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*Review*

# From Protection to Injury: Vascular Autophagy in Ischemic Stroke

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**Abstract**

Autophagy is a fundamental intracellular degradation process that maintains cellular homeostasis by recycling damaged organelles and macromolecules. In ischemic stroke, autophagy exhibits a dynamic and context-dependent dual role that evolves over time and cell types: moderate autophagy protects cells in early ischemia and reperfusion, while excessive or prolonged autophagy triggers cell damage, inflammation, and cell death. In this review, we focus on vascular autophagy, encompassing the classic autophagy-lysosome pathway in all vascular cells—endothelial cells, smooth muscle cells, and pericytes. We further identify this process as a critical yet underappreciated determinant of stroke outcome. As the first compartment exposed to ischemia-reperfusion injury, vascular cells govern blood-brain barrier (BBB) integrity, microvascular patency, and angiogenic remodeling. Emerging evidence reveals stage-dependent effects: moderate vascular autophagy preserves BBB stability, endothelial survival, and microvascular repair, whereas excessive or dysregulated vascular autophagy promotes tight-junction degradation, BBB disruption, vasogenic edema, and hemorrhagic transformation. We propose a "turning point" model in which vascular autophagy shifts from an adaptive, protective mechanism to a pathological driver of vascular injury, governed by ischemic severity, reperfusion timing, metabolic reserve, dysfunctional mitochondria, oxidative injury, and inflammation. By positioning vascular autophagy as a central regulator of neurovascular unit dysfunction, we provides a conceptual framework for precision therapeutic strategies targeting vascular autophagy to mitigate futile reperfusion and improve outcomes after ischemic stroke.

**Keywords:** autophagy; endothelial cells; blood-brain barrier; pericytes; reperfusion injury; tight-junction

## 1. Introduction

Autophagy is a highly conserved intracellular degradation process that plays a crucial role in recycling cytoplasmic components through the lysosomal pathway [1]. Beyond sustaining energy supply during nutrient deprivation, autophagy serves as an important mechanism for cellular quality control, organelle turnover, and metabolic adaptation [2]. Autophagy can be triggered by various pathophysiological stimuli, including oxidative stress, energy deprivation, and hypoxia [3]. Under physiological conditions, it functions as a highly dynamic "cellular scavenger", maintaining intracellular homeostasis by swiftly removing misfolded proteins and damaged organelles [4]. Under sustained or extreme stress, however, dysregulated or overactivated autophagy may shift toward self-destruction, leading to apoptosis or necrosis [5]. The field was propelled forward in 2016, when Yoshinori Ohsumi received the Nobel Prize for identifying autophagy-related genes and elucidating their molecular mechanisms in yeast [6], an achievement that catalyzed translational investigations into the role of autophagy in human pathophysiology.

Within hours of ischemic stroke onset, autophagic flux is rapidly activated [7], making autophagy an integral component of the pathophysiological cascade. Current evidence indicates that autophagy exhibits dual roles in ischemic brain injury [5,8,9]: moderate activation eliminates toxic proteins and damaged mitochondria, maintains intracellular energy balance, and inhibits apoptotic pathways, thereby exerting neuroprotective effects [8,10]. Conversely, excessive or sustained autophagy degrades essential cellular components, compromises structural integrity, and interacts with other cell death mechanisms, including apoptosis and necroptosis, thereby aggravating neuroinflammation and blood-brain barrier (BBB) disruption [11]. This putative turning point at which autophagy shifts from beneficial to detrimental is likely shaped by ischemia severity, reperfusion timing, and cell type-specific responses [8,12].

The vascular interface, comprising the endothelial lining of cerebral microvessels and their supporting mural cells, is the primary anatomical and functional site at which ischemia-reperfusion stress is first detected and converted into parenchymal injury [13]. In this review, we propose "vascular autophagy" to denote the classical autophagosome-lysosome pathway process operating in all vascular cells, including endothelial cells, vascular smooth muscle cells (VSMCs), and pericytes. Our rationale for adopting vascular autophagy is twofold: first, it provides a concise, vessel-specific term that distinguishes autophagy at the vascular interface from autophagy in neurons, glia, and other parenchymal cells; and second, it conceptually unifies the original endothelial engulfment mechanism with

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the broader autophagic machinery now recognized to operate across all vascular cell types in the ischemic brain.

