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Role of Autophagy in Endothelial Damage and Blood–Brain Barrier Disruption in Ischemic Stroke

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The global burden of neurological diseases including stroke has significantly increased,[1] and an urgent need exists to develop new treatment strategies. Impairment of autophagic regulation has been observed in diseases including neurodegenerative diseases and ischemic stroke, suggesting that modulation of autophagy could be a potential therapeutic target.[2] Endothelial cells (ECs) maintain homeostasis by regulating the vascular tone and permeability and endothelial dysfunction is associated with diverse cardiovascular diseases (CVDs). The integrity of the blood–brain barrier (BBB), which shows selective permeability for substances into the brain, is significantly impaired under ischemic stroke. This review focuses on autophagy in endothelial dysfunction in the context of ischemic stroke and potential targets for therapeutic manipulation.

Physiological Roles and Clinical Importance of Autophagy

Autophagy or autophagocytosis is an evolutionarily conserved mechanism for the degradation and recycling of cellular organelles and protein.[2] It occurs continually at basal levels in cells and contributes to the maintenance of cellular homeostasis. When external nutrient supplies are limited, cells attempt to generate their energy by degrading and recycling macromolecules and cellular organelles by autophagy.[3]

Autophagy is also an important defense mechanism against stress including oxidative stress and infection, enabling cellular repair, or clearance of pathogens.[1,2] Defects in autophagy flux may lead to the accumulation of damaged or senescent proteins and abnormal protein aggregates, and this is closely associated with human diseases including neurodegenerative, cardiovascular, and metabolic diseases, as well as cancer.[2,4] In contrast to the protective role of autophagy in maintaining basal cellular homeostasis, excessive autophagy may also cause dysregulation of catabolic activity and maladaptation to cellular stress, leading to autophagic cell death.[5]

Accumulating evidence shows that modulating the level of autophagy by targeting specific regulatory molecules in the autophagy machinery may impact disease onset or disease progression. It is now widely accepted that autophagy may represent a new target for drug development and therapeutic intervention for various disorders including ischemic stroke. We will start with the molecular biology of autophagy which discusses the potential targets of autophagy regulation.

Molecular Biology and the Roles of Autophagy

Molecular Autophagic Pathways

Based on morphological differences, autophagy in mammalian cells has been classified into 3 major types: microautophagy, chaperone-mediated autophagy, and macroautophagy.[1,6] Macroautophagy is known to be the most typical and prevalent type of autophagy and we will also focus on macroautophagy, hereafter referred to as autophagy, in this review.

Changes in the cellular environment, such as energy and nutrient sensing, are important initiating stimuli for autophagy. There are complex interactions among the diverse molecules in autophagic processes,[2,7–9] as shown in Figure 1. Autophagy begins with the formation of phagophores, which elongate to trap the degradable substrates as double-membrane vesicles of autophagosomes. Autophagosomes fuse with lysosomes, which contain degradation enzymes to form an autolysosome. Pharmacological or genetic interventions that target specific autophagy machinery has been developed and used in experimental and clinical studies,[7–9] and explained in Figure 1.

Selective Autophagy

Autophagy has been traditionally regarded as a nonselective, bulk degradation process; however, recent studies have suggested that it can be highly selective.[10] Selective autophagy refers to the selective degradation of specific substrates by autophagy, including organelles such as the mitochondria or

