

## Review Article

# Mechanisms and therapeutic potential of hyperbaric oxygen inducing autophagy in cerebral ischemia-reperfusion injury

Yifan Huang<sup>1\*</sup>, Bin Yang<sup>2\*</sup>, Xiaopeng Liu<sup>1</sup>, Xiaozhan Yang<sup>1</sup>, Jiankai Gao<sup>3</sup>, Ruifang Cui<sup>1</sup>, Rui Zhang<sup>3</sup>, Sisen Zhang<sup>1,3,4</sup>

<sup>1</sup>Fifth Clinical Medical College, Henan University of Chinese Medicine, 39 Hongqi Road, Zhengzhou 450002, Henan, China; <sup>2</sup>The First Affiliated Hospital of Henan University of Chinese Medicine, 19 Renmin Road, Jinshui District, Zhengzhou 450000, Henan, China; <sup>3</sup>Emergency Medicine Department, Henan University of Chinese Medicine People's Hospital/Zhengzhou People's Hospital, 33 Huanghe Road, Zhengzhou 450003, Henan, China; <sup>4</sup>The Heart-lung-brain Resuscitation Engineering Technology Research Center of Henan Province, Zhengzhou 450003, Henan, China. \*Equal contributors and co-first authors.

Received September 9, 2025; Accepted November 4, 2025; Epub November 15, 2025; Published November 30, 2025

**Abstract:** Cerebral ischemia-reperfusion injury (CIRI) is a complex pathological process involving oxidative stress, inflammation, and dysregulated autophagy. Hyperbaric oxygen therapy (HBO) has emerged as a promising intervention that mitigates neuronal injury by modulating autophagy. This review summarizes current evidence on the mechanisms of HBO through the AMPK-mTOR, HIF-1 $\alpha$ -mTOR, and PI3K-AKT pathways, emphasizing its dual role in either promoting cell survival or exacerbating injury depending on autophagic flux. Preclinical studies demonstrate that HBO upregulates LC3-II and Beclin-1 while downregulating p62, indicating enhanced autophagy, whereas clinical trials (e.g., OPENS-2) suggest synergistic effects when combined with endovascular therapy. However, challenges remain regarding the lack of standardized biomarkers and optimal treatment parameters. Future research should focus on integrating HBO with specific autophagy modulators and conducting large-scale randomized controlled trials to validate its therapeutic potential in CIRI.

**Keywords:** Hyperbaric oxygen therapy, cerebral ischemia-reperfusion injury, autophagy, mTOR signaling, neuroprotection, clinical translation

## Introduction

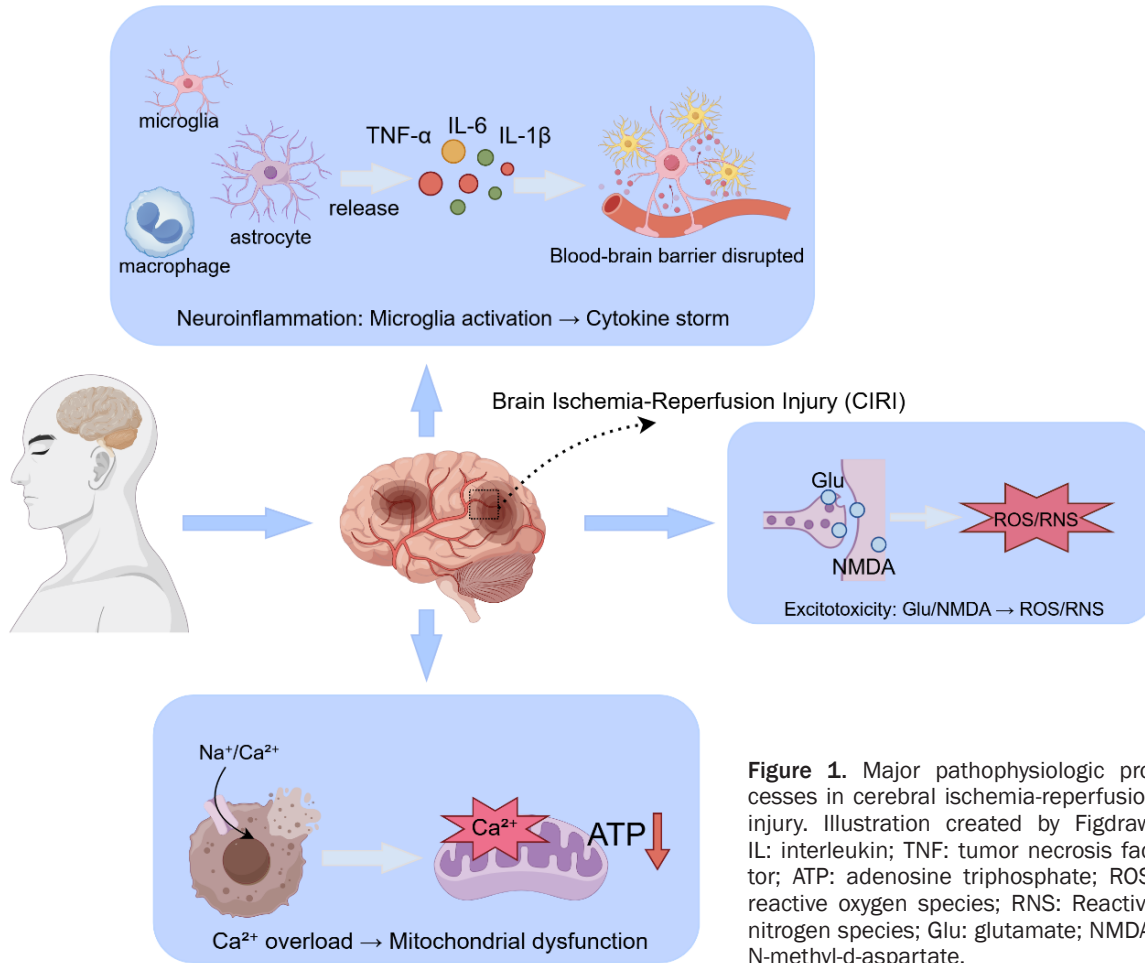
Ischemia-reperfusion injury refers to the metabolic dysfunction and structural damage of brain cells that occur following a period of cerebral ischemia and subsequent restoration of blood perfusion, leading to further aggravation of tissue and organ injury [1]. Cerebral ischemia-reperfusion injury (CIRI) is commonly observed in ischemic stroke, hypoxic-ischemic encephalopathy, and post-cardiopulmonary resuscitation brain injury. In recent years, various therapeutic strategies have been developed to alleviate the secondary injury caused by reperfusion; however, most have shown limited efficacy. Therefore, it is imperative to explore more effective interventions for preventing and treating CIRI. Autophagy plays a critical role in the