Our central inquiry is not whether vascular autophagy is uniformly beneficial or detrimental; rather, we aim to identify the critical juncture at which it transitions from an adaptive response to a vasculopathic one. We synthesize emerging evidence demonstrating stage-dependent effects [14,15]: moderate vascular autophagy supports BBB stability, endothelial survival, and microvascular repair, whereas excessive or dysregulated vascular autophagy accelerates tight-junction degradation, BBB breakdown, vasogenic edema, and hemorrhagic transformation.

## 2. Autophagy in Ischemic Stroke

Autophagy is closely implicated in the pathophysiology of ischemic stroke. Following abrupt interruption of cerebral blood flow, hypoxia, glucose deprivation, and energy failure rapidly activate cellular stress-response pathways, with autophagy among the earliest adaptive mechanisms recruited [16,17].

### *2.1 Protective Autophagy*

In the early stage of ischemia, moderately activated autophagy exerts cytoprotective effects. Pharmacological studies in rat middle cerebral artery occlusion (MCAO) models have shown that rapamycin administration to induce autophagy before or during early ischemia reduces infarct volume and neuronal apoptosis, whereas inhibition of autophagy with 3-methyladenine (3-MA) produces the opposite effect [18,19]. Genetic evidence further supports this view, as autophagy-related gene 7 (*Atg7*) knockdown aggravates infarct size and neurological deficits after cerebral ischemia-reperfusion injury in mice [20]. These protective effects are mainly attributed to the clearance of damaged organelles, maintenance of energy homeostasis, and suppression of cell death pathways. The PTEN-induced kinase 1 (PINK1)/Parkin pathway, a key mediator of mammalian mitophagy, and classical endoplasmic reticulum (ER) autophagy pathways have been implicated in limiting mitochondrial dysfunction and ER stress following ischemic injury in both cell culture and animal models [21,22,23].

### *2.2 Maladaptive Autophagy*

Although autophagy activation immediately upon reperfusion is essential for neuroprotection, its role shifts fundamentally as reperfusion progresses. Tian et al. [24] utilized *in vivo* imaging techniques in mouse MCAO models and detected autophagic signals at 1, 3, and 6 days after reperfusion, with a peak at 24 h. Ma et al. [25] showed that inhibiting excessive PINK1/Parkin-mediated autophagy alleviated oxidative stress and reduced infarct volume after cerebral ischemia/reperfusion, while Li et al. [26] showed that sustained high expression of the autophagy-related proteins Beclin-1 and LC3-II positively correlated with neuronal apoptosis through animal experiments.

Under severe or prolonged ischemia in animal models, dysregulated or excessive autophagy may aggravate brain injury. In this context, autophagy inhibition with 3-MA or bafilomycin A1 reduces infarct size and improves neurological outcomes, and autophagy-related gene 5 (*Atg5*) knockdown is similarly protective [27,28]. Autophagosome accumulation with impaired degradation disrupts cellular homeostasis, leading to energy failure and structural collapse [29,30]. Concurrently, excessive autophagy may trigger autophagy-dependent cell death, amplify inflammatory signaling, and interact with apoptosis, necroptosis, and ferroptosis to compound ischemic damage [27,31,32].

Preclinical ischemia–reperfusion studies in rodents suggest that modulating autophagy within the first few hours after ischemia onset may help extend the therapeutic time window [33]. However, beyond this critical period, excessive autophagy may contribute to futile reperfusion, a state in which neurological function fails to improve despite successful vascular recanalization [34,35]. It should be emphasized that, due to the significant differences in ischemic dynamics between animals and humans, the translational significance of this window period for the treatment of human stroke still requires cautious consideration.

### *2.3 Autophagy of Different Cells*

In stroke, autophagy is activated across all brain cell types within the damaged region, including neurons, glial cells, and microvascular cells, but these cell types differ substantially in metabolic characteristics, stress tolerance, and autophagy regulatory mechanisms. Understanding these distinctions is a prerequisite for targeted interventions [36].

Neurons, as the principal functional units of brain tissue, are highly dependent on energy supply and redox homeostasis. During early ischemia, animal studies have demonstrated that mitophagy—mediated by ubiquitin-dependent pathways (the PINK1/Parkin axis) and ubiquitin-independent pathways (BCL2-interacting protein 3 (BNIP3) and FUN14 domain-containing 1 (FUNDC1))—selectively removes damaged mitochondria, reduces the accumulation of reactive oxygen species (ROS), and inhibits pro-apoptotic signals, thereby exerting certain neuroprotective effects [21,37]. However, when ischemia persists beyond the cell's compensatory capacity, autophagosome accumulation and lysosomal dysfunction obstruct autophagic flux, ultimately triggering autophagy-dependent cell death [38].

