SMGroup

SM Journal of Neurological Disorders and Stroke

Editorial

Autophagy as the Modulator of Neuronal Homeostasis and Neurodegenerative Disorders

Xianjuan Kou[1] and Ning Chen[2]*

[1]*Hubei Exercise Training and Monitoring Key Laboratory, Hubei Provincial Collaborative Innovation Center for Exercise and Health Promotion, College of Health Science, Wuhan Sports University, China*
[2]*Department of Biochemistry and Molecular Exercise Physiology, Wuhan Sports University, China*

Article Information

Received date: Apr 11, 2016
Accepted date: Apr 12, 2016
Published date: Apr 12, 2016

***Corresponding author**

Ning Chen, Department of Biochemistry and Molecular Exercise Physiology, Wuhan Sports University, China,
Tel: +86-27-67846140;
Fax: +86-27-67846140;
Email: nchen510@gmail.com

Editorial

As the expansion of global aging population with improved lifespan and loaded social burden, the incidence of neurological disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS) presents a continuous climbing trend [1]. All of these neurological disorders afflicting health status and quality of life for elderly and increasing medical burden to their family and society are highly associated with protein quality control, because damaged, mis-folded or aggregated proteins can cause the proteotoxic stress for cell functional impairment and the intracytoplasmic deposition of aggregate-prone proteins or dysfunctional mitochondria in neurons with limited treatment strategies [2]. Autophagy is a cellular self-consumption process characterized by sequestration of bulk cytoplasm, long-lived proteins and damaged cellular organelles in double membrane vesicles called autophagosomes, which are delivered to lysosomes for the degradation [3,4]. Protein quality control via autophagy is particularly important for the timely removal of aggregated forms of pathogenic proteins in neurodegenerative diseases, including tau in AD, α-synuclein in PD and polyQ-Htt in HD [5,6]. It is also a powerful and selective degradation process for dysfunctional mitochondria in neurons for maintaining mitochondrial homeostasis. A decline in autophagic function is a common trait of the aging process. A large volume of studies indicate that defects in autophagy are involved in the pathogenesis of neurodegenerative diseases, suggesting that inducing autophagy through either pharmacologic or non-pharmacologic approaches may have certain therapeutic value. During last two decades, the accumulating evidence has demonstrated that the up-regulation of autophagy could execute the protection against neurodegenerative diseases and the enhancement of cognitive capacity [7]. However, dysfunctional autophagic pathways have also been implicated in the pathogenesis of various diseases including these neurological disorders. Meanwhile, neuronal homeostasis is also dependent on the proper functioning of quality control systems like autophagy, which is responsible for the elimination or clearance of mis-folded proteins, aggregates and the turnover of organelles within neurons. Dysfunctional status or regulation of autophagy has been reported in many neurodegenerative diseases, and the restoration of autophagy in affected neurons can be an attractive therapeutic approach to fight neurodegeneration [2].

Autophagy is a powerful process for removing the intracytoplasmic deposition of toxic, aggregate-prone proteins that cause neurodegeneration. At present, autophagy is becoming an attractive target to treat neurodegenerative disorders. The major components in autophagy signaling pathways in mammals include mTOR and AMPK. mTOR, a negative autophagy regulator, governs apoptosis and autophagy that can determine neuronal stem cell development, cell senescence, cell survival, and ultimate cell fate [1]. Given the importance of autophagy in a number of human diseases, the goal of most preclinical research programs for neurodegenerative diseases is to focus on discovering compounds that reduce the accumulation of tauopathy, amyloid β-protein and α-synaptophysin, and reverse cognitive impairment.