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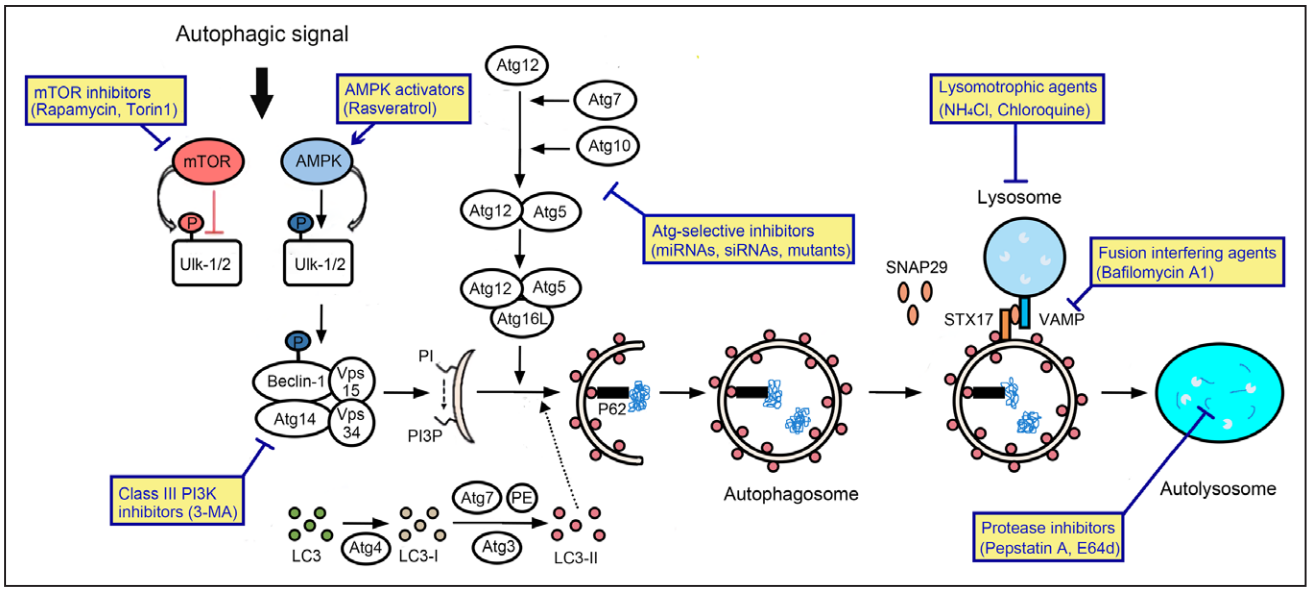

Figure 1. Molecular pathways in autophagy. The complicated interaction between diverse signaling molecules involved in autophagic processes including formation of phagophores, autophagosomes, and autolysosomes. Although the mTOR (mammalian target of rapamycin) induces inhibitory phosphorylation of Ulk-1 (Unc-51-like autophagy-activating kinase-1) in high-nutrient states, AMPK (adenosine monophosphate-activated protein kinase) phosphorylates and activates Ulk-1, initiating autophagy in nutrient-deficient states. Ulk-1 interacts with the FIP200 (family interacting protein of 200 kDa) and Atg13 (autophagy-related gene 13), involving in autophagosome formation. The formation of the Atg14L-Beclin 1-Vps (vacuolar protein sorting) 34-Vps15 complex contributes to the conversion of phosphatidylinositol (PI) to phosphatidylinositol-3 phosphate (PI3P), enabling phagophore elongation and recruitment of other Atg proteins. A multimeric complex of Apg12-Apg5-Apg16L mediates lipidation of microtubule-associated protein 1 LC3 (light chain 3). Once autophagy is initiated, LC3 in the cytosol is cleaved to LC3-I, which is then converted to LC3-II, an autophagosomes-associating form. The p62/SQSTM1 (sequestosome 1) is delivered to autophagosomes inducing autophagosome biogenesis. Subsequently, autophagic flux, referring to autophagosome maturation that leads to the degradation of trapped substrates by lysosomal enzymes occurs. The fusion of autophagosomes and lysosomes can be achieved by interaction with SNARE (N-ethylmaleimide-sensitive factor attachment receptor) proteins, which are STX17 (syntaxin-17), VAMP8 (vesicle-associated membrane protein-8), and SNAP29 (synaptosome-associated protein of 29 kDa). Pharmacological or genetic modulators targeting autophagic regulation have been developed.

