Baihui-Qubin point) acupuncture, an increase in PINK1, Parkin, and BNIP3 interacting with LC3 II can mediate autophagy, and therefore inhibit TNF alpha/NF-κB expression to reduce inflammation, p53, and neuronal apoptosis induced by caspase, thus improving the function of mitochondria and the nervous system [25,75]. MIC60 is a key component of mitochondrial contact sites and MICOS, which can restore mitochondrial ridge and morphological function, improve the level of PINK/Parkin protein after ICH to restore mitochondrial membrane stability, clear damaged mitochondria, and alleviate neuronal apoptosis and

degeneration by facilitating mitophagy [31].

Inhibition of NLRP3 can also act as an effective approach for mitophagy. FUNDC1 is located in the outer layer of mitochondria-associated membranes. It reaches its peak at 12 h after ICH, and during this time FUNDC1 enhances mitophagy and inhibits caspase-mediated neuronal apoptosis caused by NLRP3, IL-18, and IL-1β [76]. In addition to the roles of mitophagy proteins in regulating axonal nutrient transport and the physiological functions of mitochondria, PINK/Parkin can participate in the upregulation of the mitochondrial transport protein Miro1 during the removal of damaged substances [77]. High expression of Miro1 can recruit more KLF Transcription Factor 5 (KIF5) and dyneins, which is conducive to the retrograde transport of damaged mitochondria along axons with the help of dyneins and the anterograde transport of damaged substances along axons by healthy mitochondria with the help of KIF5s to restore mitochondrial transport functions [78]. Under most conditions, mitophagy after ICH can restore mitochondrial function and decrease the damage caused by inflammation and apoptosis.

The hypoxia inducible factor (HIF) acts as a transcription factor mediating an adaptive response to hypoxia and maintains homeostasis after ICH. The HIF family consists of three heterodimer members (HIF-1a, HIF-2a, and HIF-3a) and an oxygen-insensitive HIF-2b subunit [79,80]. HIF-2a can reduce brain injury by promoting angiogenesis via the vascular endothelial growth factor (VEGF)/Notch pathway [81]. HIF-1α is closely related to brain tissue callus after ICH and used as a prognostic marker, while miR-24 can be activated by thrombin and red cell lysate around blood cells to promote HIF-1α expression and restore angiogenesis [82,83]. In combination with brain-derived neurotrophic factor promote BNIP3, LC3, and other autophagy proteins promote mitophagy, restore mitochondrial function, protect cerebrovascular endothelial cells, and inhibit brain damage caused by hyperglycemia [84](Fig. 2).

3.3. Controversial Opinions on BNIP3ʹfunctions

BNIP3 and BNIP3L are in the BH3 domain and BCL2 homologous protein structure and induce cell death via autophagy. The role of BNIP3 in nervous system diseases remains controversial. Some studies have demonstrated that excessive mitophagy can induce neuronal damage, especially under adverse conditions, such as massive accumulation of metal ions, ischemia, and hypoxia. In neonatal hypoxic ischemic encephalopathy, HIF-1α and HIF-2α promote the expression of BNIP3 and play a damaging role in hypoxia-induced neuronal apoptosis [85]. The expressions of Nrf2, p53, BNIP3, and caspase-3 are time-dependent and dose-dependent with HIF-1α after traumatic brain injury, and inhibition of HIF-1α can reduce BNIP3/p53/cytochrome C-induced cortical neuronal apoptosis [86]. In ischemic stroke, BNIP3 combined with LC3 can induce mitophagy via the p53 pathway to promote apoptosis in cortical neurons and increase membrane permeability to impair neuronal apoptosis in the CA3 region of the hippocampus [87,88]. It has also been
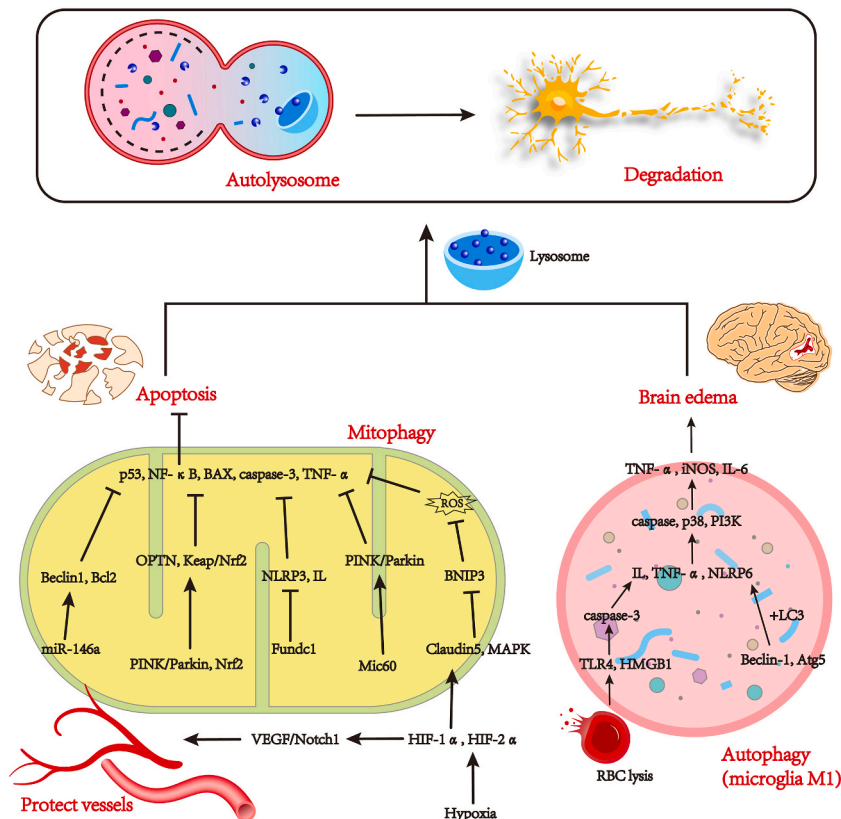

Fig. 2. Protective effect of mitophagy and pathway, and microglia autophagy pathway bring apoptotic damage and cause cerebral hematoma.

suggested that the promotion of HIF-1α/BNIP3 in SH-SY5Y cell mediating mitophagy can improve the protective effect within 12–24 h after ischemic stroke and hypoxia, and the inhibition of the caspase3-mediated neuronal apoptosis pathway is the key factor causing brain injury [89]. In a study on neuroinflammation, MAPK induced the expression of BNIP3, activated the mitophagy of microglia cells, degraded the injured mitochondria, inhibited the apoptosis of microglia BV-2 cells mediated by TNF-α-caspase pathway, improved mitochondrial energy production, and reduced cellular oxidative stress [90]. The experimental sites (lateral ventricles, basal ganglia, etc.) of ICH are different. After ICH, mitophagy can extensively inhibit neuronal apoptosis, inflammation, and oxidative stress responses to protect mitochondrial function.

BNIP3 is highly sensitive to hypoxia. Under hypoxic conditions, hypoxia-response element on BNIP3 responds to hypoxia rapidly [91]. ROS accumulation in hypoxia can drive the expression of BNIP3, and claudin-5 is involved in the mitophagy protection of endothelial cells in the neuronal system. Claudin-5 eliminates ROS and responds to early hypoxia-induced downstream BNIP3-mediated mitophagy in endothelial cells to maintain the blood-brain barrier [92].

