Contribution of autophagy to the pathogenesis of Parkinson's disease: A Review

Chrysavgi Rouva

School of Medicine, Aristotle University of Thessaloniki, Greece

chrisavgirouva@gmail.com

Leonidas Stefanis

School of Medicine, National and Kapodistrian University of Athens, Greece

Laboratory of Neurodegenerative Diseases, Biomedical Research Foundation of the Academy of Athens, Greece

Hospital Eginition, Athens, Greece

lstefanis@bioacademy.gr

Abstract

Parkinson's disease (PD) is the most common movement disorder and the second most common neurodegenerative disease. Clinically, it is characterized by tremor, bradykinesia, rigidity and postural instability, as well as various non-motor symptoms. The major histopathological findings of the disease include the loss of dopaminergic neurons in the substantia nigra and the presence of intraneural inclusions called Lewy bodies. Recent genome-wide association studies (GWAS), traditional association studies as well as targeted studies conducted in rare familial forms of PD have identified, among others, allelic variations or mutations in genes linked to the autophagy-lysosomal pathway (ALP). Dysregulation of either macroautophagy or chaperone-mediated autophagy (CMA), the two main types of autophagy, may lead to the accumulation of pathological aggregated forms of proteins, such as α-synuclein. Protein aggregation associated with mitochondrial dysfunction and oxidative stress may lead to neurodegeneration and neuronal death. Elucidation and understanding of the precise pathophysiological mechanisms linking autophagy dysfunction to PD is of great importance. It may allow the development of targeted therapeutic interventions to boost autophagic degradation pathways, in an effort to counteract aberrant protein aggregation and halt disease progression in PD and other related neurodegenerative conditions.

Key words: Parkinson's disease, autophagy, α-synuclein, gene mutations

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Introduction

A) Parkinson's disease

Parkinson's disease (PD) is the most common movement disorder and the second most prevalent neurodegenerative disease (Hou et al., 2020). Clinically, PD is characterized by motor symptoms such as resting tremor, bradykinesia, rigidity, and postural instability. However, it also encompasses a range of non-motor symptoms, including REM sleep behavior disorder (RBD), dysautonomia, sensory symptoms, cognitive impairment, mood disorders, and pain (Church, 2021). The primary histopathological features of PD involve the loss of dopaminergic neurons in the substantia nigra and other brain regions, along with the presence of intracellular inclusions called Lewy bodies, which result from the accumulation of α-synuclein (Braak and Del Tredici, 2017). Molecular mechanisms underlying PD pathogenesis include abnormal folding and aggregation of α-synuclein, mitochondrial dysfunction, impaired protein degradation involving the ubiquitin-proteasome system (UPS) and autophagy-lysosome system (ALP), neuroinflammation, and oxidative stress (Jankovic and Tan, 2020).

Although sporadic PD accounts for the majority of cases, approximately 90-95%, only 5-10% of PD cases are familial. (Hou et al., 2020). Genome-wide association studies (GWAS) have identified over 20 monogenic causes of PD and more than 100 genetic loci as risk genes for PD development (Nalls et al., 2019; Senkevich et al., 2019; Balestrino and Schapira, 2020; Blauwendraat et al., 2020). Monogenic forms of PD are linked to mutations in genes such as SNCA, PINK1, PARK7, and LRRK2, while mutations in the GBA gene are considered the most significant genetic risk factor for PD in the general population (Day and Mullin, 2021). Two recent meta-analyses of GWAS have identified various allelic variations and mutations in genes associated with intracellular degradation pathways, including both lysosomal and autophagic pathways (Chang et al., 2017; Nalls et al., 2019).

B) Physiological functions of autophagy

Neurons rely on two main systems, the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP), for the degradation of dysfunctional proteins and organelles. The UPS is responsible for the degradation of short-lived proteins in the cytoplasm and nucleus (Kenney and Benarroch, 2015). Dysfunction of the UPS, resulting in the accumulation of misfolded proteins, has been implicated in the pathogenesis of PD (Lim, 2007; Park et al., 2021). In contrast to the UPS, the ALP is responsible for the degradation of long-lived proteins, protein aggregates, and cytoplasmic organelles, including mitochondria (Kenney and Benarroch, 2015). It has been observed that the activity of both the UPS and ALP declines with aging(Xilouri et al., 2012).

