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Mutant Genes in Amyotrophic Lateral sclerosis Associated with Autophagy

Jiawen Gan[1], Chenci Xu[1], Yanxiang Li[1], Zhuoyang Zhang[1], Yang Jianwei[2]* and Yanhua Yao[1]*

[1]Cell and molecular biology teaching laboratory, Experimental teaching center, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[2]Department of Orthopaedic Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

***Corresponding author:** Yanhua Yao, Cell and molecular biology teaching laboratory, Experimental teaching center, Shanghai Jiao Tong University School of Medicine, hanghai 200025, China Yang Jianwei, Department of Orthopaedic Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

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ABSTRACT

Deficiency in intracellular transport is one key pathogenesis of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease. Autophagy, as an important part of intracellular transport, can clear protein aggregates. It can be dysregulated by several ALS-related gene mutations which will finally cause motor neuron degeneration. This review summarizes the recents findings about the function of dynactin subunit 1, valosin containing protein, sequestosome 1, optineurin, TANK binding kinase 1, C9orf72-SMCR8 complex subunit and alsin Rho guanine nucleotide exchange factor which may partly explain the possible reason of autophagy dysregulation in ALS.

Keywords: Amyotrophic Lateral Sclerosis, Intracellular Transport, Autophagy, Gene Mutations

Introduction

Amyotrophic lateral sclerosis (ALS) is also known as gradual freezing disease, which is a fatal neurodegenerative disease. ALS, as the most common acquired motor neuron disease as well as the third common neurondegenerative disease [1], will affect both upper and lower motor neurons, showing progressive muscle paralysis. After the clinical attack, the patients survived an average of three years, and finally died of respiratory failure caused by respiratory muscle paralysis. As many as 50% of ALS patients will have cognitive and behavioral disorders, and about 13% of patients will have behavioral variant frontotemporal dementia [2]. ALS is divided into sporadic ALS (sALS) and familial ALS (fALS), and sALS accounts for about 90% to 95% of all cases [3]. The average age of onset of initial symptoms of ALS is 60 years old, while the age of onset of fALS will be slightly younger [4]. The incidence of ALS is about 1-3/100,000 [5] and the prevalence is about 6-7/100,000 in Europe [6]. The specific pathogenesis of ALS has not yet been elucidated. Known patheogenesis including SOD1(superoxide dismutase 1)-related mitochondrial dysfunction [7,8], damage to neuronal cells caused by glutamates excitotoxicity, the accumulation of abnormal protein aggregates and abnormally phosphorylated neurofilament NFs in cell bodies and axons [8].

Related Gene Mutations Cause Neuronal Transport Disorders

There are multiple gene mutations involved in different pathogenic mechanisms of ALS. Different patients have different gene mutations. The genetic mutation rate is more closely related to fALS at 55.0%, and 11.7% in sALS [9]. Gene mutations are involved in multiple pathogenesis of ALS. A very important part of it is the defect of neuronal material transport, including endosomal transport, endoplasmic reticulum Golgi transport, axon transport, autophagy, etc. which are essential steps to maintain normal cell function [10]. In this review, we will focus on the ALS mutant genes associated with autophagy.

DCTN1

DCTN1(dynactin submit 1) mutation is a rare mutation in ALS, affecting the transport of autophagosomes in axons. DCTN1 encodes dynactin subunit P150-G59S. In neuronal autophagy, aging mitochondria and protein aggregates form autophagosomes at the distal ends of the axons and fused with lysosomes retrogradely along the axons to form mature autophagic lysosomes, which are finally degraded in somatic cells [11]. Distal autophagosomes are

rapidly transported to somatic cells through microtubule-based motor cytoplasmic dynein and its activator DCTN1. The mutation of p150 is associated with ALS and chronic progressive autosomal dominant form of lower motor neuron disease [12].