Although the role of BNIP3 in stroke remains controversial, we believe that BNIP3 plays a protective role, and BNIP3L plays a damaging role after ICH. At 6 h after ICH, the expression level of BNIP3 protein increases in combination with PINK1 and Parkin to exert mitophagy response, which can eliminate the expression of p53 and TNF-α/NFκB and neuronal apoptosis induced by inflammatory response, to improve the recovery of neuronal function [75]. BNIP3L is mainly expressed in neurons and is unrelated to astrocytes or oligodendrocytes. The effect of BNIP3L on ICH differed from that of BNIP3. BNIP3L binds to Bcl-2 through its BH3 domain and directly mediates mitophagy, releasing cytochrome *c*,which induces apoptosis via the caspase3 pathway and aggravates brain injury [93](Fig. 3).

In conclusion, we believe that activating BNIP3 and inhibiting BNIP3L after ICH can reduce neuronal apoptosis under hypoxic conditions and that the function of microglia and neurons can be restored through the PINK/Parkin protein.

4. Therapeutic targets

4.1. Mitophagy targets

Currently, there are few studies on the application of mitophagy targets in the treatment of intracerebral hemorrhage. For related targets, such as Nrf2, which can regulate mitophagy and inflammatory responses, the activation of related mitochondrial proteins can
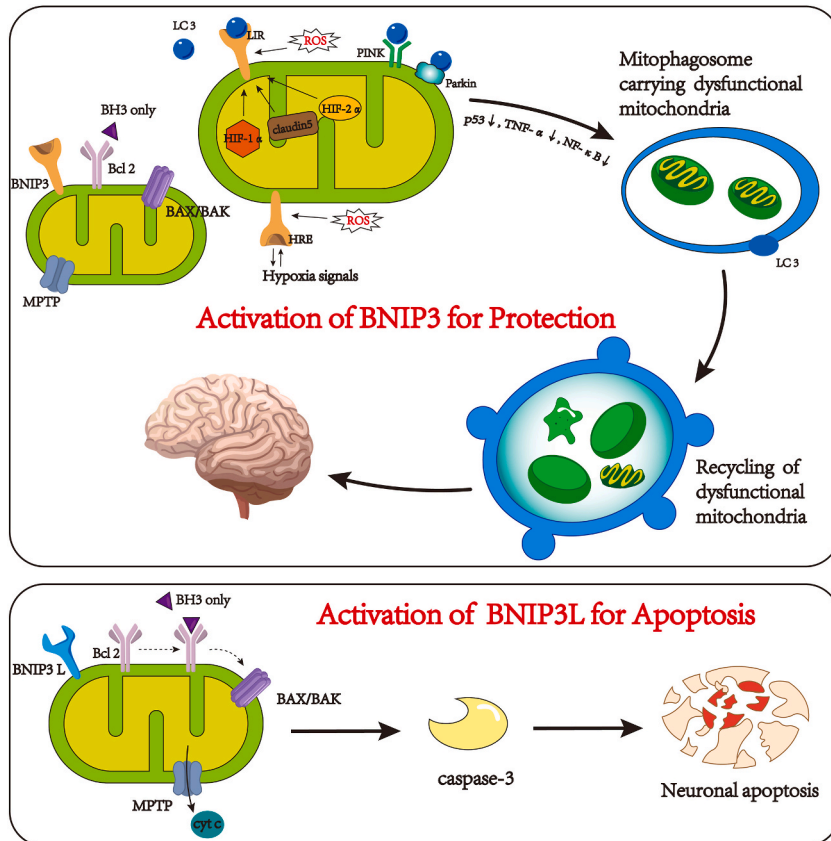

Fig. 3. BNIP3 activation promotes mitophagy for protective effect, while BNIP3L activation mediates apoptotic damage.

Table 1

Selective autophagy and mitophagy characteristics and effects in ICH

This table demonstrates treatments in ICH via autophagy and mitophagy pathways with activating their targeted proteins and genes, as well as respective effects of them including effective cells in therapies. Some proteins or genes that haven't been further studied could be the potential therapy targets in future.

Process	Major Cargo	Related Proteins	Regulation of Related Proteins	Cell	ICH Model	Treatment Time	Related Treatments	Effects	References
Mitophagy	Damaged or superfluous mitochondria	PINK/Parkin/BNIP3 pathway	upregulation	Neuron	ICH Rats	2h after ICH, once every 24 h thereafter	Acupuncture (GV20 through GB7)	Enhancing mitophagy to decrease mitochondrial apoptosis and neurobehavioral deficits	[25,75]
		P62/mTOR	downregulation	Neuron	ICH Rats	7 days after ICH	Acupuncture (GV20 through GB7)	Enhancing autophagy to improve motor/sensory functions and reduce injury in the peri hemorrhagic penumbra	
		P62-Keap1-Nrf2	upregulation	Neuron	ICH Rats	24 h after ICH	Luteolin	Enhancing autophagy to ameliorate oxyhemoglobin-induced mitochondrial injury and secondary brain injury	[73]
		FUNDC1	upregulation	Neuron	ICH Rats	–	–	Enhancing mitophagy to eliminate mitochondrial dysfunction after hypoxia and mitochondrial stress	[76]
		MIC60	upregulation	Neuron	ICH Rats	–	–	Enhancing mitophagy to mitigate ICH-induced neuronal apoptosis and neurodegeneration, maintain mitochondrial membrane structure and functions	[31]
		Nrf2/OPTN	upregulation	Neuron	ICH Rats	–	–	Enhancing mitophagy to inhibit NLRP3 and brain edema and protect the brain barrier in case of SBI (Secondary brain injury)	[28,46]
		BNIP3L/LC3	upregulation	Neuron	ICH Rats	6 h after ICH	Scalp Acupuncture	Enhancing mitophagy to mitigate cell injury-edema, inflammatory infiltration in the peri hemorrhage.	[47,59]
		HIF-1α/VEGF	downregulation	Neuron	ICH Patients	high-flow oxygen 8 L/min, 1 h each time for 6 cycles daily	Normobaric Oxygen Therapy	NBO therapy increases brain metabolic rate, attenuated cerebral edema, reduced local brain cell acidosis, and protected the BBB (Brain Barriers)	[96–99]
					ICH Rats	1 h after ICH(90 % concentrations in a single 6 h session daily)		NBO therapy suppresses HIF-1 activity and alleviates cerebral edema.	
Autophagy	Damaged or superfluous organelle	ERK/mTOR/p62/LC3	downregulation	Neuron	ICH Rats	–	Orexin-A	Inhibition of autophagy to attenuate secondary brain injury and protect against inflammation	[102]
		Glutamate/calcium-related cascades	downregulation	Neuron, astrocyte	ICH Rats	2h after ICH	Alpha-asarone	Inhibition of autophagy to ameliorate short- and long-term neurological impairments, bodyweight loss, and learning and memory ability, and alleviate neuronal damage, brain edema, and BBB dysfunction via enhancing the expression of GABA	[94]
		AMPK/mTOR	downregulation	Neuron	ICH Rats	–	Lovastatin	Inhibition of autophagy to mitigate cognitive impairment, enhance their spatial learning and memory abilities, reduce oxidative stress response and inflammatory factors which induce nervous system damage, lesion area, and brain water content after ICH	[104]

Table 1 (*continued*)