Autophagy is an intrinsic cellular process that plays a vital role in maintaining cellular homeostasis and promoting longevity and survival

through rigorous quality control of its components (Boya et al., 2018; Hansen et al., 2018). It serves as an adaptive mechanism to meet the metabolic demands of the cell and offers protection against metabolic and oxidative stress (Kenney and Benarroch, 2015). Moreover, autophagy is essential for critical developmental stages, including nutrient supply during embryogenesis, tissue growth, and differentiation (Mizushima and Levine, 2020). The pathway is also activated in response to various stressors such as exposure to toxins, infection, or oxidative stress. A key regulator of autophagy is mTOR (mammalian target of rapamycin), which inhibits the autophagy-related gene ATG1 and suppresses macroautophagy (Cao et al., 2021).

Autophagy is divided into three distinct types: Macroautophagy (commonly referred to as autophagy), chaperone-mediated autophagy (CMA), and microautophagy, as illustrated in Figure 1 (Cao et al., 2021; Ho et al., 2019). Macroautophagy is the best characterized form and can be further divided into non-selective and selective autophagy. It effectively degrades pathological proteins, aggregates, and even entire organelles such as mitochondria. On the other hand, CMA is a selective pathway in which the chaperone protein Hsc70 recognizes a specific pentapeptide sequence (KFERQ) in unfolded proteins and transports them to the lysosome, where they bind to the membrane receptor LAMP2A (Hou et al., 2020). Macroautophagy and CMA are interconnected processes, with inhibition of one often leading to activation of the other pathway (Wu et al., 2014). Microautophagy, in contrast, is a non-selective process responsible for the gradual and continuous degradation of cytoplasmic proteins, even under resting conditions (Pan et al., 2008). An important distinguishing feature among these pathways is the manner in which they deliver their respective substrates to the lysosomes (Xilouri and Stefanis, 2011).

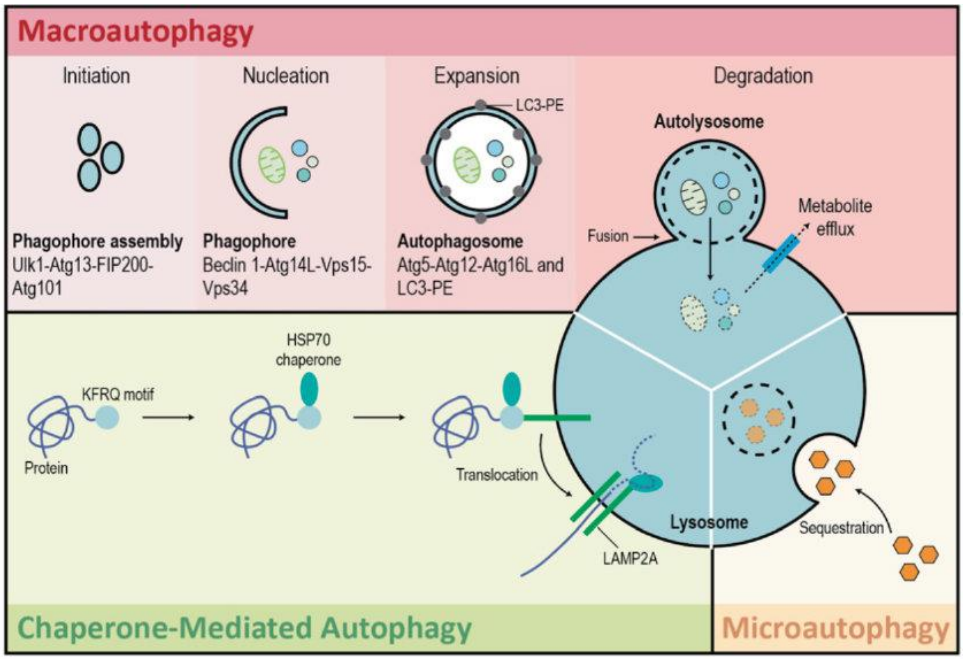

Figure 1: The three major types of autophagy and their mechanism

During the aging process, there is a decline in autophagic activity, which contributes to cellular degeneration and age-related changes. This reduction in autophagy has been implicated in various pathological conditions, including oncogenesis, autoimmunity, infection, and inflammation (Mizushima and Levine, 2020). Moreover, dysregulation of autophagy has been closely linked to the pathogenesis of both chronic neurodegenerative diseases, including Alzheimer's disease, PD, Huntington's disease, and amyotrophic lateral sclerosis (Park et al., 2020), and acute neuronal damage such as ischemia and trauma (Wolf et al., 2019). These findings highlight the crucial role of autophagy dysregulation in the development and progression of various disease states and emphasize the need for further research to understand and potentially modulate autophagy for therapeutic purposes.