peroxisomes (ie, mitophagy[11–13] or pexophagy,[14–16] respectively), and protein aggregates (aggrephagy).[17,18] Additional types of selective autophagy have been recently suggested including lipophagy,[19–21] glycophagy,[22] endoplasmic reticulum-phagy,[23] and xenophagy.[24,25] Efficient recognition and sequestration of the specific cargo within autophagosomes are mediated by autophagy receptors including p62, NBR-1 (neighbor of the Brca-1 gene), and NDP-52 (nuclear dot protein 52).[26,27]

Interestingly, activation or dysregulation of selective autophagy is closely associated with several types of diseases,[17] and it is noteworthy to identify an association between types of selective autophagy and specific disease condition. A summary of selective autophagy is included in Table 1, with potential links between these selective autophagy and endothelial dysfunction. A detailed discussion on selective autophagy is included in the Materials in the online-only Data Supplement.

Dysregulation of Autophagy in Diseases

Clinical and experimental studies have demonstrated that the activation of autophagic processes can be enhanced or inhibited in various pathological conditions,[3,11] suggesting that autophagy plays both beneficial and detrimental roles. There are several lines of evidence for the dual roles of autophagy in pathophysiology as discussed in the Materials in detail in the online-only Data Supplement.

Endothelial System in the Brain

Importance of ECs in Homeostasis and EC Dysfunction in CVDs

Blood vessels are composed of an innermost monolayer of ECs, smooth muscle cells, and connective tissues.[32] ECs serve as a barrier between the blood and tissues, but they are easily exposed to shear stress and noxious substances circulating in the blood. The EC monolayer is difficult to repair or replace easily. ECs release vasoactive mediators such as nitric oxide (NO) and endothelin for vasorelaxation and contraction, respectively. Impaired NO-mediated vasodilation associated with EC dysfunction is a critical contributing factor to various CVDs.[33] In addition to vascular tones, permeability regulation for material transport is another important role of ECs, as exemplified in the BBB and blood-placental barriers. ECs are also involved in maintaining the tissue microenvironment by participating in the neovascularization and release of inflammatory mediators.[32]

EC Repair Mechanisms and Endothelial Progenitor Cells

When the endothelium is damaged, 2 potential repair mechanisms can be activated. One is mediated by the proliferation and replacement of damaged ECs by neighboring ECs, and the other can be achieved by endothelial progenitor cells (EPCs), which are stem cells in the endothelial lineage.

Table 1. Selective Autophagy and Their Roles in Pathophysiology

Types of Selective Autophagy	Major Target Cargo	Related Diseases	References	Possible Link With EC Dysfunction	
				Evidence	References
Aggrephagy	Protein aggregates, misfolded proteins	Neurodegenerative diseases including Alzheimer and Parkinson diseases	17,18		
Mitophagy	Damaged mitochondria	CVDs including stroke, age-related diseases, developmental impairment, liver disease, Parkinson diseases, cancer	11–13,22,28	Strong	12,13,29
Pexophagy	Peroxisomes	Acute kidney damage, age-related or metabolic diseases (suggested)	14–16	Suggested	16
Lipophagy	Lipid droplet, modified LDL	Liver diseases, hyperlipidemia, atherogenesis	19–21	Suggested	19,30,31
Glycophagy	Glycogen	Diabetes mellitus, liver and heart diseases	22		
ER-phagy	Endoplasmic reticulum	ER-stress related diseases, neuropathy	23		
Xenophagy	Intracellular pathogens (bacteria and viruses)	Infection, inflammatory diseases	24	Suggested	24

CVD indicates cardiovascular disease; EC, endothelial cells; ER, endoplasmic reticulum; and LDL, low-density lipoprotein.

EPCs are recruited from the bone marrow to the injury site by homing signals to promote endothelial regeneration and neovascularization.[34] The potential of EPCs for use as clinical therapeutics for CVDs is now increasing.[35] Notably, the number of recruited EPCs, as well as their function such as mobilization, differentiation, and tube formation, is decreased under various CVDs including diabetes mellitus.[35,36] Increased oxidative stress and impaired NO signaling are suggested to be responsible, but the mechanisms underlying EPC dysfunction are still largely unknown.

