

Mini Review

Dysregulation of Autophagy Lysosomal Pathway in Alzheimer's Disease: Role of Curcumin

Panchanan Maiti^{1,2,3*} and Jayeeta Manna⁴¹Field Neurosciences Institute Laboratory for Restorative Neurology, Central Michigan University, USA²Program in Neuroscience, Central Michigan University, USA³Department of Psychology, Central Michigan University, USA⁴Department of Physiology, University of Tennessee Health Science Center, USA

*Corresponding author

Panchanan Maiti, Department of Psychology, Central Michigan University, USA, Email: maiti1p@cmich.edu

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- Tau
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- Chaperone mediated autophagy neurodegeneration

Abstract

Gradual accumulation of amyloid beta protein (A β) in extracellular spaces and phosphorylated tau (p-tau) intracellularly are the hall mark pathologies in Alzheimer's disease (AD). Protein degradation machinery, such as autophagy lysosomal pathway play a pivotal role to dispose these aggregates from the cell. Deficiency of autophagy can cause neurodegeneration, while activation of autophagy is protective against different proteinopathies. These pathways become dysfunctional or dysregulated in AD. Therefore, restoration or maintenance of these systems is essential and could be a promising strategy to remove A β -aggregates from neurons to prevent or delay further neurodegeneration in AD. Pharmacological manipulations, including use of natural compounds could be promising to keep them active. In this short review, the mechanistic details of the role of autophagy lysosomal pathway (ALP) are discussed, along with promising role of curcumin, a natural anti-amyloid polyphenol to boost this system. This brief and comprehensive review article should help the researcher to understand basic mechanism of role of ALP in AD and other neurological diseases, which are associated with protein misfolding.

ABBREVIATIONS

AD: Alzheimer's Disease; A β : Amyloid Beta Protein; P-Tau: Phosphorylated Tau; Cma-Chaperon Mediated Autophagy; Alp: Auto Phagylysosomal Pathway; Cur: Curcumin; Nc: Nano Curcumin; Hsc70: Heat Shock cognet 70; Lamp-2a-Lysosome: Associated Membrane Protein Type-2a; HSPS: Heat Shock Proteins; N2a: Neuro 2a Cell

INTRODUCTION

Biochemical, genetic and experimental evidence support that the accumulation of misfolded amyloid beta protein (A β) and phosphorylated tau (p-tau) are the key factor for neurodegeneration in AD [1]. Aggregation of excess amount of these misfolded protein aggregates are involved in impairs of synaptic communication in this disease [2]. Several protein degradation machineries, including molecular chaperones, proteasome system are responsible for degradation of most of this protein debris [3-5]. However, depending on the aggregates size, recruitment of different protease system may be occurred,

for example, some aggregates are too large to pass through the proteasome barrel, therefore cannot be disposed through this system [6]. Therefore, larger insoluble aggregates are engulfed by phagocytic mechanism, known as macro autophagy, whereas, relatively small aggregates are disposed by proteasome system with the help of molecular chaperones [6,7-9]. In contrast, relatively small soluble aggregates are degraded by lysosome through the autophagy lysosomal pathway (ALP) [6]. Importantly, failure of these systems severely affects the disposal of these toxic materials, as observed in different neurological diseases, including AD [10]. Therefore, it is vital to keep these protein clearance pathways active to avoid the misfolded protein loads buildup in the cell.

However, as a potent anti-amyloidogenic, neuroprotective, anti-inflammatory polyphenol, curcumin is a promising compound to combat against different protein-misfolding neurodegenerative diseases [5,11]. Although, its potential roles as a drug target are not fully understood in the case of neurodegenerative diseases. Recently we found that Cur can

regulate protein clearance pathways such as molecular chaperone and ALP in AD [12]. Unfortunately, because of its poor solubility in body fluids makes Cur less brain penetration, whereas nano curcumin (NC), a combination of solid lipid nano particle with Cur showed better solubility and bioavailability than dietary Cur [5,11,13,14,]. Therefore, as a potent natural polyphenol Cur and or NC can be applied to restore or maintenance or activation of protein degradation machineries to dispose misfolded amyloid proteins to combat against AD.