Astrocytes are comparatively tolerant of ischemic stimuli. Early autophagy in these cells can support neuronal survival by promoting glucose and lactate transport [39,40]. However, in continuous ischemia or late reperfusion, excessive autophagy-induced astrocyte death may amplify the neuroinflammatory response by releasing damage-associated molecular patterns [41].

Microglia, the resident immune cells of the central nervous system, exhibit close coupling between autophagic activity and inflammatory polarization. Moderate autophagy promotes M2 anti-inflammatory polarization [42,43], enhancing the clearance of cellular debris and tissue repair. However, during late ischemia-reperfusion, inhibition or imbalance of autophagy favors pro-inflammatory phenotypes, thereby exacerbating local inflammation and tissue damage [44].

The vascular endothelial compartment is the first cellular interface directly exposed to ischemia and reperfusion. Its autophagic response therefore carries immediate consequences for BBB integrity, capillary patency, leukocyte trafficking, and post-ischemic microvascular remodeling.

## 3. Vascular Autophagy

Vascular autophagy, as defined in this review, refers specifically to autophagy in brain microvascular cells induced by cerebral ischemia-reperfusion. This process warrants separate consideration because the vascular interface is the primary anatomical and functional site at which ischemia-reperfusion stress is transduced into tissue injury [45]. Understanding the fine balance between beneficial and harmful vascular autophagy is therefore critical for stroke therapy development [46].

### *3.1 Pathophysiological Processes*

Following interruption of cerebral blood flow, hypoxia, hypoglycemia and subsequent reperfusion injury act on the vascular interface, triggering a series of cellular stress responses [47].

In vascular endothelial cells exposed to oxygen-glucose deprivation/reoxygenation (OGD/R), intracellular adenosine triphosphate (ATP) generation is blocked and the mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway is inhibited, relieving inhibition of autophagy and leading to a significant increase in autophagosome formation. In brain microvascular endothelial cells under OGD/R conditions, the increase in LC3-II/LC3-I ratio accompanied by sequestosome 1 (SQSTM1/p62) reduction supports activation of autophagic flux rather than mere autophagosome accumulation. Comparable ultrastructural and molecular changes have been observed in isolated brain capillaries from rats and mice following experimental MCAO [15].

Investigation of autophagy in VSMCs and pericytes remains limited. In primary brain VSMCs, hypoxia and hypoglycemia increase autophagic flux accompanied by phenotypic shift from a contractile to a synthetic state, resulting in loss of vascular integrity. And the studies have shown that the sphingosine-1-phosphate receptor (S1PR) ligand ozanimod can attenuate this response, suggesting that moderate regulation of VSMC autophagy is crucial for maintaining vascular function [48]. In pericytes, ischemia-induced autophagy and apoptosis occur concurrently *in vivo* MCAO animal models and *in vitro* OGD/R systems; excessive autophagic activation leads to pericyte detachment from the vessel wall, compromising BBB integrity and promoting neuroinflammation [49]. Pericytes are among the earliest vascular cell types to respond to ischemia, and their autophagic status may determine the early fate of the BBB, though direct evidence in ischemic stroke remains limited [50].

A major structural consequence of dysregulated vascular autophagy is disruption of the endothelial junctional complex. These junctions are formed by transmembrane proteins such as claudin-5 and occludin, together with scaffolding proteins including zonula occludens-1 (ZO-1), zonula occludens-2 (ZO-2), zonula occludens-3 (ZO-3) [51]. Under ischemic stress, tight-junction proteins become direct targets of autophagy-related degradation. Once vascular autophagy shifts from selective quality control toward junctional protein degradation, BBB failure becomes an immediate vascular consequence.

The relationship between vascular autophagy and BBB injury is both stage- and context-dependent. During early ischemia and initial reperfusion, moderate vascular autophagy may support endothelial adaptation by clearing dysfunctional mitochondria and misfolded proteins. However, with prolonged ischemia, persistent reperfusion stress, or metabolic insults such as hyperglycemia, vascular autophagy may become excessive or flux-impaired, shifting toward junctional loss, matrix degradation, and barrier leakage [52]. In this setting, autophagy cooperates with other injurious pathways, including matrix metalloproteinase activation, to promote ZO-1 redistribution and increase BBB permeability [53].