Neurovascular Unit and BBB

The vascular system of the brain tissue shows specialized characteristics.[37] Because the brain can be adversely affected by circulating substances in the blood, a barrier is required to tightly restrict the permeation of these substances from the blood. This barrier is called the BBB and is mainly composed of the brain ECs.

Several proteins tightly seal the junctions between adjacent ECs, referred to TJ (tight junction) proteins (Figure 2).[38,39] TJ proteins are made up of several integral membrane proteins including claudins, occludin, and junction adhesion molecules, and cytoplasmic accessory proteins such as ZOs (zonula occludens). Claudins have 4 transmembrane domains.[37] Among them, claudin-5 is specifically involved in regulating the permeability of the BBB.[40] Although the carboxyl- and amino-terminals of claudins are located in the cytoplasm and interact with accessory proteins such as ZOs, their extracellular loops interact with each other, forming a primary seal between adjacent ECs.[37,41] Occludin is a tetraspan integral membrane protein that is continuously expressed along with the cerebral endothelium is the main component of TJ

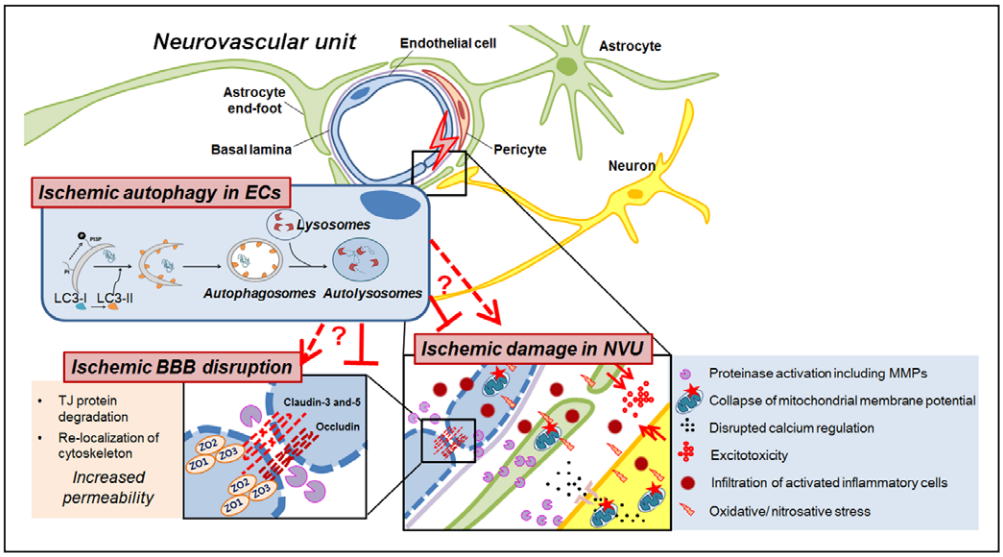

Figure 2. Ischemic autophagy in blood–brain barrier (BBB) disruption. Interaction between cellular components of endothelial cells (ECs), astrocytes, pericytes, and neurons are disrupted, and an array of pathological processes occur in the neurovascular unit (NVU) during ischemia. Degradation of TJ (tight joint) proteins and relocalization of the cytoskeleton in cerebral ECs result in increased permeability in BBB. Scheme on ischemic NVU/BBB damage was modified from Kim et al.[35] Autophagy in ECs would potentially affect ischemic impairment of BBB and NVU. LC3 indicates light chain 3; MMP, matrix metalloproteinases; and ZO, zonula occludens.

proteins. Occludin plays an important role in the stability and barrier function of TJ proteins.[40] ZOs are cytosolic proteins that support TJs. Each component of the TJ proteins plays a collaborative role, and the alteration or loss of TJ proteins may lead to BBB dysfunction.