pathophysiological process of CIRI and represents a promising therapeutic target. Hyperbaric oxygen therapy (HBO) has demonstrated neuroprotective effects against CIRI, partly through the modulation of autophagy. This review summarizes the mechanisms by which HBO regulates autophagy in CIRI and discusses its clinical translational challenges.

## Overview of CIRI

The pathogenesis of CIRI is multifactorial, involving calcium overload, mitochondrial dysfunction, inflammatory activation, apoptosis, accumulation of oxygen-free radicals, and excessive release of excitatory amino acids [1]. During the ischemic phase, insufficient cerebral oxygen and blood supply force neurons to

## Mechanisms of cerebral ischemia-reperfusion injury



**Figure 1.** Major pathophysiologic processes in cerebral ischemia-reperfusion injury. Illustration created by Figdraw. IL: interleukin; TNF: tumor necrosis factor; ATP: adenosine triphosphate; ROS: reactive oxygen species; RNS: Reactive nitrogen species; Glu: glutamate; NMDA: N-methyl-d-aspartate.

rely on anaerobic glycolysis for energy, resulting in intracellular accumulation of sodium and calcium ions. Calcium influx into mitochondria through calcium transporters inhibits adenosine triphosphate (ATP) synthesis, leading to mitochondrial impairment. Meanwhile, elevated intracellular calcium triggers massive release of the excitatory neurotransmitter glutamate. The binding of glutamate to N-methyl-D-aspartate receptors promotes the generation of reactive oxygen species (ROS) and reactive nitrogen species, causing oxidative and nitrosative stress.

When reperfusion occurs, microglia, astrocytes, and macrophages become activated, releasing large amounts of inflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$  [2]. These inflammatory mediators disrupt mitochondrial integrity, damage vascular endothelial cells, and increase the permeability of the blood-brain barrier, ultimately resulting in neuronal

and tissue injury. The main pathophysiological mechanisms are illustrated in **Figure 1**.

### *Role of autophagy in CIRI*

During CIRI, multiple cell death pathways - including inflammation [3], apoptosis, and autophagy - interact and influence neuronal survival [4]. Autophagy is a lysosome-dependent process in which autophagosomes engulf damaged organelles and misfolded proteins, forming autolysosomes that degrade and recycle cellular components. Numerous studies have confirmed [5] that autophagy is a key mechanism in the development and repair processes of CIRI. Regulating autophagy can thus promote neuronal recovery during reperfusion.

Under physiological conditions [6], autophagy maintains cellular homeostasis by eliminating damaged organelles and proteins. However, under stress, the activation of autophagy may

## Mechanisms of cerebral ischemia-reperfusion injury

exert either protective or detrimental effects depending on its intensity and duration.