Process	Major Cargo	Related Proteins	Regulation of Related Proteins	Cell	ICH Model	Treatment Time	Related Treatments	Effects	References
		ROS/PTEN/PI3K/AKT	downregulation	Neuron	ICH Rats	–	Perampanel	Inhibition of autophagy to alleviate early brain injury following ICH, relieve hemin-induced HT22 neuronal injury, neuroinflammation and necroptosis via the PTEN signaling pathway.	[105]
		Claudin-5/LC3/Beclin	upregulation	Neuron, microglia	ICH Rats	1 h after ICH followed by daily doses at 24-h intervals.	PNU-282987	PNU-282987 promotes the cerebral functional outcomes after ICH in mice through activated α7nAChR, which is attributable to promoting autophagy and reducing inflammatory reactions through AMPK-mTOR-p70S6K-associated autophagy and microglia/macrophage polarization toward to an anti-inflammatory phenotype	[103]
		miR-326/PTBP1/PI3K	upregulation	Neuron, OM-MSC	ICH Rats	–	Hypoxic preconditioning OM-MSC	Enhancing autophagy to increase survival and tissue-protective capability in the hypoxia condition via miR-326/PTBP1/PI3K signaling pathway	[109]
	Inhibition of iron-mediated secondary neuronal injury	Fe2+/ROS/Heme accumulation	downregulation	microglia/macrophage, neuron , astrocytes	ICH Rats	24 h after ICH	Deferasirox	Inhibition of autophagy to attenuate the hemin-induced cell death and neurological deficits by suppressing oxidative stress	[106]
		P62; increase in LC3-II/LC3-I conversion ratio	downregulation	Neuron, endothelial cells and astrocyte	ICH Rats	–	Hepcidin	Inhibition of autophagy to attenuate iron-mediated secondary neuronal injury and ferroptosis in case of ICH-induced neurodegeneration	[107,108]

play a protective role. To activate the Nrf2 target, the p62-Keap1-Nrf2 pathway can be activated by Luteolin to mediate mitophagy and protect neurons from oxygenated hemoglobin-induced damage [73]. For glial cell protection, Alpha-asarone can be applied to inhibit autophagy and promote sodium ion excretion, blocking axon excitatory signaling and inhibiting mitochondrial and related cell apoptosis induced by glutamic acid and calcium-related cascade reactions [94].

For neuronal protection, Baihui point and Qubin point acupuncture can mediate mitophagy by activating the PINK/Parkin and BNIP3 genes and inhibiting the expression of the mTOR pathway and p62 to activate mitophagy [75,95]. Oxygen therapy can counteract hypoxic injury after ICH. In ischemic stroke, 2 weeks of treatment with normobaric oxygen (NBO) can reduce focal infarction of 24–48 h, reduce the expression activity of microglia and astrocytes, and induce vascular remodeling [96]. The water content around intracerebral hematoma increases moderately at 6 h after experimental ICH, significantly at 48 h, and reaches a peak at 72 h. Meanwhile, HIF-1α and VEGF begin to express at 6 h after ICH and gradually increase until reaching a peak at 48–72 h, and then decrease gradually. The expression of HIF-1α and VEGF can be inhibited by oxygen therapy at 90 % concentration, and the neuronal apoptosis around a hematoma can be reduced. Meanwhile, NBO can inhibit the activation of MMP-9 and HIF-1α 30 min after ICH, reducing cerebral edema and protecting the blood-brain barrier [97,98]. Compared with hyperbaric oxygen, NBO therapy has high efficiency, convenience, and low cost, and the appropriate oxygen flow rate is 8–10 L/min [99].

4.2. Autophagy targets

Thrombin-induced autophagy of neurons can be observed around the hematoma area after ICH, and Beclin1, LC3, and plasma TAT are highly expressed. Reducing thrombin levels may inhibit autophagy in neurons [100]. PPARγ/RAD21 Cohesin Complex Component can relieve ICH injury by promoting M2-type polarization of microglia cells, inhibiting inflammatory response and thrombine-induced apoptosis [101]. Orexin-A inhibits the ERK/mTOR signaling pathway to reduce thrombin-mediated autophagy by upregulating LC3B-II/LC3B and downregulating p62. Combined with Oxidation Resistance 1, it prevents heme-induced PC12 cell damage and protects against neuronal apoptosis [102].

Autophagy-enhancing drugs promote the protective effects of autophagy by inducing anti-inflammatory phenotypes in glial cells. For example, PNU-282987, a cholinergic receptor activator, activates cholinergic receptor α7nAChR via the AMPK-mTOR-P70S6K-related autophagy pathway, which can promote the polarization of macrophages/microglia into anti-inflammatory subtypes (CD206), repair blood-brain barrier damage (ZO-1, Claudin-5, Occludin), increase autophagy proteins (LC3, Beclin), and decrease p62 expression to relieve acute cerebral edema and restore neurological function [103]. However, drugs that inhibit autophagy can also inhibit the activation of inflammatory pathways. For example, lovastatin inhibits the AMPK/mTOR signaling pathway after ICH to reduce neuronal apoptosis induced by inflammatory factors and increases the expression of the anti-inflammatory factor IL-10 to protect brain tissue [104]. Perampanel downregulates Receptor-interacting protein 1 (RIP1), RIP3, and mixed lineage kinase domains (e.g. Pseudokinase) to decrease autophagy and protein expression levels of cytokines IL-1β, IL-6, TNF-α, and NF-κB, which can induce hippocampal neuron apoptosis [105].

In the treatment of ferroptosis, Deferasirox is a ferric chelating agent that inhibits intracellular Fe2+, autophagy-induced cell death by heme accumulation, and microglial/macrophage activation [106]. Hepcidin inhibits heme-induced increases in the conversion of LC3-II/LC3-I and p62 in cortical neurons, and reduces ferroptosis and autophagy [107,108].

Hypoxia-preconditioned stem cells can also cure hypoxic injury by mediating miR-326 to upregulate autophagy through the miR-326/PTBP1/PI3K pathway to delay the aging of OM-MSC, relieve cell aging, and reduce oxidative stress and inflammatory damage [109](Table 1).

5. Prospects

At present, regarding the role of mitophagy and related genes after intracerebral hemorrhage, mitophagy derived from different neuronal cells and mitophagy targets can be further studied and explored through targeted treatments to avoid damage caused by excessive autophagy. We speculated that different cells (glial cells and neurons), different experimental sites (such as basal ganglia, lateral ventricles, and hippocampus), different times, and inconsistent combinations of autophagy proteins or genes might lead to different experimental results. Based on the results of the present study, we believe that mitophagy can clear damaged organelles, relieve and inhibit autophagy in glial cells, restore inflammation, prevent oxidative stress damage, and restore mitochondrial function. Glia-induced autophagy is associated with intracerebral hemorrhage, early neuronal cell death, and inflammatory injury. Therefore, glial cell expression of an anti-inflammatory phenotype should be regulated in a timely manner. In addition, transient ischemia and hypoxia after intracerebral hemorrhage can activate oxygen-sensitive autophagy genes, such as BNIP3/BNIP3L, and affect the recovery of intracerebral hemorrhage. Through acupuncture, BNIP3 is effectively activated to reduce brain damage [59].

We assumed that oxygen therapy within 30 min after ICH can inhibit hypoxic injury, and drugs or methods can be applied within 12 h to activate mitophagy targets (such as PINK/Parkin, Nrf2 plays a protective role in neurons and glial cells) and can be used as a highly efficient protective target to avoid secondary brain injury.