VCP/p97

VCP (valosin containing protein) gene mutations are common in classic ALS [13]. Ubiquitin-guided AAA-ATPase VCP/p97 controls the endolysosome damage response pathway (ELDR), ensuring cell survival after lysosome rupture and promoting autophagy clearance of damaged organelles [14]. After damage, p97 translocates to the lysosome and cooperates with a unique set of cofactors. p97 and its cofactors play a role in downstream of K63 ubiquitination and p62 recruitment which can specifically remove K48-linked ubiquitin conjugates on damaged lysosomes. The presence of K48 ubiquitin conjugate may be incompatible with the Microtubule-associated protein 1 light chain 3 (LC3) recruitment during macroautophagy [14]. LC3 regulats the assembly and disassembly of tubulin. Conjugating to the autophagosome membrane, LC3 promotes the fusion of autophagosomes and lysosomes [15]. Therefore, the removal of K48 conjugate can promote the formation of autophagosomes. P97 helps to clear the late endosomes/lysosomes of ruptured endocytic tau fibrils. In addition, the mutation of VCP will reduce the autophagy clearance of stress granules and P-bodies, which are conserved cytoplasmic aggregates of non-translating mRNPs, implicating in the regulation of mRNA translation and decay. mRNPs are involved in the regulation of mRNA translation and decay. Increase of aggregates are very important to neurodegenerative disease [16].

SQSTM1/p62

SQSTM1(sequestosome 1) is a scaffold protein that plays a role in a variety of signaling pathways, including amino acid detection, oxidative stress and DNA damage response. SQSTM1 and OPTN (optineurin), mediating selective autophagy, are prototype autophagy receptors commonly found in protein aggregates associated with major neurodegenerative diseases [17]. The aggregation and phosphorylation of SQSTM1 represent the stress response that causes selective autophagy. P62 co-localize with TDP-43 (TAR DNA-binding protein of 43 kDa)-immunopositive inclusions [18]. The p62 protein is involved in two main protein degradation pathways: autophagy and the ubiquitin-proteasome system. It can act as a shuttle factor of the proteasome. p62 can also directly interact with LC3. p62 and OPTN induce ubiquitination substrates to be encapsulated by autophagosomes through their LC3 binding sequence. The consumption of p62 inhibits the recruitment of LC3 to autophagosome [11,19]. In addition to self-mutation to reduce autophagy of damaged proteins, p62 may also cause damage to the mitochondrial autophagy pathway due to abnormal phosphorylation. Genes involved in this process including OPTN and TBK1(TANK binding kinase 1) will be discussed later.

OPTN and TBK1

As mentioned earlier, OPTN is also an autophagy receptor-mediated substrate related to LC3 that is encapsulated by autophagosomes. OPTN is involved in mitochondrial autophagy. Mitophagy can selectively eliminate mitochondria damaged by aging and is very important for neuronal homeostasis. In the process of mitochondrial autophagy, damaged mitochondria are targeted for degradation by ubiquitination induced by PTEN-induced putative kinase 1 (PINK1) and Parkin. Mitophagy receptors, including optineurin (OPTN), nuclear dot 52 kDa protein (NDP52), and Tax1-binding protein 1 (TAX1BP1), are recruited to mitochondria via ubiquitin binding and mediate autophagic engulfment through their association with LC3(20). It is worth mentioning that PINK1 and Parkin are two common mutant proteins in Parkinson's disease [11]. The specificity of autophagosomes to phagocytose damaged mitochondria depends on OPTN and its kinase TBK1. The recruitment of OPTN occurs simultaneously with the recruitment of upstream TBK1. TBK1-dependent phosphorylation of OPTN S177 is necessary for the efficient formation of autophagosomes around depolarized mitochondria [20]. Therefore, impaired OPTN function due to mutation or damage, the elimination and inhibition of TBK1, and the appearance of ALS-related TBK1 mutants will all affect the autophagy of depolarized mitochondria [20]. TBK1 can also act as a phosphorylation kinase of p62, increasing the affinity of p62 for ubiquitinated substrates [17].