Mitochondrial autophagy (mitophagy) selectively removes dysfunctional mitochondria [7], which are central to energy production, calcium homeostasis, and ROS regulation [8]. By clearing damaged mitochondria, mitophagy maintains mitochondrial quality and prevents the release of pro-apoptotic factors such as cytochrome c under ischemic conditions [9, 10]. Notably, mitophagy may exert different effects in distinct temporal phases of injury: it appears protective during the reperfusion phase, when clearance of damaged mitochondria limits oxidative stress and neuronal apoptosis.

### *Mechanisms of HBO therapy in CIRI*

HBO therapy is an adjunctive intervention in which patients breathe 100% oxygen at 2-3 atmospheres absolute (ATA) to elevate arterial oxygen tension and oxygen dissolution in plasma. This enhances cellular respiration and maintains ATP synthesis in ischemic and hypoxic tissues [11]. HBO also reduces oxidative stress, suppresses inflammation, promotes phagocytic clearance of damaged cells, and recruits reparative cells. Clinically, HBO has been widely used in the management of cranio-cerebral trauma, limb replantation, sepsis, and wound healing [12].

Experimental and clinical studies have demonstrated that inhaling pure oxygen at 2-3 ATA increases its solubility in plasma by approximately 12.6-21.7 fold compared with normal atmospheric pressure [13]. The neuroprotective efficacy of HBO depends on the therapeutic window, frequency, and duration of treatment [13]. Optimal outcomes are achieved when HBO at 2.0 ATA is administered immediately after middle cerebral artery occlusion (MCAO) and continued for more than six hours, significantly improving survival in rodent models [14]. Moreover, repeated HBO sessions initiated 48 hours after brain injury can still confer therapeutic benefits [15], and delayed HBO administration may attenuate inflammation and reduce neuronal injury [16]. Recent studies further reveal that HBO alleviates oxidative stress, inflammation, apoptosis, amyloid- $\beta$  deposition, and cholinergic dysfunction, thereby providing multifaceted neuroprotection [17].

### **Mechanisms of interaction between HBO and autophagy**

Autophagy is a highly conserved cellular process essential for maintaining intracellular homeostasis. It functions by degrading and recycling damaged proteins and organelles, thereby serving as a primary pathway for the clearance of senescent or dysfunctional cellular components. Adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) are two key signaling molecules that regulate cellular metabolism, energy balance, and autophagy [18].

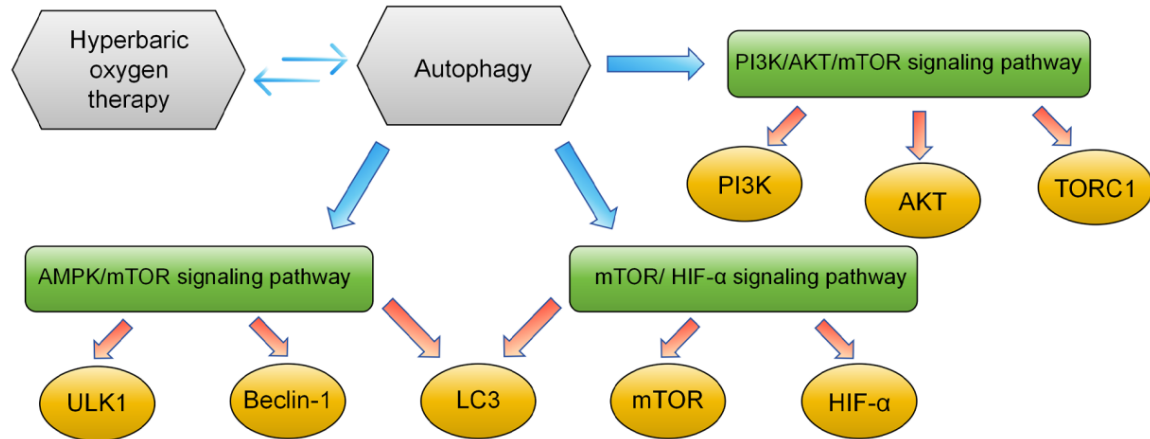
mTOR acts as a central inhibitor of autophagy [19], modulating the expression and activity of microtubule-associated protein 1 light chain 3 (LC3), p62, and Beclin-1. LC3 exists in two forms, LC3-I and LC3-II, and an increased LC3-II level or LC3-II/LC3-I ratio reflects enhanced autophagic activity [15]. The mechanistic target of rapamycin (mTOR) forms two distinct complexes - mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [20]. mTORC1 acts as the primary regulator of energy-consuming cellular processes: under nutrient-rich conditions, it promotes cell growth and biosynthesis, while under nutrient deprivation, its inhibition triggers autophagy to recycle intracellular components [21, 22].

mTOR suppresses autophagy both by inhibiting its early stages and by regulating lysosomal degradation via transcriptional control of structural and catalytic factors [23]. When mTOR is inhibited, autophagic recycling restores intracellular energy levels, which can subsequently reactivate mTORC1 - indicating that autophagy operates both downstream and upstream of mTOR. The intricate feedback regulation between mTOR and autophagy has been well characterized at the cellular level [24]. Importantly, HBO therapy has been shown to influence autophagy. For example, HBO alleviated neuropathic pain in rats by activating autophagy through the AMPK signaling pathway [25]. However, the precise mechanisms underlying HBO-autophagy crosstalk remain incompletely understood (**Figure 2**).