Funding

CRediT authorship contribution statement

Qinghua Huang: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Xiaoqin Yu:** Conceptualization. **Peijie Fu:** Writing – review & editing, Writing – original draft. **Moxin Wu:** Data curation. **Xiaoping Yin:** Project administration. **Zhiying Chen:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Manqing Zhang:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

References

[1] M. Schrag, Cardiology HKJJotACo. Management of intracerebral hemorrhage, JACC Focus Seminar 75 (15) (2020) 1819–1831, https://doi.org/10.1016/j. jacc.2019.10.066.

[2] J. Balami, A. Buchan, Complications of intracerebral haemorrhage, JTLN 11 (1) (2012) 101–118, https://doi.org/10.1016/s1474-4422(11)70264-2.

[3] J. Aronowski, X. Zhao, Molecular pathophysiology of cerebral hemorrhage: secondary brain injury, Stroke 42 (6) (2011) 1781–1786, https://doi.org/10.1161/ strokeaha.110.596718.

[4] L. Galluzzi, I. Vitale, S.A. Aaronson, J.M. Abrams, D. Adam, P. Agostinis, et al., Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018, Cell Death Differ. 25 (3) (2018) 486–541, https://doi.org/10.1038/s41418-017-0012-4.

[5] H. Katayama, H. Hama, K. Nagasawa, H. Kurokawa, M. Sugiyama, R. Ando, et al., Visualizing and modulating mitophagy for therapeutic studies of neurodegeneration, Cell 181 (5) (2020), https://doi.org/10.1016/j.cell.2020.04.025, 1176-87.e16.

[6] G. Xi, R.F. Keep, J.T. H, Mechanisms of brain injury after intracerebral haemorrhage, JTL Neurology 5 (1) (2006) 53–63, https://doi.org/10.1016/s1474-4422 (05)70283-0.

[7] D. Wan, J. Feng, P. Wang, Z. Yang, T. S, Hypoxia- and inflammation-related transcription factor SP3 may Be involved in platelet activation and inflammation in intracranial hemorrhage, JFi neurology 13 (2022), 886329, https://doi.org/10.3389/fneur.2022.886329.

[8] Z. Wang, F. Zhou, Y. Dou, X. Tian, C. Liu, H. Li, et al., Melatonin alleviates intracerebral hemorrhage-induced secondary brain injury in rats via suppressing apoptosis, inflammation, oxidative stress, DNA damage, and mitochondria injury, Transl Stroke Res 9 (1) (2018) 74–91, https://doi.org/10.1007/s12975-017-0559-x.

[9] A. Xiao, Y. Zhang, Y. Ren, R. Chen, T. Li, C. You, et al., GDF11 Alleviates Secondary Brain Injury after Intracerebral Hemorrhage via Attenuating Mitochondrial Dynamic Abnormality and Dysfunction, vol. 11, 2021, p. 3974, https://doi.org/10.1038/s41598-021-83545-x, 1.

[10] W. Fei, W. Jiao, X. Feng, X. Chen, Y. W, Intermittent hypoxia mimicking obstructive sleep apnea aggravates early brain injury following ICH via neuroinflammation and apoptosis, JMm reports 24 (5) (2021), https://doi.org/10.3892/mmr.2021.12464.

[11] S. Chen, J. Peng, P. Sherchan, Y. Ma, S. Xiang, F. Yan, et al., TREM2 Activation Attenuates Neuroinflammation and Neuronal Apoptosis via PI3K/Akt Pathway after Intracerebral Hemorrhage in Mice, vol. 17, 2020, p. 168, https://doi.org/10.1186/s12974-020-01853-x, 1.

[12] G. Yang, X. Fan, M. Mazhar, W. Guo, Y. Zou, N. Dechsupa, et al., Neuroinflammation of Microglia Polarization in Intracerebral Hemorrhage and its Potential Targets for Intervention, vol. 15, 2022, 1013706, https://doi.org/10.3389/fnmol.2022.1013706.

[13] E.J. Yoo, H.H. Lee, B.J. Ye, J.H. Lee, C.Y. Lee, H.J. Kang, et al., TonEBP suppresses the HO-1 gene by blocking recruitment of Nrf2 to its promoter, Front. Immunol. 10 (2019) 850, https://doi.org/10.3389/fimmu.2019.00850.

[14] A. Yu, X. Zhang, M. Li, P. Ye, H. Duan, T. Zhang, et al., Tim-3 Enhances Brain Inflammation by Promoting M1 Macrophage Polarization Following Intracerebral Hemorrhage in Mice, vol. 53, 2017, pp. 143–148, https://doi.org/10.1016/j.intimp.2017.10.023.

[15] W. Chen, C. Guo, S. Huang, Z. Jia, J. Wang, J. Zhong, et al., MitoQ Attenuates Brain Damage by Polarizing Microglia towards the M2 Phenotype through Inhibition of the NLRP3 Inflammasome after ICH, vol. 161, 2020, 105122, https://doi.org/10.1016/j.phrs.2020.105122.

[16] D. Li, Y. Zhao, P. Bai, Y. Li, S. Wan, X. Zhu, et al., Baihui (DU20)-Penetrating-Qubin (GB7) Acupuncture Regulates Microglia Polarization through miR-34a-5p/ Klf4 Signaling in Intracerebral Hemorrhage Rats, vol. 70, 2021, pp. 469–478, https://doi.org/10.1538/expanim.21-0034, 4.

[17] G. Shao, C. Zhou, K. Ma, W. Zhao, Q. Xiong, L. Yang, et al., MiRNA-494 Enhances M1 Macrophage Polarization via Nrdp1 in ICH Mice Model, vol. 17, 2020, p. 17, https://doi.org/10.1186/s12950-020-00247-3.

[18] S. Duan, F. Wang, J. Cao, Chunyan Wang, Exosomes derived from MicroRNA-146a-5p-enriched bone marrow mesenchymal stem cells alleviate intracerebral hemorrhage by inhibiting neuronal apoptosis and microglial M1 polarization, J Drug design d, therapy 14 (2020) 3143–3158, https://doi.org/10.2147/dddt. S255828.

[19] Y. He, Y. Gao, Q. Zhang, G. Zhou, F. Cao, S. Y, IL-4 switches microglia/macrophage M1/M2 polarization and alleviates neurological damage by modulating the JAK1/STAT6 pathway following ICH, J Neuroscience 437 (2020) 161–171, https://doi.org/10.1016/j.neuroscience.2020.03.008.

[20] L. Huang, Y. Zhang, L. Zhao, Q. Chen, L. L, Ferrostatin-1 polarizes microglial cells toward M2 phenotype to alleviate inflammation after intracerebral hemorrhage, JN care 36 (3) (2022) 942–954, https://doi.org/10.1007/s12028-021-01401-2.

[21] S. Deng, X. Chen, Q. Lei, W. L, AQP2 promotes astrocyte activation by modulating the TLR4/nfκb-p65 pathway following intracerebral hemorrhage, JFi immunology 13 (2022), 847360, https://doi.org/10.3389/fimmu.2022.847360.

[22] D. Zhang, X. Shen, K. Pang, Z. Yang, A. Y, VSIG4 alleviates intracerebral hemorrhage induced brain injury by suppressing TLR4-regulated inflammatory response, JBr bulletin 176 (2021) 67–75, https://doi.org/10.1016/j.brainresbull.2021.08.008.