The role of autophagy in the pathogenesis of Parkinson's disease

Hara et al. (2006) and Komatsu et al. (2006) conducted studies demonstrating that the selective removal of autophagy-related genes ATG5 and ATG7 in mice neurons leads to the formation of intracellular aggregates and inclusions, neuronal loss, and premature death. These findings suggest that disruption of autophagy may contribute to the development of neurodegenerative diseases in humans. Autophagy plays a critical role in degrading pathological proteins that accumulate and contribute to neurodegeneration. Mutations in ATG genes have been identified in various clinical presentations and phenotypic manifestations, including a range of neurological symptoms (Mizushima and Levine, 2020).

The ALP involves multiple steps that can malfunction, leading to abnormal protein accumulation and cell death. Dysfunctions can occur in the formation of autophagosomes or their fusion with lysosomes. Additionally, dysfunctions may involve the chaperone Hsc70, the lysosomal membrane receptor LAMP2A, or deficiencies in lysosomal enzymes (Pan et al., 2008). In the context of PD, impairments in macroautophagy and CMA may be attributed to factors such as aging, interaction between α-synuclein and dopamine in the substantia nigra, and general lysosomal dysfunction (Xilouri et al., 2008). Table 1 summarizes the pathological effects of abnormal proteins on autophagy and their possible contribution to the development of PD.

A) α-synuclein

α-Synuclein is a presynaptic neuronal protein encoded by the SNCA gene (PARK1). While its precise function is not fully understood, it is believed to be involved in synaptic vesicle transport and recycling processes (Sharma and Burré, 2023). The toxic effects of α-synuclein can occur through three mechanisms: overexpression of the wild-type protein due to SNCA gene multiplication, mutations in the protein, and modification by dopamine (Shan et al., 2021). Gene triplication is

associated with early-onset PD and cognitive impairment, in comparison to gene duplication (Singleton et al., 2003).
Normally, α-synuclein undergoes degradation through the UPS and CMA pathways. In CMA, α-synuclein directly interacts with the chaperone protein Hsc70 and is subsequently degraded by lysosomes (De Mattos et al., 2020). Wild-type and mutant α-synuclein exhibit similar affinity for binding to Hsc70. However, mutant α-synuclein has a particularly high affinity for the LAMP2A receptor, which prevents its transport into the lysosomal lumen for degradation (Yang and Mao, 2010), as illustrated in Figure 2 (Sala et al., 2016). This disruption of the CMA process leads to the inhibition of mutant α-synuclein degradation, as well as the accumulation and aggregation of other substrates. Additionally, dopamine modification of α-synuclein enables its binding to lysosomes, which further impairs the entry of protein substrates into lysosomes and ultimately compromises CMA function (Martinez-Vicente et al., 2008).

In addition to the inhibitory effect on CMA, it is important to investigate the involvement of macroautophagy in the context of α-synuclein aggregation. α-synuclein aggregates have been shown to resist degradation and hinder the overall activity of macroautophagy by suppressing autophagosome function (Tanik et al., 2013). Furthermore, the overexpression of wild-type α-synuclein disrupts macroautophagy in both mammalian cells and transgenic mice (Winslow et al., 2010). Therefore, α-synuclein aggregates can inhibit the ALP pathway either by directly affecting lysosomal components or by interfering with the transport of substrates at various stages of the pathway (Mazzulli et al., 2016).

Mao et al. (1999) elucidated the role of the MEF2D protein as a crucial factor for neuronal survival. Inhibition of MEF2D activity results in cell death, while increased MEF2D activity provides cellular protection (Tang et al., 2005; Smith et al., 2006). MEF2D directly interacts with Hsc70 and undergoes degradation via the CMA pathway. However, both wild-type and mutant forms of α-synuclein interfere with the interaction between MEF2D and Hsc70, hindering its uptake into lysosomes and subsequent degradation. Consequently, MEF2D accumulates, forms non-functional toxic aggregates, and renders neuronal cells susceptible to apoptotic stimuli (Yang et al., 2009).