Many small molecules that can induce autophagy have been developed and shown to be effective in removing pathogenic proteins. Autophagy can be induced by mTOR dependent or mTOR independent signaling pathway. Known mTOR-dependent autophagic inducers such as rapamycin are successfully used to enhance the clearance of various pathogenic protein aggregates, improve cognition and behavior, and ameliorate neurodegeneration in cell and animal models of AD, PD and HD [8,9]. In addition to the drugs with direct inhibition of mTOR, the stimulation of AMPK pathway can up-regulate autophagy in an mTOR-dependent manner. AMPK is also being actively exploited as a potential drug target, with synergistic effect between rapamycin and mTOR-independent autophagic inducers. Other mTOR independent inhibitors such as clonidine, rilmendine and methylene blue are identified as autophagy enhancers to eliminate aggregate-prone

forms of α-synuclein, huntingin and phosphorylated tau protein [10,11]. Since trehalose has been shown to reduce disease-related protein aggregates associated with several neurodegenerative diseases in vitro, its autophagic induction can improve motor and cognitive performance [12]. Therefore, both mTOR inhibitors and AMPK activators can be used to regulate autophagy positively. Furthermore, it is reported that gene therapeutic approaches such as overexpressed TFEB or Beclin1 in the brain to induce autophagy have positive clearance effects on β-amyloid or α-synuclein or toxicity in induced neurodegeneration models [13]. What's more, regular exercise is an excellent therapeutic intervention for pathologies such as obesity, type-2 diabetes, neurodegeneration and sarcopenia through autophagy-modulating cellular homeostasis or cytokines [14,15]. In terms of efficacy, regular exercise can execute synergistic treatment efficacy of drugs for these neurodegenerative diseases. Regular exercise can induce autophagy and improve cognitive function and has also been reported to delay the onset neurodegenerative diseases [16]. Therefore, regular exercise could be a novel intervention strategy of neurodegenerative diseases in the future.

Mitochondria represent the major bioenergetics hub coordinating cellular and organismal homeostasis. Defects within mitochondria can be catastrophic, thereby causing neuronal cell loss associated with a series of neurodegenerative diseases [17]. Due to the importance of mitochondrial homeostasis in neurons, mitochondrial dynamics is crucial to prevent potential damage from reactive oxygen species (ROS). The perturbation of mitochondrial dynamics may compromise the selective elimination of damaged proteins and dysfunctional organelles, thus leading to the development of neurodegenerative diseases. In order to maintain the normal cellular functions, the damaged or unwanted mitochondria need to be selectively removed by mitophagic mechanism. Mitophagy is vital for maintaining the normal function of neurons and usually acts as a protective role for cells, which also helps cells to remove damaged mitochondria. A basal level of mitophagy is essential in mitochondrial quality control in physiological conditions, while excessive mitophagy will lead to cell death in a number of diseases. Recently, more and more researchers have demonstrated that mitophagy is involved in several neurodegenerative diseases, including PD, AD and HD [18]. These findings suggest that the effects of mitophagy cannot be neglected. New therapeutic approaches have now begun to target mitochondria as a potential drug target.

The mitochondrial kinase PINK1 and the E3-ubiquitin (Ub) ligase Parkin are central to mitochondrial quality control. Parkin is widely thought to be protective for neurons. Parkin dysfunction represents not only a predominant cause of familial Parkinsonism but also a formal risk factor for PD, AD, ALS and HD [19,20]. When PINK1 reaches normal mitochondria, it will be degraded by proteolytic enzymes; while it can accumulate on defective mitochondria. PINK1 helps to maintain normal function of organelles through removing damaged mitochondria selectively, thus eliciting the translocation of Parkin from the cytosol to mediate the clearance of damaged mitochondria via mitophagy. When Parkin interacted with PINK1, Parkin can participate in mitophagy and clear the dysfunctional mitochondria. Mitochondrial degradation through parkin-mediated mitophagy has gained much attention as the important therapeutic targets with the potential of enhancing mitochondrial quality control. If one or more can be targeted to enhance PARKIN function within mitophagy pathway, it may also protect the neurons from the overwhelmed high-level stress.