Of note, cells in the cerebral vessels interact with other cells to maintain their structures and physiological functions, and this interacting cellular unit is called the neurovascular unit (NVU; Figure 2).[38,42] The NVU is composed of brain ECs, neurons, astrocytes, basal lamina, pericytes, and extracellular matrix.[37] The role of each cell has not been fully elucidated, but astrocytes and pericytes are known to affect structural characteristics of the brain ECs.[43] Structural and functional brain connectivity require highly coordinated signal transduction between different cell types in the NVU, and it is necessary to understand the pathological changes from the perspective of the NVU complex and vascular neural network.[44,45]

Endothelial Damage in Ischemic Stroke

Stroke occurs when the blood supply to the brain is depleted as a consequence of blood vessel blockage or rupture.[46] The major type is an ischemic stroke, and attempts have been made to develop therapeutic strategies by elucidating the mechanisms underlying ischemic stroke-induced brain damage. Protection of the BBB is an emerging strategy.[47,48]

Pathophysiology of Ischemic Stroke

In cerebral ischemia, nutrient and oxygen deprivation leads to an array of pathological processes including apoptotic neuronal death, neuroinflammation, and BBB disruption.[49,50] The production of adenosine triphosphate (ATP) is inhibited by oxygen depletion, which results in the failure of ATP-dependent ion transport and the increase of intracellular calcium concentrations.[49] The increased intracellular calcium causes overexcitation of the cells, resulting in apoptotic death. The excitotoxicity and increased oxidative stress activate microglia and astrocytes to release various inflammatory mediators, which activate MMPs (matrix metalloproteinases), leading to an influx of other inflammatory cells from the blood.[51] Cerebral ischemia induces vascular injury, which amplifies irreversible neuronal death and brain injury (Figure 2).

BBB Disruption in Ischemic Stroke

Ischemia-induced BBB disruption mainly results from the loss of the structural integrity of TJ proteins and degradation of the basal lamina. Extensive efforts have been made to elucidate the mechanisms of TJ protein degradation.[52,53] The major role of MMPs in BBB opening has been reported.[51,54] MMPs comprise a family of enzymes involved in the degradation of protein substrates and the extracellular matrix. Inactive pro-MMPs are expressed in ECs and astrocytes, and pro-MMPs are converted into their active form.[51] During cerebral ischemia, the activation and expression of MMPs are steadily increased.[55] Cytokines increase the expression of MMPs during ischemic inflammation.[55] An elevated level or activity or both of MMP-2 and MMP-9 has been observed in brain tissue and plasma of stroke patients, and also in the animal models of stroke.[56,57] The inhibition of MMPs restores the BBB disruption with the recovery of TJ protein levels and alleviation of the brain injury in cerebral ischemia.

Ischemia results in accumulation of H^+ in the cells cause acidosis, which generates reactive oxygen species (ROS) such as hydrogen peroxide and reactive hydroxyl radical.[58] Several studies have shown that oxidative stress mediates BBB disruption in ischemia/reperfusion (I/R) injury.[59,60] Increased oxidative stress during cerebral ischemia is also reported to enhance direct MMP activation and reduce the level of tissue inhibitors of MMPs.[61]

Potential Role of Autophagy in Ischemic BBB Degradation

Although most BBB disruption studies have focused on the MMP-mediated degradation of TJ proteins, several recent studies have suggested that autophagy may also play important roles. Autophagy-mediated by silencing HDAC (histone deacetylase) 9 in the ischemic hemisphere after I/R is responsible for the protection against BBB permeability increase.[62] Similarly, induction of autophagy by rapamycin before I/R protected the brain ECs from apoptosis.[63] Although the specific target cargo of the activated autophagy was not identified, increased autophagy protected the cells against the generation of ROS and restored the decreased ZO-1 levels. Li et al[64] also reported that promoting autophagy by miRNA regulation protected brain microvascular ECs exposed to oxygen-glucose deprivation/reperfusion injury.

