International Journal of New Technology and Research (IJNTR)
ISSN:2454-4116, Volume-1, Issue-5, September 2015 Pages 63-68

Mechanism and Role of Autophagy in Neural Stem Cells

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***Abstract*— Recent emphasis has been on autophagy of neural stem cells (NSCs), playing an important role in the innate and adaptive immune responses, although the mechanism is not very clear. Autophagy pathway function can be isolated by cell stress components, such as intracellular pathogens and damaged organelles, and prolong the life-span of cell. There are many types of autophagy and its role is to eliminate the useless and recover cellular components in the cells, as results to maintain normal metabolism, provide the necessary energy when hungry, and keep a steady state in other emergency conditions. Autophagy related gene plays an important role in the process of the occurrence and development of autophagy in NSCs, at the same time the autophagy pathways play synergistic effects with these genes. Any genetic changes are likely to occur in neurodegenerative diseases by autophagy. Autophagy can be induced, and can also be inhibited, and transformed into each other. In this paper, the effect and mechanism of autophagy and autophagy-related genes and the role of autophagy in NSCs, and the influence of nerve disease were reviewed.**

***Index Terms*— autophagy, neural stem cells, autophagy-related genes, neurodegenerative diseases, neuronal ischemia and hypoxia.**

I. INTRODUCTION

Autophagy occurs in eukaryotic cells, and is a process of self-digestion and lysosome-dependent pathway for the turnover and recycling of intracellular macromolecular and damaged organelles. [1-4]Autophagy, a highly conserved mechanism in eukaryotes, is involved in multiple physiological and pathological processes. Autophagy-related study is becoming a worldwide hot-spot of life science.[3-5] Autophagy has been suggested to play a role in developmental and anti-aging functions in animal cells. Elucidation of autophagy is thus not only of academic, but also medical interests. Through autophagy starving cells degrade materials within their own cells to provide necessary nutrients for more essential processes. [5-7]Another essential function of autophagy in higher eukaryotes is to remove potentially harmful proteins to protect the cells against diseases and infection by pathogens. Autophagy relates to the formation of a membrane containing a region of the cytoplasm, sequestering macromolecules like proteins and organelles, and the fusion of the resultant vesicle with a lysosome in which the contents are degraded. [6-9]

In this review, we briefly describe the autophagy related knowledge more and more scope, including its mechanism, the effect of neural stem cells, neural cells, and the protective effects on neuronal cells, our understanding of biological function and significance of autophagy in scientific research on this aspect is very important.

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II. FEATURES AND FUNCTIONS OF AUTOPHAGY

The characteristics of autophagy have the following several aspects.[1-3,8-11]
(1) To maintain cells homeostasis, conducive to cell survival. Under normal circumstances, few cell autophagy, unless there is a predisposing factor. Autophagy can serve as a defense mechanism to remove cell organelles in cytoplasm, impaired metabolic products, to reconstruct the subcellular level, protect the damaged cells, at the same time it is a kind of programmed cell death induced by active cell death. The autophagy process is very fast, but a few minutes were observed after the induction of autophagy, autophagy lysosomal degradation after 2 hours. [13-16]
(2) The autophagy induced autophagy-related protein synthesis: rapid synthesis of autophagy-related proteins, resulting in a large number of autophagosome formation. [4-6]
(3) and the related genes. If the autophagy-related gene mutation deactivation occurs, then neurons gathered a large number of protein, and neuronal degeneration.[10-12]There are two main aspects of autophagy function. The first is as a protective mechanism of cells, prevent cell death. Some organs have a strong ability to raise the autophagy marker Atg8 in autophagic vacuole, the cell survival have injurious effects when autophagy is inhibited. The second is to play a role in cell death. Once it reaches the damaged threshold of autophagy, cells will get into apoptosis pathway.[13-15]

A. Physiological and Pathological Function in Autophagy

Autophagy is a physiological phenomenon, and evolutionarily conserved maintaining homeostatic functions like protein degradation and organelle turnover. [17-20]Although autophagy as a phenomenon was known for decades, its molecular components were identified by a path breaking genetic study on baker's yeast in 1993. Since then, autophagy-related proteins have been found and most of them have been conserved over eukaryotes. As many autophagy-related proteins have no significant homologies with others, structural studies may shed light on their functions. However, the molecular mechanisms of autophagy have not been fully understood. The Targeted Protein Research Program aims to facilitate autophagic study based on the structural determination of proteins.[21-24]

B. Molecular Mechanism in Autophagy

Autophagy is a conserved trafficking pathway that is highly regulated by environmental conditions. [25-27] During autophagy, portions of cytoplasm are sequestered into a double-membrane autophagosome and delivered to a degradative organelle, the vacuole in yeast and the lysosome in mammalian cells, for breakdown and recycling. Autophagy is induced under starvation conditions and in mammalian cells is also invoked in response to specific hormones. [25]