[23] J. Zheng, Z. Sun, F. Liang, W. Xu, J. Lu, L. Shi, et al., AdipoRon Attenuates Neuroinflammation after Intracerebral Hemorrhage through AdipoR1-AMPK Pathway, vol. 412, 2019, pp. 116–130, https://doi.org/10.1016/j.neuroscience.2019.05.060.

[24] J. Wei, M. Wang, C. Jing, R.F. Keep, Y. Hua, G. X, Multinucleated giant cells in experimental intracerebral hemorrhage, JTs research 11 (5) (2020) 1095–1102, https://doi.org/10.1007/s12975-020-00790-4.

[25] J. Li, X. Wu, Y. He, S. Wu, E. Guo, Y. Feng, et al., PINK1 Antagonize Intracerebral Hemorrhage by Promoting Mitochondrial Autophagy, vol. 8, 2021, pp. 1951–1960, https://doi.org/10.1002/acn3.51425, 10.

[26] Y. Zhang, S. Khan, Y. Liu, G. Wu, V.W. Yong, M. Xue, Oxidative stress following intracerebral hemorrhage: from molecular mechanisms to therapeutic targets, Front. Immunol. 13 (2022), 847246, https://doi.org/10.3389/fimmu.2022.847246.

[27] M.J. Lee, J. Zhu, J.H. An, S.E. Lee, T.Y. Kim, E. Oh, et al., A transcriptomic analysis of cerebral microvessels reveals the involvement of Notch1 signaling in endothelial mitochondrial-dysfunction-dependent BBB disruption, Fluids Barriers CNS 19 (1) (2022) 64, https://doi.org/10.1186/s12987-022-00363-7.

[28] Y. Cheng, M. Liu, H. Tang, B. Chen, G. Yang, W. Zhao, et al., iTRAQ-based quantitative proteomics indicated nrf2/OPTN-mediated mitophagy inhibits NLRP3 inflammasome activation after intracerebral hemorrhage, Oxid. Med. Cell. Longev. 2021 (2021), 6630281, https://doi.org/10.1155/2021/6630281.

[29] J. Wang, S. Yang, H. Li, H. Shen, X. Lu, X. Li, et al., Downregulation of Mitochondrial Calcium Uptake Family 3 Attenuates Secondary Brain Injury after Intracerebral Hemorrhage in Rats, vol. 361, 2023, 114302, https://doi.org/10.1016/j.expneurol.2022.114302.

[30] Y. Yang, X. Chen, Z. Feng, X. Cai, X. Zhu, M. Cao, et al., MEC17-induced α-tubulin Acetylation Restores Mitochondrial Transport Function and Alleviates Axonal Injury after Intracerebral Hemorrhage in Mice, vol. 160, 2022, pp. 51–63, https://doi.org/10.1111/jnc.15493, 1.

[31] R. Deng, W. Wang, X. Xu, J. Ding, J. Wang, S. Yang, et al., Loss of MIC60 Aggravates Neuronal Death by Inducing Mitochondrial Dysfunction in a Rat Model of Intracerebral Hemorrhage, vol. 58, 2021, pp. 4999–5013, https://doi.org/10.1007/s12035-021-02468-w, 10.

[32] M.J. Lee, J. Zhu, J.H. An, S.E. Lee, T.Y. Kim, E. Oh, et al., A Transcriptomic Analysis of Cerebral Microvessels Reveals the Involvement of Notch1 Signaling in Endothelial Mitochondrial-dysfunction-dependent BBB Disruption, vol. 19, 2022, p. 64, https://doi.org/10.1186/s12987-022-00363-7, 1.

[33] Y. Zhang, T. Rui, C. Luo, Q. L, Mdivi-1 alleviates brain damage and synaptic dysfunction after intracerebral hemorrhage in mice, JEb research 239 (5) (2021) 1581–1593, https://doi.org/10.1007/s00221-021-06089-6.

[34] X. Wu, W. Cui, W. Guo, H. Liu, J. Luo, L. Zhao, et al., Acrolein Aggravates Secondary Brain Injury after Intracerebral Hemorrhage through Drp1-Mediated Mitochondrial Oxidative Damage in Mice, vol. 36, 2020, pp. 1158–1170, https://doi.org/10.1007/s12264-020-00505-7, 10.

[35] Q. Wu, C. Gao, H. Wang, X. Zhang, Q. Li, Z. Gu, et al., Mdivi-1 alleviates blood-brain barrier disruption and cell death in experimental traumatic brain injury by mitigating autophagy dysfunction and mitophagy activation, Int. J. Biochem. Cell Biol. 94 (2018) 44–55, https://doi.org/10.1016/j.biocel.2017.11.007.

[36] Y. Zhang, T. Zhang, Y. Li, Y. Guo, B. Liu, Y. Tian, et al., Metformin Attenuates Early Brain Injury after Subarachnoid Hemorrhage in Rats via AMPK-dependent Mitophagy, vol. 353, 2022, 114055, https://doi.org/10.1016/j.expneurol.2022.114055.

[37] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, R. Skouta, E.M. Zaitsev, C.E. Gleason, et al., Ferroptosis: an Iron-dependent Form of Nonapoptotic Cell Death, vol. 149, 2012, pp. 1060–1072, https://doi.org/10.1016/j.cell.2012.03.042, 5.

[38] M. Gao, J. Yi, J. Zhu, A.M. Minikes, P. Monian, C.B. Thompson, et al., Role of Mitochondria in Ferroptosis, vol. 73, 2019, https://doi.org/10.1016/j.molcel.2018.10.042 (2):354-e3.

[39] H. Imai, M. Matsuoka, T. Kumagai, T. Sakamoto, T. K, Lipid peroxidation-dependent cell death regulated by GPx4 and ferroptosis, JCti, immunology 403 (2017) 143–170, https://doi.org/10.1007/82_2016_508, microbiology.

[40] Q. Li, X. Han, X. Lan, Y. Gao, J. Wan, F. Durham, et al., Inhibition of Neuronal Ferroptosis Protects Hemorrhagic Brain, vol. 2, 2017, e90777, https://doi.org/10.1172/jci.insight.90777, 7.

[41] T. Liu, X. Li, Y. Cui, P. Meng, G. Zeng, Y. Wang, et al., Bioinformatics Analysis Identifies Potential Ferroptosis Key Genes in the Pathogenesis of Intracerebral Hemorrhage, vol. 15, 2021, 661663, https://doi.org/10.3389/fnins.2021.661663.

[42] Q. Li, A. Weiland, X. Chen, X. Lan, X. Han, F. Durham, et al., Ultrastructural characteristics of neuronal death and white matter injury in mouse brain tissues after intracerebral hemorrhage: coexistence of ferroptosis, Autophagy, and Necrosis 9 (2018) 581, https://doi.org/10.3389/fneur.2018.00581.

[43] J. Zheng, Jn Lu, S. Mei, H. Wu, Z. Sun, Y. Fang, et al., Ceria Nanoparticles Ameliorate White Matter Injury after Intracerebral Hemorrhage: Microglia-Astrocyte Involvement in Remyelination, vol. 18, 2021, p. 43, https://doi.org/10.1186/s12974-021-02101-6, 1.

[44] Y. Zhang, X. Zhang, V. Wee Yong, M. Xue, Vildagliptin improves neurological function by inhibiting apoptosis and ferroptosis following intracerebral hemorrhage in mice, Neurosci. Lett. 776 (2022), 136579, https://doi.org/10.1016/j.neulet.2022.136579.