On the other hand, autophagy was increased by oxygen-glucose deprivation, and the BBB component claudin-5 was degraded by autophagy-lysosome activation in brain ECs, suggesting a detrimental role for autophagy in BBB disruption.[65] Wei et al[66] demonstrated that enhanced autophagy during brain ischemia in diabetic mice is responsible for excessive BBB disruption, based on the observation that autophagy inhibition improved functional recovery. Increased autophagy and BBB damage were observed in $p50^{-/-}$ mice, and these were reversed by autophagic inhibition, suggesting that autophagy contributes to ischemic neuronal and vascular damage by regulation of nuclear factor kappa B.[67] We recently observed the activation of ischemic autophagy in oxygen-glucose deprivation–exposed brain ECs and brain capillaries isolated from rats with ischemia and found that degradation of occludin with permeability disruption is mediated by autophagy (Kim et al, unpublished data, 2018).

In addition to studies on ischemic insults, the potential involvement of autophagy in BBB function by other stimuli has also been reported. Autophagy triggered by methylglyoxal, a reactive metabolite produced during glucose metabolism, may defend brain microvascular ECs against injuries.[68] Antibacterial autophagy might play important roles in bacterial infection of BBB in meningitis.[24] ROS generation and mitochondrial damage were observed in brain ECs exposed to homocysteine, suggesting that excessive mitophagy contributed to cellular damage.[12]

Evidence for the involvement of autophagy in BBB function is summarized in Table 2. Because studies on the role of autophagy in BBB dysfunction are only commencing, the evidence of BBB autophagy is limited. The possible involvement of selective autophagy has not been

Table 2. Autophagic Regulation in BBB Function

Types of BBB Model	Stress	Changes in Autophagy	Related Cellular Alteration	Role of Autophagy	Evidence of Autophagy Role	References
Primary BMECs	OGD/R (1 h/different duration)	↑	↑HDAC9 induction, ↑cytokine release, ↑permeability, ↓TJ proteins	Protective	↓Cell damage by further activation of autophagy by siHDAC9 or rapamycin	62
Rats	MCAO/R (2 h/24 or 48 h)	ND	↑HDAC9 induction, ↑ischemic brain damage (infarct size, behavioral deficit, edema, and permeability)	Protective (suggested)	↓Ischemic damage by silencing HDAC9	
Primary BMECs	OGD/R (6 h/4 h)	↑	↑Apoptosis, ↑ROS generation, ↓ZO-1	Protective	↓Cell damage by rapamycin, ↑Cell damage by inhibition of autophagy by 3-MA	63
Rats	MCAO/R (2 h/22 h)	ND	↑BBB permeability, ↑brain water content	Protective	↓BBB permeability and edema by rapamycin, ↑BBB permeability and edema by 3-MA	
Primary BMECs	OGD/R (16 h/duration not specified)	↑	Cell death↑	Protective	↓Cell death by further induction of autophagy by lithium, ↑cell death by 3-MA	64
Mouse BMEC cell line	OGD (4 h)	↑	↓Claudin-5 ↓, ↑Cav1 redistribution, ↑NO production	Detrimental	↓Claudin-5 degradation by 3-MA or lysosome inhibitor CQ	65
Normal and STZ/NA-induced diabetic mice	MCAO (12 or 24 h)	↑	↓Occludin, ↑ischemic brain damage (infarct size, apoptosis, and functional assessment)	Detrimental	↓Occludin degradation and ischemic brain damage in diabetic stroke by 3-MA	66
Wild-type and p50$^{-/-}$ mice	MCAO (up to 7 d)	↑	↑BBB disruption (collagen IV-positive vessel deterioration, occludin degradation), ↑ischemic neuronal damage	Detrimental	↓BBB damage and ischemic neuronal damage by 3-MA	67
Human BMEC cell line	MGO (1 mmol/L, 24 h)	↑	↑Cell death, ↑apoptosis	Protective	↑Cell death by autophagy inhibition by 3-MA, BAF, or siBECN1	68
Normal and STZ-induced diabetic rats	MCAO (24 h)	↑	↑BBB permeability	Protective	↑BBB permeability by CQ	
Human BMEC cell line	Bacterial infection (Group B *Streptococcus*; GBS)	↑	↑Colocalization of bacteria and LC3	Protective	↑Number of intracellular GBS by autophagic inhibition by BAF or gene silencing (ATG5 or FIP200)	24
Mice	Bacterial infection (GBS)	↑ in brain ECs	↓Survival, because of infection, ↑Colocalization of bacteria and LC3	Protective (suggested)	ND, but mentioned in discussion	
Mouse BMEC cell line	Hcy (500 μmol/L, 24 h)	↑(mitophagy)	↑Cell death, ↑ROS generation, ↑mitochondria fusion/fission, ↓mitochondrial ATP content	Detrimental	↓Hcy-induced mitophagy and cellular/mitochondrial damage by treatment of tetrahydrocurcumin	12