Dysregulation of CMA in the central nervous system (CNS) leads to the relatively restricted buildup of substrates. On the other hand, the lack of selectivity in the macroautophagy process has more widespread effects in the CNS when the pathway is disrupted (Xilouri et al., 2008). Overall, previous research indicates that abnormal α-synuclein in familial forms of PD disrupts the autophagy process, resulting in the accumulation of cellular components and ultimately leading to the loss of dopaminergic neurons.

B) PRKN (PARK2), PINK1 (PARK6), DJ-1 (PARK7)

The proteins Parkin, PINK1, and DJ-1 are encoded by the PARK2 (PRKN), PARK6, and PARK7 genes, respectively. Mutations in these genes are

associated with autosomal recessive PD and result in impaired mitophagy, leading to the accumulation of abnormal mitochondria and an increase in oxidative stress (Day and Mullin, 2021). Notably, a decrease or loss of mitochondrial complex I activity has been observed in cells of PD patients (Petrillo et al., 2019). Moreover, the disruption of mitochondrial complex I function has been shown to cause progressive parkinsonism in genetically modified mice (González-Rodríguez et al., 2021). These findings collectively suggest that mitochondrial dysfunction may play a role in the pathogenesis of PD.

In healthy cells, PINK1 accumulates on the surface of dysfunctional mitochondria and recruits and activates Parkin, an E3 ubiquitin ligase. This activation of Parkin induces mitophagy, promoting the removal of damaged mitochondria and maintenance of cellular homeostasis (Quinn et al., 2020). Additionally, Bendikov-Bar et al. (2014) demonstrated that Parkin is involved in the degradation of mutant β-glucocerebrosidase through the proteasome. These findings support the notion that mutations in Parkin and PINK1 interfere with the targeting and degradation of both dysfunctional mitochondria and pathological proteins. Furthermore, DJ-1 has been implicated in neuronal survival maintenance (De Miranda et al., 2018). Loss of DJ-1 in Drosophila has been shown to result in altered mitochondrial homeostasis and impaired autophagic response (De Lazzari et al., 2023). Therefore, deletions or mutations in the PARK7 gene may play a significant role in the development of PD and neurodegeneration in general.

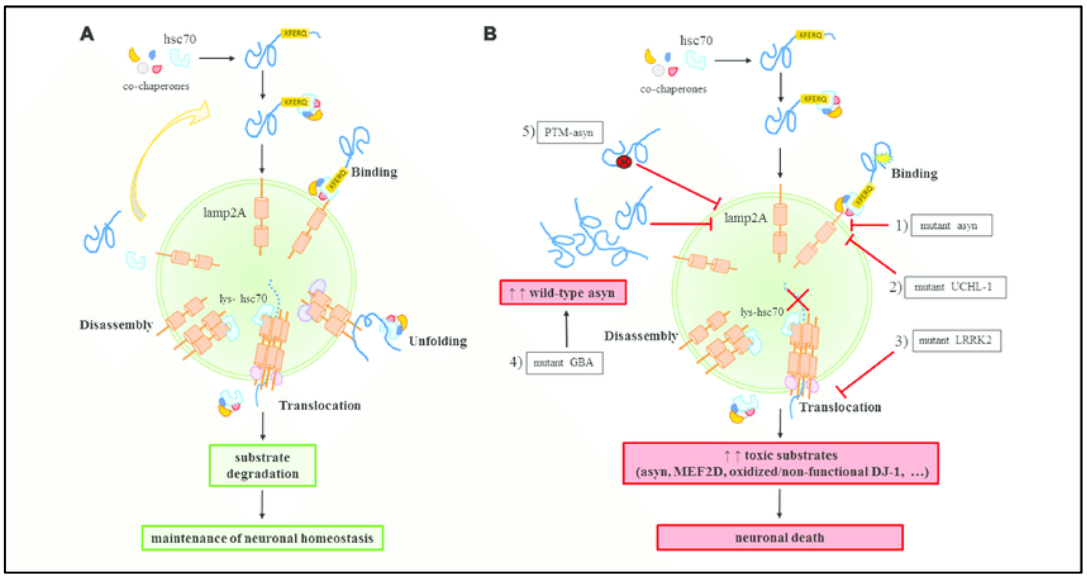

Figure 2: Alterations associated with both familial and sporadic forms of PD impair CMA and play a significant role in neuronal death.