### *3.2 Beneficial and Detrimental Effects of Vascular Autophagy*

#### 3.2.1 Beneficial Effects

Experimental evidence from rodent MCAO models and cell culture systems substantially supports a protective role for endothelial autophagy during early ischemia and initial reperfusion. Activation of autophagy maintains normal ZO-1 distribution, reduces Evans blue extravasation in the ischemic hemisphere, and decreases brain water content [54]. Mechanistically, protective autophagy demonstrates bidirectional regulatory capacity: when claudin-5 and caveolin-1 (Cav-1) accumulate abnormally in the cytoplasm, autophagy clears these aggregates to preserve barrier architecture, while autophagy blockade exacerbates protein aggregation and BBB damage [55].

Maintaining vascular cell survival is another important mechanism for protective autophagy. In cultured brain microvascular endothelial cells, it inhibits apoptosis by eliminating damaged mitochondria and reducing ROS accumulation, with both mTOR-dependent and mTOR-independent pathways contributing [56,57]. In mouse pericytes, Sigma-1 receptor activation promotes pericyte sur-

vival by regulating the balance between autophagy and apoptosis, thereby preserving BBB integrity [49]. This suggests that this balance may represent a shared survival regulatory node across vascular cell types, although validation in VSMCs and across multiple experimental paradigms is still required.

Further mechanistic studies in cell cultures and animal models reinforce a protective role of moderate vascular autophagy in endothelial stress adaptation [58]. Dissociation of the Beclin-1/B-cell lymphoma 2 (Bcl-2) complex enhances vascular autophagy and suppresses endothelial apoptosis [33]. Likewise, metastasis-associated lung adenocarcinoma transcript 1 (*Malat1*), a long noncoding RNA, promotes unc-51 like autophagy activating kinase 2 (ULK2) upregulation, and sirtuin 1 (SIRT1)-AMP-activated protein kinase (AMPK) activation supports autophagic flux under OGD/R conditions in cultured endothelial cells [59,60]; and hypoxia-inducible factor 1-alpha (HIF-1α)-dependent BNIP3 signaling links hypoxic stress to adaptive mitophagy and BBB preservation [61]. In thalamic vessels of mice, autophagy has also been implicated in angiogenesis and neural repair after stroke [14], expanding its protective function from damage reduction to active tissue remodeling. Finally, Atg7-mediated autophagy reduces inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) phosphorylation and downregulates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity, thereby decreasing pro-inflammatory cytokine production [41]. This anti-inflammatory effect represents an additional protective dimension of appropriately regulated vascular autophagy during early ischemia.

#### 3.2.2 Detrimental Effects

When ischemia persists or reperfusion enters the later stage, excessive autophagy activation or blockade of autophagic flux causes vascular autophagy to shift from a protective mechanism to a pathological force. In experimental animal models, this transition is associated with markedly elevated LC3-II/LC3-I ratios, significant decreases in tight-junction protein expression, substantially increased BBB permeability, elevated cerebral water content, and expanded infarct volume [15,62].

Notably, LC3 serves as a canonical marker of autophagic activity [63]. During autophagy, cytosolic LC3-I is lipidated to form membrane-associated LC3-II, and the LC3-II level or LC3-II/LC3-I ratio is widely used to assess autophagosome formation and accumulation. However, this metric alone cannot distinguish between productive autophagic activation and impaired degradation, as both increased autophagosome biogenesis and lysosomal dysfunction elevate LC3-II [64]. Sustained LC3-II/LC3-I elevation in the late phase of ischemia-reperfusion in rodent models is therefore more indicative of impaired autophagic flux than of simple autophagy activation. Under these conditions, autophagosomes accumulate but fail to fuse efficiently with lysosomes or complete cargo degradation, leading to intracellular structural accumulation, energy homeostasis dysregulation, and aggravated neuronal injury [65]. LC3-II/LC3-I changes should accordingly be interpreted alongside the dynamic behavior of p62/SQSTM1 and other autophagy cargo receptors; concurrent accumulation of these markers typically reflects blockade of the autophagosome–lysosome degradation pathway and a shift from protective clearance toward pathological autophagy impairment.