3-MA indicates 3-methyladenine; ATG, autophagy-related gene; BAF, bafilomycin A1; BBB, blood–brain barrier; BMECs, brain microvascular endothelial cells; Cav1, caveolin-1; CQ, chloroquine; ECs, endothelial cells; FIP200, family interacting protein of 200 kDa; GBS, Group B Streptococcus; Hcy, homocysteine; HDAC9, histone deacetylase 9; LC3, light chain 3; MCAO/R, middle cerebral artery occlusion/reperfusion; MGO, methylglyoxal; NA, nicotinamide; ND, No data; OGD/R, oxygen-glucose deprivation/reperfusion; ROS, reactive oxygen species; siBECN1, siRNA against Beclin1; siRNA, RNA interference-mediated knockdown of beclin-1; STZ, streptozotocin; TJ, tight junction; and ZO, zonula occludens.

identified yet. Considering the unique structure and complicated interaction between NVU components, future studies on autophagy in BBB function would be very important.

Autophagy Regulation in Other Types of ECs

Previous observations of autophagy in EC dysfunction will also be helpful in understanding ischemic autophagy in the BBB. Notably, many of the reports on EC autophagy were

related to diabetic or atherogenic conditions, which are major risk factors for ischemic stroke.[69,70]

Xie et al[71] observed that AGEs (advanced glycation end-products), which contribute to the pathogenesis of diabetes mellitus and atherosclerosis, induced autophagy along with increased ROS generation in HUVECs (human umbilical vein ECs). EC injury was enhanced by autophagic inhibition. Vasko et al[16] showed that peroxisomal dysfunction and impaired pexophagy promotes oxidative damage in ECs in lipopolysaccharide-induced acute kidney injury. EC autophagy also played key roles in shear stress-induced NO generation.[72] Autophagy is involved in the protective mechanisms of bioactive drug candidates against CVDs. Epigallocatechin gallate, a major polyphenol in green tea, increased autophagy in bovine aortic ECs, which reduced lipid accumulation.[19] Atheroprotective effects of gossypetin, a natural compound, against ox-LDL (oxidized low-density lipoprotein)–induced injury in HUVEC were also mediated by the activation of autophagy.[30] In these cases, EC injury was enhanced by accumulation of impaired organelles and lipid droplets, and activation of autophagy contributed to removing these unwanted toxic mediators.