[45] L. Zhang, Y. Lin, W. Bai, L. Sun, M. Tian, Human umbilical cord mesenchymal stem cell-derived exosome suppresses programmed cell death in traumatic brain injury via PINK1/Parkin-mediated mitophagy, CNS Neurosci. Ther. (2023), https://doi.org/10.1111/cns.14159.

[46] Y. Cheng, M. Liu, H. Tang, B. Chen, G. Yang, W. Zhao, et al., iTRAQ-Based Quantitative Proteomics Indicated Nrf2/OPTN-Mediated Mitophagy Inhibits NLRP3 Inflammasome Activation after Intracerebral Hemorrhage, vol. 2021, 2021, 6630281, https://doi.org/10.1155/2021/6630281.

[47] M.-Y. Li, X.-H. Dai, X.-P. Yu, W. Zou, W. Teng, P. Liu, et al., Scalp Acupuncture Protects against Neuronal Ferroptosis by Activating the P62-Keap1-Nrf2 Pathway in Rat Models of Intracranial Haemorrhage, vol. 72, 2022, pp. 82–96, https://doi.org/10.1007/s12031-021-01890-y, 1.

[48] Z.-X. Zhou, Q. Cui, Y.-M. Zhang, J.-X. Yang, W.-J. Xiang, N. Tian, et al., Withaferin A Inhibits Ferroptosis and Protects against Intracerebral Hemorrhage, vol. 18, 2023, pp. 1308–1315, https://doi.org/10.4103/1673-5374.355822, 6.

[49] B. Yuan, H. Shen, L. Lin, T. Su, L. Zhong, Z. Y, Autophagy promotes microglia activation through beclin-1-atg5 pathway in intracerebral hemorrhage, JM neurobiology 54 (1) (2017) 115–124, https://doi.org/10.1007/s12035-015-9642-z.

[50] Y. Zhang, C. L, Autophagy and hemorrhagic stroke, JAie, biology 1207 (2020) 135–147, https://doi.org/10.1007/978-981-15-4272-5_8, medicine.

[51] J. Liu, J. He, L. Ge, H. Xiao, Y. Huang, L. Zeng, et al., Hypoxic Preconditioning Rejuvenates Mesenchymal Stem Cells and Enhances Neuroprotection Following Intracerebral Hemorrhage via the miR-326-Mediated Autophagy, vol. 12, 2021, p. 413, https://doi.org/10.1186/s13287-021-02480-w, 1.

[52] S. Deng, Q. Hu, X. Chen, Q. Lei, W. L, GM130 protects against blood-brain barrier disruption and brain injury after intracerebral hemorrhage by regulating autophagy formation, JE gerontology 163 (2022), 111772, https://doi.org/10.1016/j.exger.2022.111772.

[53] C. Lei, Y. Li, X. Zhu, H. Li, X. C, HMGB1/TLR4 induces autophagy and promotes neuroinflammation after intracerebral hemorrhage, JB research 1792 (2022), 148003, https://doi.org/10.1016/j.brainres.2022.148003.

[54] H. Shi, J. Wang, J. Wang, Z. Huang, Z. Y, IL-17A induces autophagy and promotes microglial neuroinflammation through ATG5 and ATG7 in intracerebral hemorrhage, JJo neuroimmunology 323 (2018) 143–151, https://doi.org/10.1016/j.jneuroim.2017.07.015.

[55] Z. Yang, B. Liu, L. Zhong, H. Shen, C. Lin, L. Lin, et al., Toll-like Receptor-4-Mediated Autophagy Contributes to Microglial Activation and Inflammatory Injury in Mouse Models of Intracerebral Haemorrhage, vol. 41, 2015, pp. e95–e106, https://doi.org/10.1111/nan.12177, 4.

[56] H. Xiao, H. Chen, R. Jiang, L. Zhang, L. Wang, H. Gan, et al., NLRP6 Contributes to Inflammation and Brain Injury Following Intracerebral Haemorrhage by Activating Autophagy, vol. 98, 2020, pp. 1319–1331, https://doi.org/10.1007/s00109-020-01962-3, 9.

[57] Z. Zhang, P. Guo, S. Huang, Z. Jia, T. Chen, X. Liu, et al., Inhibiting microglia-derived NLRP3 alleviates subependymal edema and cognitive dysfunction in posthemorrhagic hydrocephalus after intracerebral hemorrhage via AMPK/Beclin-1 pathway, Oxid. Med. Cell. Longev. 2022 (2022), 4177317, https://doi.org/10.1155/2022/4177317.

[58] M. Zhao, J. Gao, C. Cui, Y. Zhang, X. Jiang, J. Cui, Inhibition of PTEN ameliorates secondary hippocampal injury and cognitive deficits after intracerebral hemorrhage: involvement of AKT/FoxO3a/ATG-Mediated autophagy, Oxid. Med. Cell. Longev. 2021 (2021), 5472605, https://doi.org/10.1155/2021/5472605.

[59] P. Liu, X. Yu, X. Dai, W. Zou, X. Yu, M. Niu, et al., Scalp acupuncture attenuates brain damage after intracerebral hemorrhage through enhanced mitophagy and reduced apoptosis in rats, Front. Aging Neurosci. 13 (2021), 718631, https://doi.org/10.3389/fnagi.2021.718631.

[60] P. Belenguer, J.M.N. Duarte, P.F. Schuck, G.C. Ferreira, Mitochondria and the brain: bioenergetics and beyond, Neurotox. Res. 36 (2) (2019) 219–238, https://doi.org/10.1007/s12640-019-00061-7.

[61] T. Yoshimori, Autophagy: paying Charon's toll, Cell 128 (5) (2007) 833–836, https://doi.org/10.1016/j.cell.2007.02.023.

[62] R. Guan, W. Zou, X. Dai, X. Yu, H. Liu, Q. Chen, et al., Mitophagy, a Potential Therapeutic Target for Stroke, vol. 25, 2018, p. 87, https://doi.org/10.1186/s12929-018-0487-4, 1.

[63] J. Li, J. Wu, X. Zhou, Y. Lu, Y. Ge, X. Zhang, Targeting neuronal mitophagy in ischemic stroke: an update, Burns Trauma 11 (2023), https://doi.org/10.1093/burnst/tkad018 tkad018.

[64] S. Li, J. Zhao, Y. Xi, J. Ren, Y. Zhu, Y. Lu, et al., Dl-3-n-butylphthalide exerts neuroprotective effects by modulating hypoxia-inducible factor 1-alpha ubiquitination to attenuate oxidative stress-induced apoptosis, Neural Regen Res 18 (11) (2023) 2424–2428, https://doi.org/10.4103/1673-5374.371366.

[65] R.Y. Shi, S.H. Zhu, V. Li, S.B. Gibson, X.S. Xu, J.M. Kong, BNIP3 interacting with LC3 triggers excessive mitophagy in delayed neuronal death in stroke, CNS Neurosci. Ther. 20 (12) (2014) 1045–1055, https://doi.org/10.1111/cns.12325.

[66] B. Han, W. Jiang, P. Cui, K. Zheng, C. Dang, J. Wang, et al., Microglial PGC-1α Protects against Ischemic Brain Injury by Suppressing Neuroinflammation, vol. 13, 2021, p. 47, https://doi.org/10.1186/s13073-021-00863-5, 1.