### *AMPK/mTOR signaling pathway*

AMPK and mTOR are major regulators of the autophagy process [26]. AMPK is a trimeric

## Mechanisms of cerebral ischemia-reperfusion injury



**Figure 2.** Interaction between hyperbaric oxygen (HBO) therapy and autophagy.

enzyme complex consisting of a catalytic  $\alpha$ -subunit and regulatory  $\beta$ - and  $\gamma$ -subunits. The  $\alpha$ -subunit is predominantly expressed in brain tissue, and its activation depends on the intracellular AMP/ATP ratio. Once activated, AMPK stimulates multiple metabolic pathways that enhance energy production and inhibit energy consumption [27].

mTOR, a serine/threonine kinase, modulates cell growth, metabolism, and proliferation. Its activation promotes the synthesis of macromolecules such as proteins, nucleotides, and lipids, while suppressing autophagy [28]. AMPK can directly activate the ULK1 complex to initiate autophagy and can also inhibit mTOR to promote autophagy under energy-deficient conditions, thus maintaining a dynamic equilibrium between anabolic and catabolic processes [29-31].

Wang et al. conducted a systematic transcriptomic analysis and found that HBO significantly activated the AMPK/mTOR signaling pathway, promoting autophagosome formation as evidenced by increased expression of Beclin-1 and LC3 proteins [32].

### *mTOR/HIF-1 $\alpha$ signaling pathway*

HIF-1 $\alpha$  is a transcription factor that responds to ischemic and hypoxic stress and plays a pivotal role in angiogenesis, tumor progression, and hypoxia-induced autophagy [33]. HIF-1 $\alpha$  is regulated downstream of mTOR, which enhances its transcriptional activity, stimulates protein synthesis, accelerates metabolism, and modulates autophagic responses [34].

Experimental results from Wang et al. showed that HBO effectively reduced cerebral infarction and edema by modulating the expression of mTOR, LC3-II, and HIF-1 $\alpha$  in the hippocampus, thereby influencing autophagic activity and improving ischemia-reperfusion outcomes [35].

### *PI3K/AKT/mTOR signaling pathway*

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mTOR signaling pathway plays a critical role in autophagy regulation following acute central nervous system injury. Akt, a serine-threonine kinase, is activated downstream of PI3K [29]. PI3K links Akt and mTOR through inactivation of the tuberous sclerosis complex subunit 2 (Tsc2) [30].

Evidence suggests that HBO induces autophagy via the Akt/Tsc2/mTOR pathway, thereby alleviating neuropathic pain [31]. The PI3K/AKT/mTOR axis is one of the most crucial signaling pathways involved in autophagy regulation [36]. Upon activation, PI3K generates the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3), which recruits phosphoinositide-dependent kinase 1 (PDK1) and Akt through their PH domains. This interaction results in phosphorylation of Akt by PDK1, leading to Akt activation [37, 38]. Activated Akt subsequently phosphorylates and activates mTOR to form mTORC1, which governs protein synthesis and autophagy [39].

Previous studies demonstrated that the PI3K/AKT/mTOR pathway contributes to cerebral ischemic injury in Sprague-Dawley rats; phar-

## Mechanisms of cerebral ischemia-reperfusion injury

macological inhibition of PI3K or mTOR altered autophagy levels and neuronal survival [40]. Moreover, HBO has been shown to mediate the Akt/Tsc2/mTOR pathway to induce autophagy and relieve neuropathic pain [41, 42]. Therefore, evaluating the expression of autophagy-related proteins such as PI3K, Akt, and mTOR can reflect autophagic activity in CIRI and its modulation by HBO.

### **Preclinical and clinical evidence associated with autophagy in CIRI treatment**

#### *Animal studies*

Autophagy exhibits a dual nature: appropriately activated autophagy supports neuronal survival after focal cerebral ischemia [43], whereas excessive activation can trigger cell death [6]. Preclinical studies have shown that HBO enhances autophagic activity, thereby exerting neuroprotective effects against cerebral ischemic injury. In one study, intracerebroventricular administration of the autophagy inhibitor 3-methyladenine (3-MA) prior to HBO preconditioning suppressed the HBO-induced upregulation of LC3-II and Beclin-1, and consequently attenuated its neuroprotective effects. In contrast, rapamycin pretreatment increased LC3-II and Beclin-1 expression after reperfusion, mimicking the neuroprotective effects of HBO preconditioning [44].

Lu et al. reported that autophagy blockade via activation of extracellular signal-regulated kinase 1/2 (ERK1/2) expanded the cerebral infarct area and aggravated CIRI in MCAO rats [45]. Similarly, Chen et al. found that HBO attenuated myocardial ischemia-reperfusion injury by inhibiting excessive autophagy through activation of the mTOR pathway [46].