C9ORF72

The GGGGCC amplification in C9ORF72(C9orf72-SMCR8 complex submit) is one of the typical lesions in ALS, and it is currently a hot research direction. C9ORF72 forms a complex with SMCR8 and WDR41 [21]. SMCR8 regulated by TBK1 phosphorylation interacts with various RAB GTPases, and the C9ORF72-SMCR8 complex promotes the in vitro GDP/GTP exchange of Rab8a and Rab39b, acting as the GDP/GTP exchange factor (GEF) of RAB8a and RAB39b [22]. Rab-GTPase controls the intracellular transport pathway, including the different steps of vesicle formation, movement and membrane fusion [23]. Rab-GTPase alternates between two conformational states: the activated guanylate triphosphate (GTP) binding state and the guanosine diphosphate (GDP) binding inactive state. The exchange of GDP with GTP is catalyzed by GEF. When TBK1 is depleted, it can be recovered by Rab39b, indicating that TBK1, SMCR8, C9ORF72, and RAB39b belong to the common pathway to regulate autophagy [21]. The decrease of C9ORF72 will lead to impaired autophagy and increase the abnormal protein aggregates of p62 and TDP-43 [21,22,24]. Also enhances the aggregation and toxicity of ALS-linked factor Ataxin-2 (ATXN2) [21]. In addition, C9ORF72, as an effector of Rab1A, can control the transport of ULK1 complex to regulate the initiation of ULK1-dependent autophagy. The reduction of C9ORF72 will reduce the formation of LC3-positive autophagosomes [25].

ALS2

ALS2 (Alsin Rho Guanine Nucleotide Exchange Factor ALS2) is a gene involved in defective endosomal transport in ALS. ALS2 contains a ATS1/RCC1-like domain, a RhoGEF domain and a vacuolar protein sorting 9 (VPS9) domain. Alsin-2 acts as the GEF of Rab5 and localizes with Rab5 in the early endosomal compartment [24]. Rab5 is closely related to the budding of vesicles and mediates endocytosis and endosome fusion of clathrin-coated vesicles (CCVs) facilitating receptor trafficking [23]. The defective mutation of Rab5 has been found can stimulate the fusion of homotypic primary endosomes and form giant early endosomes, indicating that the active GTP binding form of Rab5 participates in the fusion of endosomes [23,26]. Therefore, when the function of ALS2 is impaired, Rab5 is still in GDP-bound state due to lack of GEF, so the degree of interaction with downstream effectors is small. ALS2 indirectly affects autophagy through vesicle transport.

Discussion

The above-mentioned genes regulate autophagy-related proteins such as LC3, GEF, etc., and participate in the formation of autophagosomes in neurons (ie, autophagy precursors and lysosomal membrane synthesis of autophagolysosomes). VCP can help damaged autophagosomes to remove K48 conjugates and promote the recruitment of LC3 [14]. The selectivity of autophagy is mediated by autophagy receptors such as SQSTM1/p62 and OPTN. With the help of its phosphorylation kinase TBK1, it interacts with LC3 to recognize and recruit substrates into autophagosomes [17,20]. TBK1 is also the phosphokinase of the C9ORF72-SMCR8 complex, which interacts with a variety of Rab-GTPases and participates in the common pathway of regulating autophagy [21]. ALS2(alsin Rho guanine nucleotide exchange factor) is involved in the budding and transport of vesicles and indirectly affects autophagy [27]. Although the direct pathological role between these genes and the pathogenesis of ALS is not clear, it is certain that mutations in these genes directly or indirectly hinder the elimination of organelles and abnormal proteins in neurons which is an important cause of the final degeneration of motor neurons. The current research and clinical treatment options for ALS are very limited. As a small part of the pathogenesis of ALS, neuronal autophagy defects cannot be directly applied to the clinic, but the research on the function of these genes will definitely provide more possiblility for ALS intervention Treatment.

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Yanhua Yao. Biomed J Sci & Tech Res

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