For yeast, a constitutive biosynthetic pathway at nutrient-rich conditions, termed the cytoplasm to vacuole targeting pathway. Autophagy and the cytoplasm to vacuole targeting pathway have been extensively studied and comprehensively reviewed in the past few years. [16,28-32]

Autophagy is the membrane-trafficking pathway that delivers cytoplasmic material to the vacuole for degradation and recycling. Macroautophagy involves the formation of a cytosolic double-membrane vesicle, an autophagosome, which sequesters bulk cytoplasm. [17-20]Upon completion, autophagosomes fuse with the vacuole membrane releasing a single membrane autophagic body inside the vacuole lumen. The autophagic body is degraded by vacuolar hydrolases.

During microautophagy, the sequestration event occurs directly at the vacuole surface. The process also results in a single-membrane vesicle that is ultimately degraded inside the vacuole. Peroxisomes can be selectively taken into the vacuole for degradation by the pexophagy pathway, a specific type of autophagy. Whereas macropexophagy requires the formation of a sequestering vesicle in the cytosol, micropexophagy occurs directly at the vacuole surface.[24,33-36]

C. Types and Genes in Autophagy

Autophagy is an intracellular bulk degradation system through which cytoplasmic components are delivered to lysosomes to be degraded. The main process of autophagy includes formation and maturation of the phagophore, autophagosome, and autolysosome. LC3, a mammalian homolog of yeast Atg8, is localized in autophagosome membranes after processing to LC3-II and can be degraded by the autolysosome. Autophagy provides nucleic, amino, and fatty acids for the synthesis of DNA/RNA, protein, and ATP. [25-28,37-40]Types and process of selective autophagy are listed in Table 1. [26-30]Autophagy can also target selective cargo for degradation such as organelles, proteins, microbes, and RNA.

Table 1: Types and comments of Autophagy

Aggrephagy	Aggrephagy refers to the autophagic process of degrading proteins that are assembled into large protein aggregates, which are less toxic to the cell than more numerous small protein aggregates.
Allophagy	Allophagy refers to the autophagic degradation of paternally-derived mitochondria upon fertilization in the zygote.
Exophagy	Autophagy is also associated with non degradative processes involved in protein secretion known as exophagy.
Heterophagy	Heterophagy is distinguished from autophagy in the sense that it is a process devoted to degrade extracellular material that has been internalized within the cell, in contrast to the degradation of pre-existing intracellular material.
Immunophagy	More broadly, autophagy plays a larger role in both innate and adaptive immunity in a process termed immunophagy.
Lipophagy	Lipophagy involves the metabolic regulation of lipids through degradation of lipid droplets (LDs) by autophagy.
Lysophagy	The lysosome, a membrane-bound acidic organelle, is selectively sequestered by autophagy when its membrane is injured; this phenomenon is called "lysophagy". [26]
Mitophagy	Mitophagy is the selective degradation of mitochondria through autophagy, although the process may be cell specific within mammals.
Nucleophagy	A selective form of autophagy, known as nucleophagy, can be used to accomplish the degradation of nucleus-derived material.[27]
Pexophagy	Pexophagy, the selective degradation of peroxisomes through autophagy, is probably the most utilized of the three known mechanisms, which also includes LON protease mediated and 15-LOX-mediated turnover, to eliminate damaged or superfluous peroxisomes.
Ribophagy	Some information on ribosome recycling derives from studies on starved yeast cells that use a specialized type of autophagy, called ribophagy, to differentially target ribosomes for degradation.[28]
Rnautophagy	Lysosomes are sites for the degradation of diverse cellular components. The novel lysosomal systems termed RN autophagy and DN autophagy was recently discovered.[29]
Xenophagy	Viruses, bacteria and parasites can be eliminated in an autophagic process involved in innate immunity defense termed xenophagy, which has been previously reviewed.
Zymophagy	This is a novel selective form of autophagy named zymophagy, a cellular process to specifically detect and degrade secretory granules containing activated enzymes before they can digest the organ. [30]

III. AUTOPHAGY IN NEURAL STEM CELLS

Autophagy is a cellular response to starvation conditions in a variety of cell biology, basic conditions of autophagy has been widely recognized this is a to maintain cellular homeostasis mechanisms, especially after mitosis in neurons. [1-4,46-50] In fact, the cytoplasm of the autophagy process was observed half a century ago, but the observation of the neurons is after the invention of the electron microscope. The mechanism of ubiquitin proteasome degradation is recognized, and the roles of autophagy play a new insight in the development of some neurodegenerative diseases. [31-33]