AUTOPHAGY LYSOSOMAL PATHWAY (ALP)

Autophagy-lysosomal pathway plays a pivotal role in removing misfolded protein debris in neurodegenerative diseases. It includes micro autophagy, macro autophagy and chaperone-mediated autophagy (CMA) (Figure 1). Among all these, CMA is the most specific and promising as a therapeutic approach to remove protein aggregates in the cells for neurodegenerative diseases, such as AD [10]. This process involves protein substrate recognition, the selective transport of those cytosolic proteins across the lysosomal membrane and internalization of that substrate protein to lysosomal lumen for

ultimate degradation. Indeed, most protein substrates for CMA contain a penta-peptide motif(KFERQ), which is recognized by an important molecular chaperone called heat shock cognet (HSC70) [6].When bound to the HSC70, the substrate is then targeted to the surface of the lysosomes, where it interacts with the cytosolic tail of a single-span membrane protein called lysosome-associated membrane protein type-2A (LAMP-2A) [9]. This interaction helps to internalization of the misfolded protein aggregates to the lysosomal lumen and then ultimately becomes degraded by lysozyme [7-9]. Thus, CMA is involved in protein quality control by amino acid recycling in different cellular stress conditions, including oxidative stress and different neurological diseases [7-9].

Role of autophagy lysosomal pathway in AD

The dysfunction of CMA triggers neuronal dysfunction and increases vulnerability to stress. In case of AD and tauopathies, tau undergoes degradation by CMA [6,10,15]. Similarly, amyloid beta protein has been co-localized with CMA complex in endoplasmic reticulum [16-19]. Therefore, impairment or dysfunction of CMA is intimately linked to the pathogenesis of AD. Misfolded A β