On the other hand, evidence of the detrimental role of autophagy in EC function and survival has also been reported. Autophagic cell death mediated peripheral vascular injury induced by nicardipine, and inhibition of autophagy by 3-methyladenine reversed nicardipine-induced cell death in human dermal microvascular ECs.[73] Necroptosis induced by accumulation of palmitic acid, which is known to enhance lipotoxicity, was mediated by autophagy in HUVEC-derived cell line.[31] Nutrient deprivation increased ROS generation and vulnerability of ECs to proinflammatory factors, mediated through autophagy.[74] Hypoxia/reoxygenation-induced marked autophagy in microvascular ECs, and inhibiting autophagy attenuated hypoxia/reoxygenation-induced injury by upregulating mTOR (mammalian target of rapamycin) phosphorylation.[75] Zeng et al[76] showed I/R-induced p65-Beclin 1–dependent autophagic death in HUVEC, showing that I/R autophagy is exacerbating the myocardial injury. Similarly, EC dysfunction in obesity-associated hypertensive rats is attributable to excessive autophagy.[77] Inflammatory mediators such as migration inhibitory factor increased EC permeability, thereby contributing to the vascular leakage, mediated by migration inhibitory factor-induced autophagy in sepsis.[78] Interestingly, EC dysfunction induced by toxicants including silica nanoparticles or diesel exhaust particles was found to be mediated by ROS and excessive autophagy.[29,79] Schrijvers et al[80] concluded that basal autophagy could protect atherosclerotic plaque cells against ROS and mitochondrial damage, but excessive stimulation of autophagy in ECs may cause dysfunction and autophagic death which is detrimental to the structure of the plaque.

Autophagy in EPCs

Several lines of evidence suggest that autophagy is a key regulator for EPC survival and function. Wang et al[81] demonstrated that modulation of autophagy is beneficial to the survival of transplanted EPCs. EPC growth and angiogenesis were reduced by autophagy inhibition.[82] Autophagy was significantly reduced in EPCs isolated from diabetic patients, and adenosine treatment restored EPC autophagy, enhancing diabetic EPC proliferation.[83] The protective effects of quercitrin, a natural flavonoid, against ox-LDL–induced EPC damage were found to be mediated by autophagic activation.[84] On the other hand, we reported that autophagy activation with the increased oxidative stress, mitochondrial dysfunction, and impaired angiogenesis in high-glucose exposed-EPCs.[85] AGE significantly increased oxidative mitochondrial damage and autophagy in EPCs.[86] Inhibiting or enhancing autophagy significantly increased or decreased EPC migration, respectively.[87]

Sharma and Wu[88] reported that autophagy is involved in the proliferation and differentiation of EPCs, and the balance between autophagy and apoptosis is important in EPC survival. Further insights into the role of autophagy in EC function can be found in recent reviews.[89,90]

Autophagy in Other Components of the NVU

As noted above, the NVU is an integrated unit to support brain function and morphology, but it is known that autophagy may be differently regulated in each component of the NVU including ECs, neurons, or glial cells including astrocytes and microglia under ischemic conditions.[12,24,62–68,91–94] Although we have mainly focused on the autophagy in ECs in this review, it is important to understand autophagy in each component of the NVU in an integrated way. Interestingly, it has been found that autophagy is associated with protection against ischemic brain edema induced by preconditioning,[95] postconditioning,[96] ischemic-remote-perconditioning,[97] and several neuroprotective agents,[98,99] suggesting that autophagy modulation affects the overall functional integrity of the NVU. A more detailed understanding of the role of autophagy in the ischemic NVU damage is needed.

Conclusions

Autophagy represents an adaptive mechanism by which cells defend against external/internal stresses. When the stress is mild, autophagy is activated to ensure survival. Damaged, detrimental, and unwanted components are efficiently removed. However, when cellular stress is overwhelming, this tightly regulated process fails and the cells self-digest essential cell components, resulting in autophagic death. Although the beneficial or detrimental roles of autophagy in neuronal damage have also been reported in both in vitro and in vivo ischemic stroke models,[28,100] studies on autophagy in BBB damage have only commenced recently. A more comprehensive understanding of the time frame, stimuli, and target cargo of autophagy in ischemic BBB dysfunction is essential and approaches elucidating the role of selective autophagy would also be required. Success in these efforts could make a modification of autophagy a viable therapeutic strategy for protecting the brain during ischemia.

Disclosures

None.

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