C) LRKK2 (PARK8)

LRRK2,also known as Dardarin, is an protein encoded by the PARK8 (LRRK2) gene, the most common autosomal dominant gene associated with

PD. The most prevalent LRRK2 mutation is G2019S , found in both familial and sporadic PD (Simpson et al., 2022). Abnormal LRRK2 affects autophagy on multiple levels. Mutant LRRK2 induces autophagosome formation, but at the same time blocks autophagosome fusion with lysosomes, leading to their continuous accumulation. Furthermore, abnormal LRRK2 interacts with the lysosomal membrane receptor LAMP2A preventing transport of CMA substrates into lysosome for degradation, and promotes formation of α-synuclein fibrils onto lysosomal membranes (Figure 2). These abnormalities may contribute to α-synuclein aggregation and development of PD (Pang et al., 2022).

D) GBA

Glucocerebrosidase (GCase) is a lysosomal enzyme encoded by the GBA gene, the most common risk gene for the development of PD. Homozygous or compound heterozygous variants in the GBA gene cause Gaucher disease, whereas heterozygous GBA variants can lead to PD (Day and Mullin, 2021). Mutations in GBA lead to loss of enzyme function and deregulation of the ALP pathway. Decreased activity of the enzyme GCase results in the buildup of its substrate called glucosylceramide (GlcCer), which encourages formation of α-synuclein fibrils (Figure 2). The aggregation of α-synuclein impedes the transport of GCase from the endoplasmic reticulum (ER) to the lysosome, resulting in a further decrease in GCase activity within the lysosomes. This vicious cycle may play a significant role in the development of PD (Murphy et al., 2014; Pang et al., 2022).

E) ATP13A2

ATPase 13A2 is a lysosomal enzyme encoded by the ATP13A2 gene (PARK9), and mutations in this gene are associated with autosomal recessive parkinsonism (Day and Mullin, 2021). Downregulation of ATP13A2 results in defective autophagy, accumulation and aggregation of α-synuclein, and increased neurodegeneration in experimental models of PD (Wan et al., 2020; Dhanushkodi et al., 2023). Decreased levels or dysfunction of ATPase 13A2 in lysosomes inhibit lysosomal autophagy and degradation, ultimately resulting in the abnormal accumulation of α-synuclein (Bento et al., 2016; Zhang et al., 2022).

Table 1: Summary of Proteins, Genes, Chromosomes, and Pathological Effects in Parkinson's Disease

Involved Proteins	Encoding Genes	Chromosomal Location	Pathological Effects on Autophagy
α-synuclein	SNCA/PARK1	1q22	Interaction with LAMP2A & disruption of CMA Impaired degradation of mutant α-synuclein Aggregation of substrate proteins

			Suppression of autophagosome function and disruption of macroautophagy
Parkin	PRKN/PARK2	6q26	Impaired degradation of dysfunctional mitochondria and pathological proteins
PINK1	PARK6	1p36.12	Impaired degradation of dysfunctional mitochondria and pathological proteins
DJ-1	PARK7	1p36.23	Altered mitochondrial homeostasis and impaired autophagic response
LRRK2	LRRK2/PARK8	12q12	Inhibition of autophagosome-lysosome fusion Disruption of CMA through interaction with LAMP2A Accumulation of α-synuclein and other substrates
GCase	GBA	1q22	Dysregulation of the autophagy-lysosome pathway Aggregation of α-synuclein and other substrates
ATPase 13A2	ATP13A2/PARK9	1p36.13	Inhibition of lysosomal autophagy and degradation Abnormal accumulation of α-synuclein and other substrates