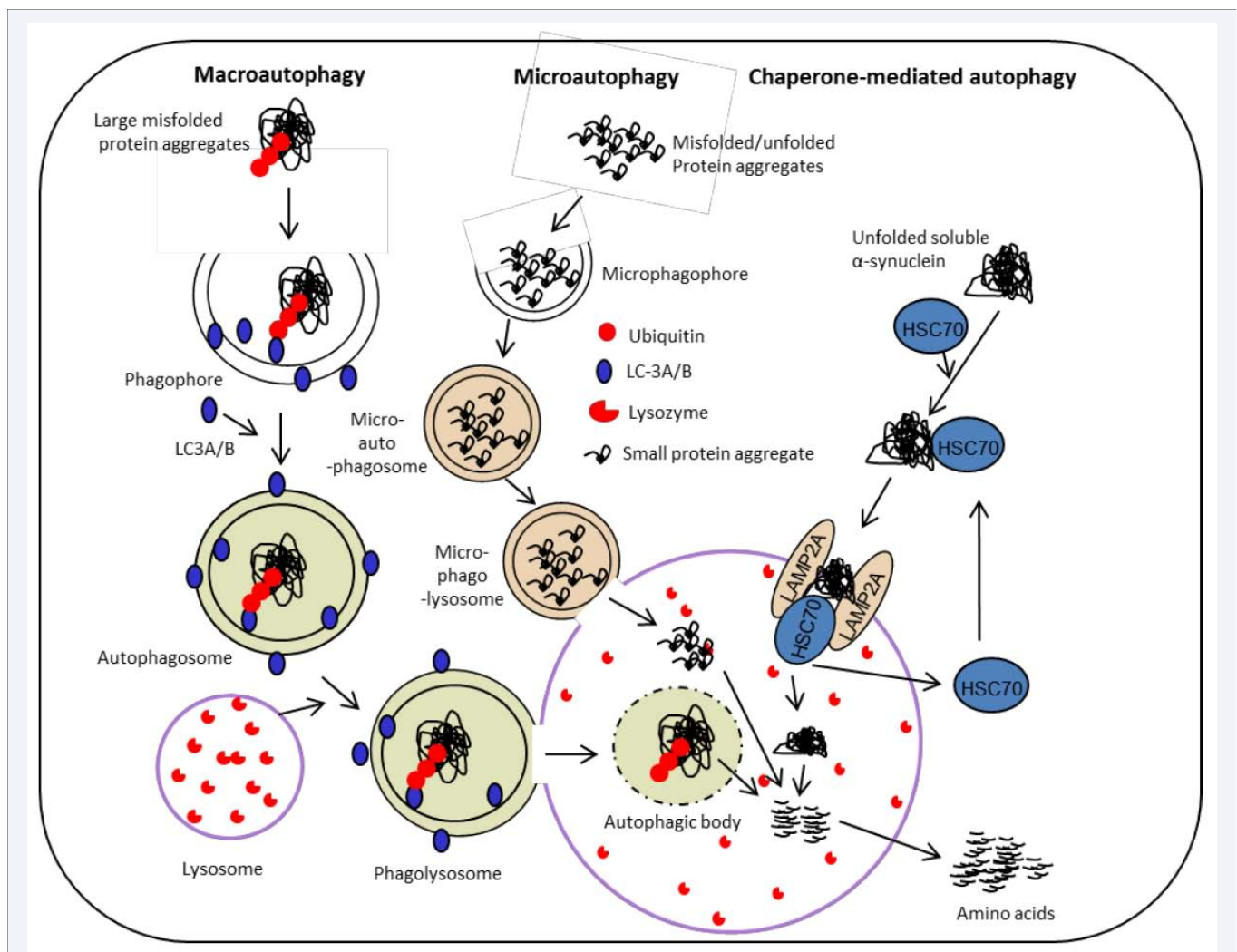


Figure 1 Schematic diagram show different process of autophagy lysosomal pathway (ALP) in degradation of misfolded amyloid proteins in neurodegenerative diseases. The ALP includes macroautophagy, microautophagy and chaperone mediated autophagy.

binds to the CMA-specific receptor LAMP-2A on the lysosomal membrane and is subsequently degraded by CMA [15,20,21]. Similarly, microtubule-associated protein 1A/1B-light chain 3 (LC3A/B) is the most widely used auto phagosomal marker involved in autophagy-related misfolded protein degradation in lysosome [15,20-22]. The expression of LAMP-2A and LC3A/B are severely affected by different neurodegenerative diseases including AD [10]. In fact, A β and p-tau undergoes degradation by CMA, where constitutive chaperone heat shock cognet 70 (HSC70) play a vital role for recognition of these proteins [16]. Therefore, CMA is considered one of the vital mechanisms of autophagy and a potential indicator for drug intervention in neurological diseases, such as AD [16].

Role of curcumin to activate autophagy lysosomal pathway

Curcumin is a natural polyphenol derived from the herb *Curcuma longa*. Chemically, it is a diferuloyl methane and lipophilic in nature. It has several pharmacological benefits including anti-amyloid, anti-oxidant, and anti-inflammatory and anti-carcinogenic properties [23-25]. It is also safe with high dose (up to 12g/day), and it can easily cross the blood brain barrier [23-25]. Whereas, the major obstacle for successful delivery of Cur to brain is its poor solubility to body fluids, poor absorption and rapid elimination through the excretory system. Several formulas of curcumin are available to increase its absorption and bioavailability. Recently, we used a solid lipid nanoparticle formula of Cur (nanocurcumin, NC) which showed greater solubility, more brain penetration and better neuroprotective effect than dietary Cur [5,26]. In our recent experiment, we found that NC is able to restore or maintain the downregulated molecular chaperones, such as several HSPs in mouse model of AD and *in vitro* [5,12,27]. We also found that NC is able to stimulate the markers for autophagy lysosomal pathway in rat cortical neurons (N2a). It also decreases A β -induced neuronal apoptosis, oxidative stress and increases cell survival marker proteins *in vitro* [12]. Therefore, stimulation of CMA or ALP using curcumin is useful to fight against A β or p-tau-induced neurodegeneration in mouse models of AD.

CONCLUSIONS

Autophagy lysosomal pathway play a vital role in disposal of toxic protein aggregates noted in several neurodegenerative diseases, including AD. Restoration or maintenance of these systems is essential in order to prevent or delay further neurodegeneration in AD. As a natural polyphenol curcumin might be a promising compound to boost these system, thus could be a potential therapy for AD.

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