#### *Clinical trials*

Clinically, HBO serves as a versatile adjunctive therapy for CIRI. Its combination with traditional Chinese medicine, targeted temperature management, endovascular therapy, and transcranial magnetic stimulation (TMS) has shown enhanced therapeutic outcomes.

In the OPENS-2 trial, the combination of normobaric high-oxygen therapy and endovascular treatment significantly improved 90-day modified Rankin Scale scores, with a favorable safety profile. Combined HBO also delayed the tran-

sition of the ischemic penumbra to the infarct core compared with thrombolysis alone [47].

Furthermore, both repetitive TMS (rTMS) and HBO were shown to facilitate recovery in comatose patients. HBO not only repaired neuronal injury but also provided metabolic energy that augmented neurotransmitter synthesis induced by rTMS. The combination of rTMS and HBO was markedly more effective in promoting awakening than HBO monotherapy, highlighting its potential for broader clinical adoption [15].

#### *Clinical efficacy testing of biomarkers*

The expression of autophagy-related proteins serves as an important biomarker for evaluating both CIRI pathogenesis and HBO efficacy [48]. Among these, p62 - a substrate and regulator of autophagy, is negatively correlated with autophagic activity. Clinical studies have reported that elevated peak serum p62 levels in patients with traumatic brain injury were significantly associated with poor neurological outcomes ( $P < 0.05$ ), suggesting that excessive accumulation of autophagosomes may aggravate secondary brain injury. This finding identifies p62 as a potential molecular marker for monitoring autophagy imbalance [49].

In animal models exploring HBO's therapeutic mechanisms, dynamic regulation of p62 and other autophagy markers has been confirmed [50]. HBO pretreatment markedly downregulated p62 expression while increasing the LC3-II/LC3-I ratio and Beclin-1 expression. Notably, inhibition of cystatin C (CysC) abolished HBO-induced p62 reduction and concomitantly suppressed LC3-II and Beclin-1 upregulation, indicating that CysC may be a key mediator in HBO-induced autophagy regulation. These results suggest that dynamic changes in p62 may reflect the reparative capacity of HBO on autophagic balance.

Future studies should explore the translational potential of these biomarkers using multimodal assessments - such as cerebrospinal fluid p62 quantification and PET/MRI autophagy imaging - to refine the optimal therapeutic window for HBO intervention.

### **Controversies and future directions**

Despite extensive preclinical evidence, research on HBO-mediated modulation of autophagy

## Mechanisms of cerebral ischemia-reperfusion injury

in CIRI remains limited. Although numerous basic studies have demonstrated HBO's neuroprotective effects through autophagy-related pathways, clinical translation is still insufficient. Most investigations focus on isolated autophagy markers rather than comprehensive monitoring of autophagic flux [51].

Clinically, current trials remain limited by small sample sizes, the absence of standardized efficacy evaluation systems, and a lack of studies examining the synergistic effects of HBO with neuroprotective agents or autophagy modulators. Moreover, the bidirectional role of autophagy - protective under moderate activation but detrimental when excessive - complicates interpretation of HBO's dose-response relationship. Therefore, determining the optimal HBO dosage, treatment frequency, and timing for precise autophagy regulation remains an urgent priority.

In summary, HBO confers neuroprotection in CIRI by bidirectionally modulating autophagy through the AMPK/mTOR, HIF-1 $\alpha$ , and related signaling pathways. However, its clinical efficacy is constrained by the therapeutic time window and the dynamic balance of autophagy. Future research should elucidate the interactions among autophagy, inflammation, and apoptosis regulated by HBO [52] - for instance, its influence on NLRP3 inflammasome activation via Beclin-1-dependent mechanisms [53].

Large, multicenter randomized controlled trials are warranted to evaluate combination regimens integrating HBO with autophagy modulators or neuroprotective agents. For patients without contraindications to pneumatic therapy, HBO should be administered alongside peripheral monitoring of autophagic activity to enable individualized treatment. As clinical evidence accumulates, a precise HBO-based therapeutic framework centered on autophagy modulation may significantly improve neurological outcomes in CIRI.

Although HBO shows considerable promise for managing cerebral ischemia-reperfusion injury, its mechanisms of action remain incompletely understood. Determining optimal treatment timing, dosing parameters, and safety profiles is essential before widespread clinical adoption. Nevertheless, accumulating experimental

evidence continues to support HBO as a promising adjunctive strategy for stroke therapy.

### Acknowledgements

This work was supported by the Natural Science Foundation of Henan Project (232300420059); Key Laboratory of Cardiopulmonary Cerebral Resuscitation in Henan Province (Engineering Technology Research Center) Research Special Project (202201281); Science and Technology Project of Henan Province (242102310260); Henan University of Traditional Chinese Medicine 2024 Graduate Student Research and Innovation Capacity Enhancement Program (2024KYCX090).

