

Perspective: Role of Autophagy in Neuroprotective Properties of Traditional Chinese Medicines

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Introduction

The role of autophagy in neurodegenerative diseases

Autophagy is an essential degradation process that sequesters and transfers the idle cytoplasmic materials to the lysosome for digestion and recycling via the formation of autolysosome [1,2]. Although both autophagy-lysosomal and ubiquitin-proteasomal pathways are the two principal pathways for cellular protein degradation [3], large membrane-bound proteins, oligomeric and aggregated proteins such as long mutant polyglutamine (polyQ) tract in the huntingtin protein, and A53T α -synuclein mutant protein, which causes Huntington's disease (HD) and Parkinson's disease (PD), respectively, cannot pass through the narrow entrance of the proteasome barrel, are degraded by autophagy [4]. According to recent literatures, activation of autophagy can alleviate the levels and toxicity of mutant huntingtin and mutant α -synuclein in both mouse and *Drosophila* models [5,6]. Autophagy-related gene (ATG) knockdown lead to formation of protein aggregates and increased toxicity in *C. elegans* [7,8]. In addition, the accumulation of abnormal mitochondria or endoplasmic reticulum accompanied by an increase in the size and number of lipid droplets were observed in ATG gene knockout animal models [9-12]. Under this circumstance, autophagy inducers with neuroprotective potential can be evaluated through measuring their efficacy in enhancing the clearance of mutant or aggregated proteins. Therefore, the pharmacological activation of autophagy to regulate neurodegenerative diseases may be beneficial to neuro-therapy.

Parkinson's Disease (PD)

α -synuclein has been recognized as one of the major compositions of Lewy bodies that were characterized as the hallmarks of PD. Different conformations of α -synuclein, including misfolding or aggregation of α -synuclein, are highly correlated to the pathogenesis of PD. Three types of mutations in the α -synuclein gene, including A30P, E46K, and A53T substitutions in α -synuclein lead to autosomal dominant early-onset of PD. Besides, A30P or A53T α -synuclein lead to motor deficits and neuronal inclusions in transgenic PD flies model [13]. A53T and A30P which caused PD are recognized as substrates of autophagy, and their clearance is highly dependent on autophagy [14,15]. Concomitantly, pharmacological activation of autophagy reduces the levels and toxicity of mutant α -synuclein and mutant tau in either mouse or *Drosophila* models [5,6], suggesting the potential protective role of autophagy in PD.

Alzheimer's Disease (AD)

Alzheimer's disease is caused by the formation of tau tangles and β -amyloid aggregated proteins [16]. Although the exact role of

autophagy in pathogenesis of AD remains controversial, some evidences suggested the malfunction of autophagy lead to the impairment of autophagic degradation of β -amyloid and failure of β -amyloid clearance in the brains of AD patients [17].

Huntington Disease (HD)

A variety of neurodegenerative diseases are caused by toxic, aggregate-prone or oligomeric proteins [18-21]. For example, HD is caused by an over 35 CAG trinucleotide repeat expansion, which results in a long mutant polyQ tract formation in the huntingtin protein. These polyQ expansions are highly associated with the formation of aggregates and lead to toxicity in cells [14,22]. Autophagy, however, can reduce mutant huntingtin levels and its toxicity in cell and mouse models [18,19].

Neuropharmacology of traditional Chinese medicines (TCMs) - Autophagic degradation of neurodegenerative disease proteins

Recently, natural compounds isolated from medicinal herbs were found to be effective in modulating neurodegenerative disorders [23] potentially via the induction of autophagy. For example, salidroside from *Rhodiola Radix* [24], curcumin from *Curcuma longa* [25-27] and huperzine A from *Huperzia serrate* [28] were reported to have neuroprotective effects. For this reason, through screening of our library of natural product extracts isolated from TCMs, our group have successfully identified hederagenin and α -hederin from *Hedera helix* [29]; neferine from the lotus seed embryo of *Nelumbo nucifera* [30]; and onjisaponin B from *Radix Polygalae* (Yuan Zhi) [31,32] as novel autophagy inducers [30] with protective effect in enhancing the removal of neurodegenerative disease proteins via autophagy. Consistent with the long history of using *Radix Polygalae* (Yuan Zhi) in TCMs to relieve insomnia, anxiety and heart palpitation [33] in Chinese community, we proved that *Radix Polygalae* is capable of enhancing the *in vitro* clearance of both mutant huntingtin and α -synuclein, confirming the potential neuroprotective molecular mechanisms of the putative agents. Concomitantly, isorhynchophylline, a natural alkaloid isolated from *Uncaria rhynchophylla*, promotes the degradation of α -synuclein in neuronal cells via inducing autophagy [34], and improves cognitive impairment in β -amyloid rats [35]. A few more single compounds such as baicalein [36], trehalose [14] and resveratrol [37] isolated from natural products were also reported for their *in vitro* neuroprotective effects exerted possibly via autophagy induction, however, the exact molecular mechanisms remain to be further investigated.

Conclusion and Perspectives

In fact, recent literatures have identified new chemicals that enhance the clearance of neurodegenerative disease proteins via autophagy [38]. For example, rapamycin, a well-studied autophagy inducer, can increase autophagic clearance of mutant proteins *in vivo* significantly [5,19,39]. However, it possesses severe adverse effects in protein synthesis, cell proliferation and immunological function [1,40]. For this reason, identification of novel active chemicals that can facilitate the autophagic degradation of aggregate-prone or mutant proteins with minimal side effects would be an appropriate direction for novel drug discovery in neuro-therapy. However, incorrect dosage, uncertain or high toxicity of herbal decoction and improper selection of solvent for herbal compounds are the major problems in clinical application of TCMs currently. Therefore, special cautions are required when applying TCMs for clinical practices [41]. As a matter of fact, there has been a long history of using TCMs prescription in modulating neurodegenerative [42] or aged-related disorders such as dementia and AD [43]; or aged-related physical symptoms such as insomnia or anxiety in the Chinese community [44]. To this end, connecting the traditional therapeutic functions of TCMs with modern neuropharmacology, together with the precise isolation and characterization of the active components from active TCMs, would be an important and practical topic for novel drug discovery and development of neuro-therapy in the future.

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