[67] D.A. Sliter, J. Martinez, L. Hao, X. Chen, N. Sun, T.D. Fischer, et al., Parkin and PINK1 Mitigate STING-Induced Inflammation, vol. 561, 2018, pp. 258–262, https://doi.org/10.1038/s41586-018-0448-9, 7722.

[68] Y. Cai, E. Yang, X. Yao, X. Zhang, Q. Wang, Y. Wang, et al., FUNDC1-dependent mitophagy induced by tPA protects neurons against cerebral ischemia-reperfusion injury, Redox Biol. 38 (2021), 101792, https://doi.org/10.1016/j.redox.2020.101792.

[69] H. Wang, S. Chen, Y. Zhang, H. Xu, H, S, Electroacupuncture ameliorates neuronal injury by Pink1/Parkin-mediated mitophagy clearance in cerebral ischemia-reperfusion, J No 91 (2019) 23–34, https://doi.org/10.1016/j.niox.2019.07.004, biology, chemistry.

[70] C. Li, T. Guan, X. Chen, W. Li, Q. Cai, J. Niu, et al., BNIP3 Mediates Pre-myelinating Oligodendrocyte Cell Death in Hypoxia and Ischemia, vol. 127, 2013, pp. 426–433, https://doi.org/10.1111/jnc.12314, 3.

[71] Z. Zhang, X. Yang, S. Zhang, X. Ma, J, K, BNIP3 upregulation and EndoG translocation in delayed neuronal death in stroke and in hypoxia, J Stroke 38 (5) (2007) 1606–1613, https://doi.org/10.1161/strokeaha.106.475129.

[72] Y. Li, M.W. H, The MAP kinase phosphatase MKP-1 modulates neurogenesis via effects on BNIP3 and autophagy, J Biomolecules 11 (12) (2021), https://doi.org/10.3390/biom11121871.

[73] X. Tan, Y. Yang, J. Xu, P. Zhang, R. Deng, Y. Mao, et al., Luteolin Exerts Neuroprotection via Modulation of the p62/Keap1/Nrf2 Pathway in Intracerebral Hemorrhage, vol. 10, 2019, p. 1551, https://doi.org/10.3389/fphar.2019.01551.

[74] S. Huan, J. Jin, C.-X. Shi, T. Li, Z. Dai, X.-J. F, et al., Overexpression of miR-146a inhibits the apoptosis of hippocampal neurons of rats with cerebral hemorrhage by regulating autophagy, J Human 39 (9) (2020) 1178–1189, https://doi.org/10.1177/0960327120907131.

[75] R. Guan, Z. Li, X. Dai, W. Zou, X. Yu, H. Liu, et al., Electroacupuncture at GV20-GB7 Regulates Mitophagy to Protect against Neurological Deficits Following Intracerebral Hemorrhage via Inhibition of Apoptosis, vol. 24, 2021, https://doi.org/10.3892/mmr.2021.12131, 1.

[76] S. Zheng, D. Jian, H. Gan, L. Wang, J. Zhao, X. Z, FUNDC1 inhibits NLRP3-mediated inflammation after intracerebral hemorrhage by promoting mitophagy in mice, JN letters 756 (2021), 135967, https://doi.org/10.1016/j.neulet.2021.135967.

[77] G. López-Doménech, J.H. Howden, C. Covill-Cooke, C. Morfill, J.V. Patel, R. Bürli, et al., Loss of neuronal Miro1 disrupts mitophagy and induces hyperactivation of the integrated stress response, EMBO J. 40 (14) (2021), e100715, https://doi.org/10.15252/embj.2018100715.

[78] B. Li, Y. Zhang, H. Li, H. Shen, Y. Wang, X. Li, et al., Miro1 Regulates Neuronal Mitochondrial Transport and Distribution to Alleviate Neuronal Damage in Secondary Brain Injury after Intracerebral Hemorrhage in Rats, vol. 41, 2021, pp. 795–812, https://doi.org/10.1007/s10571-020-00887-2, 4.

[79] E. Brown, C. Rowan, M.J. Strowitzki, R.R. Fagundes, K.N. Faber, A. Güntsch, et al., Mucosal Inflammation Downregulates PHD1 Expression Promoting a Barrier-Protective HIF-1α Response in Ulcerative Colitis Patients, vol. 34, 2020, pp. 3732–3742, https://doi.org/10.1096/fj.201902103R, 3.

[80] B. Zhang, Y. Chen, X. Shi, M. Zhou, L. Bao, K.J. Hatanpaa, et al., Regulation of branched-chain amino acid metabolism by hypoxia-inducible factor in glioblastoma, Cell. Mol. Life Sci. 78 (1) (2021) 195–206, https://doi.org/10.1007/s00018-020-03483-1.

[81] H. Chen, H. Xiao, H. Gan, L. Zhang, L. Wang, S. Li, et al., Hypoxia-inducible Factor 2α Exerts Neuroprotective Effects by Promoting Angiogenesis via the VEGF/Notch Pathway after Intracerebral Hemorrhage Injury in Rats, vol. 448, 2020, pp. 206–218, https://doi.org/10.1016/j.neuroscience.2020.07.010.

[82] Y. Cai, Y.-K. Zhuang, X.-Y. Wu, X.-Q. Dong, Q. Du, W.-H. Yu, et al., Serum Hypoxia-Inducible Factor 1alpha Levels Correlate with Outcomes after Intracerebral Hemorrhage, vol. 17, 2021, pp. 717–726, https://doi.org/10.2147/tcrm.S313433.

[83] H. Cui, A. Yang, H. Zhou, Y. Wang, J. Luo, J. Zhou, et al., Thrombin-induced miRNA-24-1-5p Upregulation Promotes Angiogenesis by Targeting Prolyl Hydroxylase Domain 1 in Intracerebral Hemorrhagic Rats, vol. 134, 2020, pp. 1515–1526, https://doi.org/10.3171/2020.2.Jns193069, 5.

[84] H. Jin, Y. Zhu, Y. Li, X. Ding, W. Ma, X. Han, et al., BDNF-Mediated Mitophagy Alleviates High-Glucose-Induced Brain Microvascular Endothelial Cell Injury, vol. 24, 2019, pp. 511–528, https://doi.org/10.1007/s10495-019-01535-x, 5-6.

[85] L. Zhu, B. Qi, Daorong Hou, Roles of HIF1α- and HIF2α-regulated BNIP3 in hypoxia-induced injury of neurons, J Pathology r, practice 215 (4) (2019) 822–827, https://doi.org/10.1016/j.prp.2019.01.022.

[86] A. Li, X. Sun, Y. Ni, X. Chen, A. G, HIF-1α involves in neuronal apoptosis after traumatic brain injury in adult rats, JJomn MN 51 (3) (2013) 1052–1062, https://doi.org/10.1007/s12031-013-0084-7.

[87] Y. Kuang, X. Zheng, L. Zhang, X. Ai, V. Venkataramani, E. Kilic, et al., Adipose-derived Mesenchymal Stem Cells Reduce Autophagy in Stroke Mice by Extracellular Vesicle Transfer of miR-25, vol. 10, 2020, e12024, https://doi.org/10.1002/jev2.12024, 1.