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Sisen Zhang, Fifth Clinical Medical College, Henan University of Chinese Medicine, 39 Hongqi Road, Zhengzhou 450002, Henan, China. Tel: +86-13937120886; E-mail: zhangsisen@hactcm.edu.cn

### References

- [1] Sunshine MD, Bindi VE, Nguyen BL, Doerr V, Boeno FP, Chandran V, Smuder AJ and Fuller DD. Oxygen therapy attenuates neuroinflammation after spinal cord injury. *J Neuroinflammation* 2023; 20: 303.
- [2] Lan X, Wang Q, Liu Y, You Q, Wei W, Zhu C, Hai D, Cai Z, Yu J, Zhang J and Liu N. Isoliquiritigenin alleviates cerebral ischemia-reperfusion injury by reducing oxidative stress and ameliorating mitochondrial dysfunction via activating the Nrf2 pathway. *Redox Biol* 2024; 77: 103406.
- [3] Xia Q, Zhan G, Mao M, Zhao Y and Li X. TRIM45 causes neuronal damage by aggravating microglia-mediated neuroinflammation upon cerebral ischemia and reperfusion injury. *Exp Mol Med* 2022; 54: 180-193.
- [4] Liu X, Xie C, Wang Y, Xiang J, Chen L, Yuan J, Chen C and Tian H. Ferritinophagy and ferroptosis in cerebral ischemia reperfusion injury. *Neurochem Res* 2024; 49: 1965-1979.
- [5] Zhao L, Chen Y, Li H, Ding X and Li J. Deciphering the neuroprotective mechanisms of RACK1 in cerebral ischemia-reperfusion injury: pioneering insights into mitochondrial autophagy and the PINK1/Parkin axis. *CNS Neurosci Ther* 2024; 30: e14836.