Defective or dysfunctional autophagy is the major cause of most neurodegenerative diseases including but not limited to AD, PD, HD, and ALS. A large volume of research in autophagy has also documented the links between autophagy and neurodegenerative diseases. However, systematic linking networks and underlying molecular mechanisms are still unclear. Nevertheless, the induction of autophagy by pharmacological or non-pharmacological methods has gained tremendous attentions in neurodegenerative diseases. Although promising treatment efficacy of drugs that enhance autophagy through inhibiting mTOR or activating AMPK, the detrimental effects of long-term administration of these compounds that impede mTOR activity are still debated. On the other hand, preclinical studies demonstrate that certain autophagy-inducing agents fail to induce their beneficial effects in host organisms that are deficient in autophagy genes [13]. Therefore, further clinical studies are needed to determine the optimal regimens for mTOR inhibitors for resulting in safe and effective autophagy induction and improved clinical outcomes. Despite research limitations, therapeutic approaches targeting autophagy are highly expected to contribute to the prevention and treatment of neurodegenerative diseases.

References

1. Maiese K. Targeting molecules to medicine with mTOR, autophagy, and neurodegenerative disorders. Br J Clin Pharmacol. 2015.
2. Menzies FM, Fleming A, Rubinsztein DC. Compromised autophagy and neurodegenerative diseases. Nat Rev Neurosci. 2015; 16: 345-357.
3. Chen N, Karantza-Wadsworth V. Role and regulation of autophagy in cancer. Biochim Biophys Acta. 2009; 1793: 1516-1523.
4. Chen N, Karantza V. Autophagy as a therapeutic target in cancer. Cancer Biol Ther. 2011; 11: 157-168.
5. Lee JH, Yu WH, Kumar A, Lee S, Mohan PS, Peterhoff CM et al. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. Cell. 2010; 141: 1146-1158.
6. Nixon RA, Yang DS, Lee JH. Neurodegenerative lysosomal disorders: a continuum from development to late age. Autophagy. 2008; 4: 590-599.
7. Nah J, Yuan J, Jung YK. Autophagy in neurodegenerative diseases: from mechanism to therapeutic approach. Mol Cells. 2015; 38: 381-389.
8. Spilman P, Podlutskaya N, Hart MJ, Debnath J, Gorostiza O, Bredesen D, et al. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease. PLoS One. 2010; 5: e9979.
9. Berger Z, Ravikumar B, Menzies FM, Oroz LG, Underwood BR, Pangalos MN, et al. Rapamycin alleviates toxicity of different aggregate-prone proteins. Hum Mol Genet. 2006; 15: 433-442.
10. Williams A, Sarkar S, Cuddon P, Ttofi EK, Saiki S, Siddiqi FH, et al. Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. Nat Chem Biol. 2008; 4: 295-305.
11. Xie L, Li W, Winters A, Yuan F, Jin K, Yang S, et al. Methylene blue induces macroautophagy through 5' adenosine monophosphate-activated protein kinase pathway to protect neurons from serum deprivation. Front Cell Neurosci. 2013; 7: 56.
12. Frake RA, Ricketts T, Menzies FM, Rubinsztein DC. Autophagy and neurodegeneration. J Clin Invest. 2015; 125: 65-74.
13. Kroemer G. Autophagy: a drug gable process that is deregulated in aging and human disease. J Clin Invest. 2015; 125: 1-4.

14. Chen N, Li Q, Liu J, Jia S. Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. Diabetes Metab Res Rev. 2016; 32: 51-59.

15. Fan J, Kou X, Jia S, Yang X, Yang Y, Chen N, et al. Autophagy as a Potential Target for Sarcopenia. J Cell Physiol. 2016; 231: 1450-1459.

16. Hands chin C, Spiegel man BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature. 2008; 454: 463-469.

17. Lionaki E, Markaki M, Palikaras K, Tavernarakis N. Mitochondria, autophagy and age-associated neurodegenerative diseases: New insights into a complex interplay. Biochim Biophys Acta. 2015; 1847: 1412-1423.

18. Costa V, Scorrano L. Shaping the role of mitochondria in the pathogenesis of Huntington's disease. EMBO J. 2012; 31: 1853-1864.

19. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, et al. Mutations in the parkin gene cause autosomal recessive juvenile Parkinsonism. Nature. 1998; 392: 605-608.

20. Zhang CW, Hang L, Yao TP, Lim KL. Parkin Regulation and Neurodegenerative Disorders. Front Aging Neurosci. 2015; 7: 248.