A. *Autophagy Regulation*

For the neuronal stem cells (NSCs), signaling pathways of regulate autophagy are framed as autophagy activators including limitation for growth factors and nutrients. [31] Autophagy is regulated by common nutrient, growth factor, hormone, and stress signals. Purple lines depict events that positively regulate autophagy. Yellow lines depict those that negatively regulate autophagy. Many pathways converge on the AMPK-mTORC1(mechanistic target of rapamycin complex 1) axis. Green lines depict pathways that are mTOR-independent. [20,31]

Selected components and functions of both mTORC1 and mTORC2 complexes are described. [32, 55-57] Growth factors such as insulin/IGF1 stimulate mTORC1 *via* the AKT-PI3K and Ras-ERK pathways and mTORC2 *via* unknown pathways. AKT- and ERK-mediated phosphorylations inhibit TSC2, a GTPase- activating protein for Rheb, thus activating mTORC1. The low energy status negatively regulates mTORC1 *via* AMPK by contrast. Activition of mTORC2 is positively regulated by TSC2. It is feedback loops by S6K1-IRS1 and mTORC1-Grb10 dampen AKT-PI3K signaling.[32] The mTOR pathway is a central controller of growth and homeostasis, and, as such, is implicated in disease states where growth is deregulated, namely cancer, metabolic diseases, and hamartoma syndromes like TSC. [32-34,58-60] Accordingly, mTOR is also a pivotal regulator of the homeostasis of several distinct stem cell pools in which it finely tunes the balance between stem cell self-renewal and differentiation. Hyperactivation of mTOR in NSCs has been etiologically linked to the development of TSC-associated neurological lesions, such as brain hamartomas and benign tumors. Animal models generated by deletion of mTOR upstream regulators in different types of NSCs reproduce faithfully some of the TSC neurological alterations. Thus, mTOR dysregulation in NSCs seems to be responsible for the derangement of their homeostasis, thus leading to TSC development. Here we review recent advances in the molecular dissection of the mTOR cascade, its involvement in the maintenance of stem cell compartments, and in particular the implications of mTOR hyperactivation in NSCs *in vivo* and *in vitro*. Target of rapamycin (TOR) in nutrient signaling and growth control was reported by Loewith *et al*. [33,61-63]

Like hematopoietic stem cells (HSCs), autophagy has been extensively studied in neurodegenerative diseases, and the potential role of autophagy is unknown in the regulation of NSCs. [64-66] NSCs have been extensively characterized by the use of markers in adult brain. Studies suggested that hypoxia inducible factor 1, α subunit (basic helix-loop- helix transcription factor; HIF1A)-dependent expression of BNIP3 promotes mitophagy to control excess ROS production and ROS-induced cell death under conditions of prolonged hypoxia. [10-14,67-69]

B. *Autophagy-Related Genes*

In NSCs, autophagy is a highly regulated process about which relatively little is known, particularly concerning the transcriptional control of autophagy regulation. Autophagy-related genes are a key regulator for the expression of autophagy in providing insights into the signalling pathways modulating autophagy (Table 2). [34-36,70-74] Indeed, neural-specific conditional knockout of essential autophagy genes such as Atg5, Atg7 or Rb1cc1/Fip200 result in abnormal accumulation of ubiquitinated protein aggregates, SQSTM1/p62 and damaged mitochondria, increased apoptosis and neurodegeneration, providing direct support for a role of basal autophagy in protecting against neurodegenerative diseases. [75-77] Wang *et al*. [35] reported that Atg5 promotes astrocyte differentiation by autophagic degradation of SOCS2 and activation of the JAK2-STAT3 pathway in embryonic brain development. The astrocyte differentiation is enhanced by Atg5 depletion inhibits and overexpression of Atg5.

Table 2: The auphagy-related genes

Yeast	Human	Mouse	Comments
Atg1	ULK1		Unc-51-like kinase interacts with GATE-16 and GABARAP
Atg3	hAtg3/hApg3	mAtg3/mAap3	an E2-like enzyme forLC3,GABARAP, and GATE-16
Atg4	hAtg4A/HsAtg4A/HsApg4A/autophagin-2		Cysteine protease for GATE-16
	hAtg4B/HsAtg4B/hApg4B/autophagin-1		Cysteine protease for LC3, GABARAP, and GATE-16; Delipidating enzyme for LC3-Ò and GABARAP
	hAtg4C/HsAUTL1//autophagin-3	Cysteine protease	
	hAtg4D/autophagin-4		
Atg5			hAtg5/hApg5 target protein of Atg12
Atg6	beclin 1	beclin 1	related to tumor genesis
Atg7	hAtg7 /HsGsA7 /hApg7	mAtg7/mApg7	an E1-like enzyme for Atg12 and Atg8 homologues
Atg8	LC3		modifier for autophagosomes
	GABARAP		modifier
	GATE-16		modifier
Atg10		mAtg10/mApg10	an E2-like enzyme for Atg12
Atg12	hAtg12 /hApg12	mAtg12/mApg12	modifier for autophagosome
Atg16		Atg16L/Apg16L	Interacts with Atg5