At the endothelial level, Kim et al. [15] systematically elucidated the mechanism of autophagy-mediated BBB destruction using cultured bEnd.3 mouse brain endothelial cells and rat MCAO models. Under ischemic conditions, nitric oxide (NO) promotes Cav-1–mediated delivery of claudin-5 to autophagosomes, leading to autophagy-lysosome-dependent degradation of claudin-5 in brain endothelial cells [66]. Concurrently, p62/SQSTM1 functions not merely as a passive autophagy substrate but as a signaling hub [67,68]. Under physiological conditions, p62 is continuously degraded along with intact autophagic flux, but when flux is impaired, p62 accumulates and competitively binds Kelch-like ECH-associated protein 1 (Keap1) via its Keap1-interacting region, preventing Keap1-mediated degradation of nuclear factor erythroid 2-related factor 2 (NRF2). This promotes NRF2 nuclear translocation and activates the transcription of antioxidant and stress-response genes [69]. Although this axis may be transiently protective in the acute phase, prolonged aberrant activation during late ischemia-reperfusion disrupts redox homeostasis and can sensitize endothelial cells to ferroptosis through alterations in iron metabolism and lipid peroxidation [70].

Under conditions of sustained ischemia in rodent models, autophagy and apoptosis can act synergistically to promote endothelial cell death. Naito et al. [71] demonstrated in mice that sequential activation of necroptosis and apoptosis compounds vascular and neuropathological injury in stroke, exacerbating BBB disruption and cerebral damage. Furthermore, excessive autophagy can trigger autophagic cell death, a form of programmed cell death distinct from apoptosis and necrosis, in which widespread organelle and protein degradation under ischemia-reperfusion conditions ultimately results in cell death [72]. Excessive autophagy can also induce endothelial cell cytoskeletal reorganization, disrupting intercellular adhesion junctions, and further aggravating BBB disruption [73].

Using a hyperglycemia-combined ischemia-reperfusion model in rats, Zhang et al. [53] demonstrated that impaired autophagosome-lysosome fusion obstructs autophagic flux, with incomplete autophagy paradoxically exacerbating endothelial cell injury and increasing BBB permeability, underscoring that autophagy completeness is critical for determining functional outcome. Xia et al. [74] showed that small extracellular vesicles secreted

from human induced pluripotent stem cell (iPSC)-derived mesenchymal stem cells enhance angiogenesis via signal transducer and activator of transcription 3 (STAT3)-dependent autophagy inhibition, promoting neurovascular repair following ischemia and suggesting that autophagy inhibition can effectively protect the BBB.

In primary cultured pericytes and rodent models of cerebral infarction, excessive autophagy activation following cerebral infarction leads to pericyte detachment from the vascular wall, damaging capillary structural integrity, promoting BBB leakage, and activating neuroinflammation [75]. The balance between autophagy and apoptosis in pericytes is considered a pivotal node governing the early fate of the BBB, though direct evidence in ischemic stroke remains limited.

## 4. The "Turning Point" Model of Vascular Autophagy

Autophagy is a highly conserved stress-response mechanism that is strongly activated after ischemic stroke, yet its functional consequences are profoundly context-dependent. The evidence reviewed here makes clear that autophagy cannot be simply categorized as beneficial or detrimental; rather, its impact on stroke outcome is controlled by precise spatiotemporal conditions and cell-type–specific responses. Early, appropriately regulated autophagy supports cellular adaptation by maintaining metabolic homeostasis and organelle integrity, whereas sustained or dysregulated autophagy drives structural degradation, inflammatory amplification, and progressive tissue injury [5,76].

A central theme of this review is the critical role of vascular autophagy in shaping neurovascular outcomes after ischemic stroke. As the primary interface between circulating blood and brain parenchyma, endothelial cells are uniquely positioned to convert ischemic and reperfusion stress into BBB dysfunction, microvascular failure, and ultimately futile reperfusion. Moderate vascular autophagy facilitates endothelial survival, preserves tight-junction architecture, and supports microvascular remodeling, whereas excessive or incomplete vascular autophagy accelerates BBB breakdown, edema formation, and hemorrhagic transformation.

To reconcile these apparently contradictory observations, we propose a conceptual "turning-point" model in which vascular autophagy transitions from an adaptive, barrier-preserving process to a maladaptive driver of vascular injury. This turning point is unlikely to represent a single molecular switch; instead, it more plausibly reflects the convergence of ischemic severity, reperfusion timing, metabolic reserve, inflammatory burden, and endothelial-specific signaling dynamics. This framework is offered as an integrative hypothesis that synthesizes current findings and highlights critical knowledge gaps rather than a definitive mechanistic conclusion.

From the molecular perspective, signaling axes such as mTOR, AMPK, Beclin-1/Bcl-2, SIRT1-AMPK, and HIF-1α-BNIP3 likely play a crucial regulatory role in this transition. Concurrently, differences in energy metabolism, stress thresholds, and autophagy regulation among different vascular cell types determine that the turning point occurs at different times and with varying sensitivities in each population. Accordingly, this model should be understood as a cell-specific, staged, and dynamically variable process of pathological evolution [77].