## Mechanisms of cerebral ischemia-reperfusion injury

- [6] Liu S, Yao S, Yang H, Liu S and Wang Y. Autophagy: regulator of cell death. *Cell Death Dis* 2023; 14: 648.
- [7] Li A, Gao M, Liu B, Qin Y, Chen L, Liu H, Wu H and Gong G. Mitochondrial autophagy: molecular mechanisms and implications for cardiovascular disease. *Cell Death Dis* 2022; 13: 444.
- [8] Zhang B, Pan C, Feng C, Yan C, Yu Y, Chen Z, Guo C and Wang X. Role of mitochondrial reactive oxygen species in homeostasis regulation. *Redox Rep* 2022; 27: 45-52.
- [9] De Nicolo B, Cataldi-Stagetti E, Diquigiovanni C and Bonora E. Calcium and reactive oxygen species signaling interplays in cardiac physiology and pathologies. *Antioxidants (Basel)* 2023; 12: 353.
- [10] Jia J, Jin H, Nan D, Yu W and Huang Y. New insights into targeting mitochondria in ischemic injury. *Apoptosis* 2021; 26: 163-183.
- [11] Bin-Alamer O, Abou-Al-Shaar H, Efrati S, Hadanny A, Beckman RL, Elamir M, Sussman E and Maroon JC. Hyperbaric oxygen therapy as a neuromodulatory technique: a review of the recent evidence. *Front Neurol* 2024; 15: 1450134.
- [12] He C, Huang D and Liu L. Hyperbaric oxygen therapy as a renewed hope for ischemic cranio-maxillofacial diseases. *Healthcare (Basel)* 2025; 13: 137.
- [13] Memar MY, Yekani M, Alizadeh N and Baghi HB. Hyperbaric oxygen therapy: antimicrobial mechanisms and clinical application for infections. *Biomed Pharmacother* 2019; 109: 440-447.
- [14] Trotman-Lucas M and Gibson CL. A review of experimental models of focal cerebral ischemia focusing on the middle cerebral artery occlusion model. *F1000Res* 2021; 10: 242.
- [15] Chen Y, Wang L, You W, Huang F, Jiang Y, Sun L, Wang S and Liu S. Hyperbaric oxygen therapy promotes consciousness, cognitive function, and prognosis recovery in patients following traumatic brain injury through various pathways. *Front Neurol* 2022; 13: 929386.
- [16] Awad-Igbaria Y, Ferreira N, Keadan A, Sakas R, Edelman D, Shamir A, Francous-Soustiel J and Palzur E. HBO treatment enhances motor function and modulates pain development after sciatic nerve injury via protection the mitochondrial function. *J Transl Med* 2023; 21: 545.
- [17] Shwe T, Bo-Htay C, Ongnok B, Chunchai T, Jaiwongkam T, Kerdphoo S, Kumfu S, Pratchayasakul W, Pattarasakulchai T, Chattipakorn N and Chattipakorn SC. Hyperbaric oxygen therapy restores cognitive function and hippocampal pathologies in both aging and aging-obese rats. *Mech Ageing Dev* 2021; 195: 111465.
- [18] Dikic I and Elazar Z. Mechanism and medical implications of mammalian autophagy. *Nat Rev Mol Cell Biol* 2018; 19: 349-364.
- [19] Gao X, Yu M, Sun W, Han Y, Yang J, Lu X, Jin C, Wu S and Cai Y. Lanthanum chloride induces autophagy in primary cultured rat cortical neurons through Akt/mTOR and AMPK/mTOR signaling pathways. *Food Chem Toxicol* 2021; 158: 112632.
- [20] Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, Raza AS, Sengupta S, Kumar D and Garg M. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. *Signal Transduct Target Ther* 2023; 8: 375.
- [21] Smiles WJ, Ovens AJ, Kemp BE, Galic S, Petersen J and Oakhill JS. New developments in AMPK and mTORC1 cross-talk. *Essays Biochem* 2024; 68: 321-336.
- [22] He L, Cho S and Blenis J. mTORC1, the maestro of cell metabolism and growth. *Genes Dev* 2025; 39: 109-131.
- [23] Ballesteros-Álvarez J and Andersen JK. mTORC2: the other mTOR in autophagy regulation. *Aging Cell* 2021; 20: e13431.
- [24] Deleyto-Seldas N and Efeyan A. The mTOR-autophagy axis and the control of metabolism. *Front Cell Dev Biol* 2021; 9: 655731.
- [25] Zhou YY, Ren RR, Cen Y, Liu WW and Chen H. Advances in the treatment of neuropathic pain with hyperbaric oxygen. *Undersea Hyperb Med* 2021; 48: 13-23.
- [26] Saikia R and Joseph J. AMPK: a key regulator of energy stress and calcium-induced autophagy. *J Mol Med (Berl)* 2021; 99: 1539-1551.
- [27] Schmitt DL. Imaging subcellular AMPK activity using an excitation-ratiometric AMPK activity reporter. *Curr Protoc* 2023; 3: e771.
- [28] Tarasiuk O, Miceli M, Di Domizio A and Nicolini G. AMPK and diseases: state of the art regulation by AMPK-targeting molecules. *Biology (Basel)* 2022; 11: 1041.
- [29] Zlotorynski E. The translation m(o)TOR that propels regeneration. *Nat Rev Mol Cell Biol* 2023; 24: 690.
- [30] Agostini F, Bisaglia M and Plotegher N. Linking ROS levels to autophagy: the key role of AMPK. *Antioxidants (Basel)* 2023; 12: 1406.
- [31] Park JM, Lee DH and Kim DH. Redefining the role of AMPK in autophagy and the energy stress response. *Nat Commun* 2023; 14: 2994.
- [32] Chen M, Wang X, Bao S, Wang D, Zhao J, Wang Q, Liu C, Zhao H and Zhang C. Orchestrating AMPK/mTOR signaling to initiate melittin-induced mitophagy: a neuroprotective strategy against Parkinson's disease. *Int J Biol Macromol* 2024; 281: 136119.