The direct studies for self-renewal of NSCs are the lack. Expressions of Atg7, Becn1, Map1lc3a and Ambra1 were

increased in recent study.[37-39] Neuronal differentiation was found to be impaired in Ambra1 knockout mice, as shown by decreased expression of several neural markers during embryogenesis.[78-80] Therefore, similar to observations showing altered differentiation in HSCs with loss of RB1CC1/FIP200 or Atg7 or preadipocytes lacking Atg5 or Atg7 as well as reduced terminal differentiation of autophagy-deficient reticulocytes, autophagy plays a critical role in the promotion of NSC differentiation.[40-43]

A. Autophagy in Neuronal Diseases

Autophagy of neural cell metabolism, maintain the ischemia and hypoxia stress survival, plays an important role in the removal of aging cells organelles and misfolded proteins. Confirmed in the model of cerebellar ataxia, inhibition of autophagy by HEK293 cells may promote cell death. In some special conditions, autophagy is an important reason leading to cell death. Through the hypoxia ischemia animal model and cell cultured experiments, autophagy has a protective effect on the nutrient deficiency of nerve cells, and can promote nerve cell survival. Application of 3-MA can reduce the occurrence of autophagy and promote the neuronal cell death. [39-42,82,83]

Neurodegenerative diseases can be classified as protein conformational disease. [38-40,76-78] When one or a group of specific protein misfolding and allosteric or in cells can lead to neurodegenerative diseases occur in the structure when the accumulation toxicity. Research shows that defect of autophagy related pathways may lead to Parkinson s disease (PD), Alzheimers disease (AD) and Huntington' s disease (HD) and other neurodegenerative diseases. The autophagy pathway if not effectively degrading waste cytoplasm, leads to the intracellular accumulation, thus induced diseases. There is a close relationship between AD and autophagy function disorder, but the specific mechanism is not very clear. The abnormal function of autophagy is one of the causes of PD, and PD related protein DJ-1 regulates autophagy through JNK pathway.[6-9,38-41]When the nerve cells during ischemia and hypoxia, the molecular mechanisms regulating autophagy is activated, causing the cell metabolism. Studies show that autophagy in neurons in the occurrence and development play a very important role, and its mechanism is complex and not very clear. [16-18]The signal pathway of autophagy was inhibited by including the I PI3K pathway, the main signal coming from the insulin receptor (high blood sugar levels and inhibition of autophagy); mTOR pathway, to accept a variety of upstream signals, such as PI3K, IGF-1/2 and MAPK, and the changes of nutrition and energy. [32-34] Autophagy is activated signal is realized through III PI3K pathway in nerve cells with ischemia and hypoxia.[43,20,32,85]

About autophagy dysfunction linked to several neuronal diseases, our understanding is still incomplete but may highlight up-to-date findings on how autophagy is executed and regulated at the molecular level and its role in neurodegenerative diseases including AD, HD, PD, amyotrophic lateral sclerosis (ALS), brain ischemia, and myelin diseases, etc.[86] Many neurodegenerative diseases were described by autophagic dysfunction. By understanding the manifold impact of autophagy disruption, future therapeutic strategies for these disorders will be guided in part on neurodegenerative diseases.[86,87]

III. SUMMARY

Autophagy is an autophagic process that the cells capture their cytoplasm and organelles and lysosomes are processed, resulting in the decomposition products of cellular metabolism, by using them to produce energy and the establishment of new proteins and cells. An important role of autophagy is to protect cells and tissues of healthy, prevent damage to cellular components and replacement of obsolete. During starvation, autophagy provides an internal energy as a nutrient source to maintain the survival of cells. Autophagy can promote the metabolism balance of cells and whole animal level in order to prevent the degenerative diseases. Nerve cell metabolism process of autophagy is more important. Another important function of autophagy is the removal of potentially harmful proteins to protect cells from diseases and infections erosion. In addition, autophagy in development and anti-aging functions of animal cells also have an important role, especially has been widespread attention in the medical field, is considered the medical interest in expanding.

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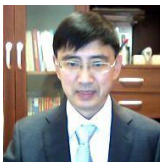

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