Once this threshold is crossed, abnormal vascular autophagy activation or autophagic flux blockade no longer exerts a restorative effect but instead becomes an important link in amplifying injury. The turning point model emphasizes that vascular autophagy in ischemic stroke is not a question of simple enhancement or inhibition, but of a dynamic balance constrained by the therapeutic time window, ischemia severity, and cell type. Identifying this inflection point deepens understanding of post-stroke vascular pathology and provides a theoretical foundation for precise vascular autophagy modulation in future therapeutic development.

## 5. Discussion

Vascular autophagy, as defined in this review, broadly encompasses autophagy occurring in vascular cells, including endothelial cells, VSMCs, and pericytes. However, the current evidence base is unevenly distributed. Most studies supporting the proposed turning-point model have focused on endothelial cells, particularly in relation to mitochondrial quality control, ROS regulation, tight-junction integrity, and BBB maintenance. By contrast, evidence regarding ischemia-related autophagy in VSMCs and pericytes remains sparse and is derived largely from limited experimental observations and mechanistic inference. Extension of the turning-point model to these mural cell populations should thus be considered hypothetical. Their temporal patterns of autophagic flux, functional consequences, and contributions to post-ischemic vascular remodeling require further validation using cell-specific genetic models, dynamic flux measurements, and *in vivo* approaches.

Despite meaningful progress in autophagy research in ischemic stroke, existing evidence remains predominantly concentrated at the neuronal level. A systematic, mechanistic understanding of vascular autophagy is lacking, particularly regarding its dynamic changes across disease stages, cell type-specific differences, and pathological outcomes. Future research should adopt the neurovascular unit as its frame of reference, focusing on temporal dependence, flux state, and functional distinctions of autophagy in endothelial cells, pericytes, and VSMCs to clarify the biological significance of vascular autophagy across the phases of stroke onset, progression, and reperfusion injury. In particular, the critical juncture at which vascular autophagy shifts from protective adaptation to pathological damage, and the

upstream signaling networks that collaboratively regulate autophagy initiation, extension, maturation, and lysosomal degradation, requires further elucidation.

Most mechanistic and temporal evidence regarding vascular autophagy after ischemic stroke is derived from cultured-cell experiments and rodent models of cerebral ischemia. Human evidence remains preliminary. Accordingly, the proposed molecular pathways, temporal windows, and turning-point model should be regarded as preclinical concepts requiring validation in human tissue, imaging studies, and prospective clinical trials.

Methodologically, future studies should move beyond reliance on individual autophagy-related proteins as proxies for vascular autophagy status. Multi-dimensional indicators, including cell type-specific models, ultrastructural analysis, and dynamic imaging, are needed to evaluate the autophagic flux integrity systematically and to delineate its functional contributions across stroke phases. From a translational perspective, the field must shift from descriptive characterization toward precise regulation. Given the clear temporal dependence of vascular autophagy, developing reliable biomarkers that reflect its dynamic state, combinable with imaging and liquid biopsy for real-time monitoring, could provide a foundation for stratified patient assessment and precision treatment therapy.

The interaction network connecting vascular autophagy with neuroinflammation, oxidative stress, ferroptosis, and BBB damage likely constitutes an important pathological determinant for stroke prognosis. Systematic investigation of these relationships will not only strengthen the theoretical framework of vascular autophagy in stroke but may also identify potential targets for novel neurovascular protective strategies. Research integrating high-resolution temporal analysis, endothelial-specific genetic tools, and clinically relevant models will be essential for validating the turning-point model and may ultimately reveal new therapeutic avenues for improving neurological recovery after ischemic stroke.

## 6. Conclusions

Vascular autophagy is a stage-dependent determinant of neurovascular outcome after ischemic stroke. Early, moderate autophagy preserves endothelial survival and BBB integrity, whereas sustained or flux-impaired autophagy drives junctional loss, edema, hemorrhagic transformation, and futile reperfusion. Defining when and where vascular autophagy crosses from protection to injury should ultimately enable more precise, time-window-based therapeutic strategies for ischemic stroke.

## Author Contributions

WL: Writing - original draft, Visualization. YD: Conceptualization, Writing - review & editing, Project administration. JK: Conceptualization, Investigation, Writing - review & editing. FL: Conceptualization, Investigation, Writing - review & editing, Project administration. XG: Conceptualization, Writing - review & editing, Project administration, Funding acquisition. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflicts of Interest

The authors declare no conflicts of interest.

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