## Mechanisms of cerebral ischemia-reperfusion injury

- [33] Wang S, Chen B, Yuan M, Liu S, Fan H, Yang X, Zou Q, Pu Y and Cai Z. Enriched oxygen improves age-related cognitive impairment through enhancing autophagy. *Front Aging Neurosci* 2024; 16: 1340117.
- [34] Abd El-Baset SA, Mazen NF, Abdul-Maksoud RS and Kattaia AAA. The therapeutic prospect of zinc oxide nanoparticles in experimentally induced diabetic nephropathy. *Tissue Barriers* 2023; 11: 2069966.
- [35] Kawakita E, Yang F, Shi S, Takagaki Y, Koya D and Kanasaki K. Inhibition of dipeptidyl peptidase-4 activates autophagy to promote survival of breast cancer cells via the mTOR/HIF-1 $\alpha$  pathway. *Cancers (Basel)* 2023; 15: 4529.
- [36] Wang C, Niu F, Ren N, Wang X, Zhong H, Zhu J and Li B. Hyperbaric oxygen improves cerebral ischemia/reperfusion injury in rats probably via inhibition of autophagy triggered by the downregulation of hypoxia-inducing factor-1  $\alpha$ . *Biomed Res Int* 2021; 2021: 6615685.
- [37] Shaw AL and Burke JE. Molecular insight on the role of the phosphoinositide PIP3 in regulating the protein kinases Akt, PDK1, and BTK. *Biochem Soc Trans* 2025; 53: 737-749.
- [38] Chen K, Jiao J, Xue J, Chen T, Hou Y, Jiang Y, Qian L, Wang Y, Ma Z, Liang Z, Sun B and Ren Q. Ginsenoside CK induces apoptosis and suppresses proliferation and invasion of human osteosarcoma cells through the PI3K/mTOR/p70S6K1 pathway. *Oncol Rep* 2020; 43: 886-896.
- [39] Kwon Y, Bang Y, Moon SH, Kim A and Choi HJ. Amitriptyline interferes with autophagy-mediated clearance of protein aggregates via inhibiting autophagosome maturation in neuronal cells. *Cell Death Dis* 2020; 11: 874.
- [40] Yin S, Yang S, Pan X, Ma A, Ma J, Pei H, Dong Y, Li S, Li W and Bi X. MicroRNA-155 promotes ox-LDL-induced autophagy in human umbilical vein endothelial cells by targeting the PI3K/Akt/mTOR pathway. *Mol Med Rep* 2018; 18: 2798-2806.
- [41] Brenna CT, Khan S, Katznelson R and Brull R. The role of hyperbaric oxygen therapy in the management of perioperative peripheral nerve injury: a scoping review of the literature. *Reg Anesth Pain Med* 2023; 48: 443-453.
- [42] Lee YR, Chen M and Pandolfi PP. The functions and regulation of the PTEN tumour suppressor: new modes and prospects. *Nat Rev Mol Cell Biol* 2018; 19: 547-562.
- [43] Liu YD, Wang ZB, Han G, Jin L and Zhao P. Hyperbaric oxygen relieves neuropathic pain through AKT/TSC2/mTOR pathway activity to induce autophagy. *J Pain Res* 2019; 12: 443-451.
- [44] Chen C, Chen W, Nong Z, Nie Y, Chen X, Pan X, Guo Y, Yao M and Deng W. Hyperbaric oxygen alleviated cognitive impairments in mice induced by repeated cerebral ischemia-reperfusion injury via inhibition of autophagy. *Life Sci* 2020; 241: 117170.
- [45] Lu Y, Kang J, Bai Y, Zhang Y, Li H, Yang X, Xiang X, Wang X, Huang Y, Su J, Chen Y, Li B and Sun L. Hyperbaric oxygen enlarges the area of brain damage in MCAO rats by blocking autophagy via ERK1/2 activation. *Eur J Pharmacol* 2014; 728: 93-99.
- [46] Chen C, Chen W, Li Y, Dong Y, Teng X, Nong Z, Pan X, Lv L, Gao Y and Wu G. Hyperbaric oxygen protects against myocardial reperfusion injury via the inhibition of inflammation and the modulation of autophagy. *Oncotarget* 2017; 8: 111522-111534.
- [47] Li W, Lan J, Wei M, Liu L, Hou C, Qi Z, Li C, Jiao L, Yang Q, Chen W, Liu S, Yue X, Dong Q, Yuan H, Gao Z, Wu X, Wen C, Li T, Jiang C, Li D, Chen Z, Shi J, Shi W, Yuan J, Qin Y, Li B, Fisher M, Feng W, Liu KJ and Ji X; OPENS-2 Investigators. Normobaric hyperoxia combined with endovascular treatment for acute ischaemic stroke in China (OPENS-2 trial): a multicentre, randomised, single-blind, sham-controlled trial. *Lancet* 2025; 405: 486-497.
- [48] Fleming A, Bourdenx M, Fujimaki M, Karabiyik C, Krause GJ, Lopez A, Martín-Segura A, Puri C, Scivo A, Skidmore J, Son SM, Stamatakou E, Wrobel L, Zhu Y, Cuervo AM and Rubinsztein DC. The different autophagy degradation pathways and neurodegeneration. *Neuron* 2022; 110: 935-966.
- [49] Au AK, Aneja RK, Bayir H, Bell MJ, Janesko-Feldman K, Kochanek PM and Clark RSB. Autophagy biomarkers beclin 1 and p62 are increased in cerebrospinal fluid after traumatic brain injury. *Neurocrit Care* 2017; 26: 348-355.
- [50] Fang Z, Feng Y, Li Y, Deng J, Nie H, Yang Q, Wang S, Dong H and Xiong L. Neuroprotective autophagic flux induced by hyperbaric oxygen preconditioning is mediated by cystatin C. *Neurosci Bull* 2019; 35: 336-346.
- [51] He Z, Du J, Zhang Y, Xu Y, Huang Q, Zhou Q, Wu M, Li Y, Zhang X, Zhang H, Cai Y, Ye K, Wang X, Zhang Y, Han Q and Xiao J. Kruppel-like factor 2 contributes to blood-spinal cord barrier integrity and functional recovery from spinal cord injury by augmenting autophagic flux. *Theranostics* 2023; 13: 849-866.
- [52] Lei C, Li Y, Zhu X, Li H and Chang X. HMGB1/TLR4 induces autophagy and promotes neuroinflammation after intracerebral hemorrhage. *Brain Res* 2022; 1792: 148003.
- [53] Chen Y, Chen J, Xing Z, Peng C and Li D. Autophagy in neuroinflammation: a focus on epigenetic regulation. *Aging Dis* 2024; 15: 739-754.