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Autophagy in Cerebral Ischemia: Therapist or Killer

Rong Pan*

Department of Pharmaceutical Sciences, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA

As the third leading cause of death and the leading cause of disability, stroke has a great effect on public health. Many efforts have been directed toward understanding the molecular events involved in cerebral ischemia. Emerging from these studies, neuronal death is the central issue in cerebral ischemic injury. Base on biochemical and morphological criteria, there are at least three possible mechanisms of cell death, including apoptosis (Type I), autophagic cell death (Type II) and necrosis (Type III) [1]. Traditionally, most researchers thought that neurons died from necrosis or apoptosis after injure in ischemia. However, in recently, studies demonstrated that autophagy also takes a significant part in cerebral ischemia.

Autophagy is a "housekeeping" regulated process of degrading long-lived proteins and dysfunctional cellular organelles. There are three main types of autophagy: macroautophagy, microautophagy and chaperone-mediated autophagy [2]. In chaperon-mediated autophagy, chaperons recognize substrates and deliver them to lysosomes [3], while in microautophagy, cytosolic proteins are taken into lysosome by direct invagination of lysosomal membrane [4]. Macroautophagy is the most active form of autophagy. In macroautophagy, proteins and organelles are packed in autophagosones, and then degraded through fusion with lysosome (Figure 1). Macroautophagy plays a major role in intracellular degradation, and is commonly referred to as autophagy [5]. Autophagy is essential for cellular health and survival. It can survive cells in nutrient-limiting condition by generating required free amino acids and fatty acids to maintain function, and keep cell healthy by removing damaged organelles and proteins. However, autophagy can also be a mediator of cell death through excessive self-digestion and degradation of essential cellular constituents or through triggering apoptosis [6-8].

Since autophagy has dual role in cell fate determination, what does autophagy do in cerebral ischemia? Is it a therapist or a killer? The answer to this question is controversial from the start and never stopped. Nowadays, this kind of issue keeps on heating. Dozens of papers have been published within recently one year (Table 1). Most studies show that autophagy is harmful after cerebral ischemia, mainly through the overactivation of autophagy after ischemia. Autophagy overativation could induce autophagic neuron death and caspase dependent apoptosis, leading to neuron death [9-11]. However, some other researchers believe that autophagy is neuroprotective by remove harmful product after ischemia, especially dysfunctional mitochondria [12]. The neuroprotective functions of autophagy also come from mobilizing immune response [13], and other neuroprotective pathways after ischemia. Several researchers pointed out that the effect of autophagy in cerebral ischemia is very complex. From those investigations, the extent of autophagy became a key factor on the effect of autophagy in ischemia. Moderate autophagy may keep neuron heath, while excessive autophagy may induce neuron death, depending on the quality control for proteins and organelles. The investigation of autophagy in cerebral ischemia is in its early stage. To determine in what condition autophagy is neuroprotective or harmful in response of cerebral ischemia, more work needs to done. The understanding of the effect of autophagy in cerebral ischemia might help on finding potential therapeutic targets for the treatment of cerebral ischemic injury.

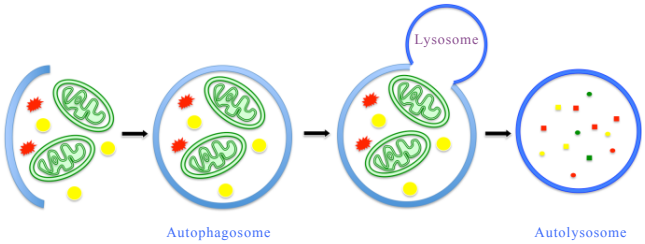

Figure 1: Process of macroautophagy.

Entire organelles and proteins are sequestrated in autophagosome. Then autophagosome merges with lysosome where the organelles and proteins will be degraded.

Animal/Cell	Model	Phenotypes	Effect of autophagy	Ref.
C57BL/6 mice	pMCAO	Immune-related GTPase M knockout inhibit autophagy	Benefit	[13]
PC12 cells	2h OGD/24h RP	β-Asarone inhibit autophagy	Harmful	[14]
PC12 cells Sprague-Dawley rats	6h OGD/RP tMCAO	Propofol inhibit autophagy	Harmful	[10,11]
Primary cortical neurons SH-SY5Y cells	6h OGD/RP	3-methyladenine inhibit autophagy	Harmful	[15]
C57BL/6 mice	pMCAO tMCAO	3-methyladenine or Atg7 knockdown inhibit autophagy	Benefit	[12]
Sprague-Dawley rats	tMCAO	Myeloid cell leukemia-1 inhibit autophagy	Harmful	[16]
Sprague-Dawley rats	pFI	Salubrinal inhibit autophagy	Harmful	[17]
Sprague-Dawley rats	tMCAO	Physical exercise reduce autophagy	Harmful	[18]
B6, 129P-Nfkb1 mice	pMCAO	p50 knockout increase autopahgy	Harmful	[19]
Wistar rats	2min IPC 10min ischemia	Hamartin increase autophagy	Benefit	[20]
ICR mice	tMCAO	PPAR-γ inhibit autophagy	Harmful	[21]
Sprague-Dawley rats	tMCAO	RIPostC increase autophagy	Benefit	[9]

Table 1: Effect of autophagy in cerebral ischemic injury.

***Corresponding author:** Rong Pan, Department of Pharmaceutical Sciences, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA, E-mail: rpan@salud.unm.edu

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