[88] R. Schmidt-Kastner, C. Aguirre-Chen, T. Kietzmann, I. Saul, R. Busto, M.D. G, Nuclear localization of the hypoxia-regulated pro-apoptotic protein BNIP3 after global brain ischemia in the rat hippocampus, JB research 1001 (1–2) (2004) 133–142, https://doi.org/10.1016/j.brainres.2003.11.065.

[89] R. Wei, L. Song, Z. Miao, K. Liu, G. Han, H. Zhang, et al., Hydroxysafflor Yellow A Exerts Neuroprotective Effects via HIF-1α/BNIP3 Pathway to Activate Neuronal Autophagy after OGD/R, vol. 11, 2022, https://doi.org/10.3390/cells11233726, 23.

[90] Q. Lei, J. Tan, S. Yi, N. Wu, Y. Wang, H. W, et al., Mitochonic acid 5 activates the MAPK-ERK-yap signaling pathways to protect mouse microglial BV-2 cells against TNFα-induced apoptosis via increased Bnip3-related mitophagy, J Cellular 23 (2018) 14, https://doi.org/10.1186/s11658-018-0081-5.

[91] X. Feng, X. Liu, W. Zhang, W, X, p53 directly suppresses BNIP3 expression to protect against hypoxia-induced cell death, JTE journal 30 (16) (2011) 3397–3415, https://doi.org/10.1038/emboj.2011.248.

[92] P. Yu, Y. Li, G. Zhong, W. Li, B. Chen, J. Z, Claudin-5 affects endothelial autophagy in response to early hypoxia, JFi physiology 12 (2021), 737474, https://doi.org/10.3389/fphys.2021.737474.

[93] Y. Rui, K. Ke, L. Li, H. Zheng, W. Xu, X. Tan, et al., Up-regulated Expression of Bnip3L after Intracerebral Hemorrhage in Adult Rats, vol. 44, 2013, pp. 497–505, https://doi.org/10.1007/s10735-013-9506-7, 5.

[94] X. Gao, R. Li, L. Luo, D. Zhang, Q. Liu, J. Zhang, et al., Alpha-asarone Ameliorates Neurological Deterioration of Intracerebral Hemorrhagic Rats by Alleviating Secondary Brain Injury via Anti-excitotoxicity Pathways, vol. 105, 2022, 154363, https://doi.org/10.1016/j.phymed.2022.154363.

[95] H. Liu, B. Zhang, X.W. Li, J. Du, P.P. Feng, C. Cheng, et al., Acupuncture inhibits mammalian target of rapamycin, promotes autophagy and attenuates neurological deficits in a rat model of hemorrhagic stroke, Acupunct. Med. 40 (1) (2022) 59–67, https://doi.org/10.1177/09645284211028873.

[96] E. Esposito, E.T. Mandeville, K. Hayakawa, A.B. Singhal, E.H. L, Effects of normobaric oxygen on the progression of focal cerebral ischemia in rats, JE neurology 249 (2013) 33–38, https://doi.org/10.1016/j.expneurol.2013.08.005.

[97] P. You, M. Lin, K. Li, X. Ye, J. Zheng, Normobaric oxygen therapy inhibits HIF-1α and VEGF expression in perihematoma and reduces neurological function defects, Neuroreport 27 (5) (2016) 329–336, https://doi.org/10.1097/wnr.0000000000000542.

[98] W. Zhou, M. Marinescu, R. V, Only very early oxygen therapy attenuates posthemorrhagic edema formation and blood-brain barrier disruption in murine intracerebral hemorrhage, JN care 22 (1) (2015) 121–132, https://doi.org/10.1007/s12028-014-0013-9.

[99] Z. Chen, J. Ding, X. Wu, X. Bao, X. Cao, X. Wu, et al., Safety and Efficacy of Normobaric Oxygenation on Rescuing Acute Intracerebral Hemorrhage-Mediated Brain Damage-A Protocol of Randomized Controlled Trial, vol. 22, 2021, p. 93, https://doi.org/10.1186/s13063-021-05048-4, 1.

[100] C. Wu, X. Yan, Y. Liao, L. Liao, S. Huang, Q. Zuo, et al., Increased perihematomal neuron autophagy and plasma thrombin-antithrombin levels in patients with intracerebral hemorrhage: an observational study, Medicine (Baltim.) 98 (39) (2019), e17130, https://doi.org/10.1097/md.0000000000017130.

[101] Y. Jiao, S. Ren, L. Wang, G. Wu, PPARγ/RAD21 alleviates peripheral secondary brain injury in rat cerebral hemorrhage model through promoting M2 polarization of microglial cells, Int Immunopharmacol 114 (2023), 109572, https://doi.org/10.1016/j.intimp.2022.109572.

[102] D. Zhang, Y. Cui, M. Zhao, X. Zheng, C. Li, J. Wei, et al., Orexin-A exerts neuroprotective effect in experimental intracerebral hemorrhage by suppressing autophagy via OXR1-mediated ERK/mTOR signaling pathway, Front. Cell. Neurosci. 16 (2022), 1045034, https://doi.org/10.3389/fncel.2022.1045034.

[103] Y. Su, W. Zhang, R. Zhang, Q. Yuan, R. Wu, X. Liu, et al., Activation of cholinergic anti-inflammatory pathway ameliorates cerebral and cardiac dysfunction after intracerebral hemorrhage through autophagy, Front. Immunol. 13 (2022), 870174, https://doi.org/10.3389/fimmu.2022.870174.

[104] X. Deng, J. Yang, R. Qing, H. Yuan, P. Yue, Suppressive role of lovastatin in intracerebral hemorrhage through repression of autophagy, disease STJMb 38 (1) (2023) 361–372, https://doi.org/10.1007/s11011-022-01101-6.

[105] L. Yang, Y. Wang, C. Zhang, T. Chen, H. Cheng, Perampanel, an AMPAR antagonist, alleviates experimental intracerebral hemorrhage-induced brain injury via necroptosis and neuroinflammation, Mol. Med. Rep. 24 (2) (2021), https://doi.org/10.3892/mmr.2021.12183.

[106] T. Imai, S. Tsuji, H. Matsubara, T. Ohba, T. Sugiyama, S. Nakamura, et al., Deferasirox, a trivalent iron chelator, ameliorates neuronal damage in hemorrhagic stroke models, Naunyn-Schmiedeberg's Arch. Pharmacol. 394 (1) (2021) 73–84, https://doi.org/10.1007/s00210-020-01963-6.

[107] G. Yang, C. Qian, C. Zhang, Y. Bao, M.Y. Liu, F. Jiang, et al., Hepcidin attenuates the iron-mediated secondary neuronal injury after intracerebral hemorrhage in rats, Transl. Res.: J. Lab. Clin. Med. 229 (2021) 53–68, https://doi.org/10.1016/j.trsl.2020.09.002.

[108] C. Zhang, C. Qian, G. Yang, Y.X. Bao, Z.M. Qian, Hepcidin inhibits autophagy in intracerebral hemorrhage models in vitro and in vivo, Mol. Cell. Neurosci. 111 (2021), 103589, https://doi.org/10.1016/j.mcn.2021.103589.

[109] J. Liu, J. He, L. Ge, H. Xiao, Y. Huang, L. Zeng, et al., Hypoxic preconditioning rejuvenates mesenchymal stem cells and enhances neuroprotection following intracerebral hemorrhage via the miR-326-mediated autophagy, Stem Cell Res. Ther. 12 (1) (2021) 413, https://doi.org/10.1186/s13287-021-02480-w.