Therapeutic Strategies

The objective of the developed therapeutic strategies is not solely focused on improving PD symptoms but also on neuroprotection and disease modification. However, despite the persistent endeavors of researchers, this kind of treatments has not yet been developed (Mari and Mestre, 2022). Enhancement of the UPS system as a therapeutic approach for PD is not deemed effective due to the fact that the proteasome's substrates encompass both toxic proteins and vital

intracellular regulators with a limited lifespan, such as the tumor suppressor protein p53. Conversely, enhancement of the ALP pathway demonstrates potential benefits in preventing neuronal death, with numerous studies advocating its significance as a therapeutic target (Pan et al., 2008; Rana et al., 2021). Numerous researchers have emphasized the significance of promoting autophagy as a therapeutic intervention and advocate for a careful restoration of its levels, instead of uncontrolled activation, to mitigate potential adverse effects, including mitochondrial dysfunction, neurodegeneration, and cell death (Xilouri et al., 2021).

The restoration of autophagy can be accomplished by enhancing either CMA or macroautophagy. Studies have demonstrated that overexpression of the LAMP2A receptor and transcription factor EB (TFEB) can upregulate CMA, leading to a decrease in α-synuclein accumulation and toxicity both in vitro and in vivo (Decressac et al., 2013; Xilouri et al., 2013; Issa et al., 2018). Another therapeutic approach to enhance autophagy involves inhibiting the mTOR pathway using rapamycin or its analogs. In a study conducted by Webb et al. (2003) using cellular models, it was demonstrated that rapamycin-induced autophagy leads to the degradation of all forms of α-synuclein and exhibits cytoprotective properties. Subsequent studies have further shown that rapamycin reduces the accumulation of α-synuclein, improves motor function, and prevents neuron death in experimental models of PD (Crews et al., 2010; Malagelada et al., 2010; Bai et al., 2015). Additionally, mTOR-independent enhancement of autophagy can be induced by small molecule enhancers (SMERs) such as lithium and trehalose, which have demonstrated the ability to degrade pathological A53T α-synuclein (Sarkar et al., 2005; Sarkar et al., 2007).

The study conducted by McNeill et al. (2014) brought attention to the potential therapeutic use of ambroxol, a mucolytic drug, in PD. The study examined individuals with Gaucher disease, as well as heterozygous carriers of the GBA mutant gene (with and without PD), and compared their levels and activity of glycosylceramidase with those of healthy individuals. The results showed reduced levels and activity of glycosylceramidase and increased production of reactive oxygen species (ROS) in the patient groups. However, after treatment with ambroxol, there was an observed improvement in these biochemical parameters within the lysosomes, indicating an increase in glycosylceramidase activity and a decrease in oxidative stress markers. Thus, the use of ambroxol in the therapeutic approach of PD holds potential benefits.

The study conducted by Vicente Miranda et al. (2017) identified glycation as a potential therapeutic target for synucleinopathies and neurodegenerative diseases in general. The process of glycation, a post-translational modification, was found to enhance α-synuclein toxicity both in vitro and in vivo, as observed in experimental Drosophila and mouse models. This effect was attributed to a decrease in the degradation of α-synuclein and the subsequent accumulation of its oligomers. However, when glycation was inhibited, α-synuclein degradation was restored, aggregates were reduced, and the motor

phenotype in Drosophila improved. These findings suggest that targeting glycation could have therapeutic implications for synucleinopathies and other neurodegenerative diseases.

Recent studies have placed emphasis on investigating the therapeutic potential of natural compounds in the treatment of neurodegeneration and PD, revealing promising results in terms of neuroprotection (Stacchiotti and Corsetti, 2020; Chen et al., 2021). Last but not least, the use of monoclonal antibodies to inhibit the accumulation and propagation of α-synuclein aggregates has shown promising neuroprotective effects (Jankovic et al., 2018; Brys et al., 2019; Fleming et al., 2022).

Discussion

Parkinson's disease is a neurodegenerative movement disorder closely associated with the inhibition of autophagy. Mutations in genes responsible for or predisposing to the development of the disease impair various stages of autophagy through diverse mechanisms. The accumulation of abnormal protein aggregates, coupled with mitochondrial dysfunction, leads to neurodegeneration and cell death. Understanding the precise pathophysiological mechanisms that link autophagy dysfunction to Parkinson's disease may pave the way for targeted therapeutic interventions aimed at enhancing autophagic degradation pathways. Such interventions could help counteract aberrant protein aggregation and halt disease progression in Parkinson's disease and other related neurodegenerative conditions.

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