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Review

# Optineurin: The autophagy connection

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ABSTRACT

Optineurin is a cytosolic protein encoded by the *OPTN* gene. Mutations of *OPTN* are associated with normal tension glaucoma and amyotrophic lateral sclerosis. Autophagy is an intracellular degradation system that delivers cytoplasmic components to the lysosomes. It plays a wide variety of physiological and pathophysiological roles. The optineurin protein is a selective autophagy receptor (or adaptor), containing an ubiquitin binding domain with the ability to bind polyubiquitinated cargoes and bring them to autophagosomes via its microtubule-associated protein 1 light chain 3-interacting domain. It is involved in xenophagy, mitophagy, aggrephagy, and tumor suppression. Optineurin can also mediate the removal of protein aggregates through an ubiquitin-independent mechanism. This protein in addition can induce autophagy upon overexpression or mutation. When overexpressed or mutated, the optineurin protein also serves as a substrate for autophagic degradation. In the present review, the multiple connections of optineurin to autophagy are highlighted.



**Contents**



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## 1. Introduction

*Optineurin* is a gene linked to normal tension glaucoma (NTG) and amyotrophic lateral sclerosis (ALS) (Kachaner et al., 2012b; Osawa et al., 2011; Ying and Yue, 2012). It is also associated with Paget's disease of the bone (Albagha et al., 2010). This gene encodes a cytosolic protein that interacts with a number of proteins and participates in basic cellular functions such as vesicle trafficking, maintenance of the Golgi apparatus, NF-κB pathway, anti-bacterial and antiviral signaling, cell division control, and autophagy. Mutation or level alteration of optineurin results in adverse consequences in the cells leading to diseases (Gao et al., 2014; Park et al., 2010; Turturro et al., 2014). The molecular mechanisms, however, are largely not understood.

The ubiquitin–proteasome system (UPS) and autophagy are two main systems by which the cell degrades cytoplasmic constituents. The UPS targets short-lived or abnormally folded proteins, while the autophagy targets long-lived macromolecular complexes and organelles (Glickman and Ciechanover, 2002; Kirkin et al., 2009).

Degradation of a protein via the UPS involves two successive steps: tagging of the substrate protein by covalent attachment of single or multiple ubiquitin molecules and the subsequent degradation of the tagged protein by the 26S proteasome. At the tagging or conjugation stage, ubiquitin is covalently attached to the protein substrate through a series of ATP-dependent enzymatic reactions by E1 (ubiquitin activating), E2 (ubiquitin conjugating) and E3 (ubiquitin ligating) enzymes (Glickman and Ciechanover, 2002; Pickart, 2004). This process renders the ubiquitinated protein to be recognized by the proteasome and be degraded to small peptides (Zheng et al., 2014).

Autophagy (cellular self-eating or self-digestion) is a basic catabolic mechanism that involves bulk cell degradation of cellular components (Klionsky, 2005). There are three forms of autophagy: macroautophagy, microautophagy (Mijaljica et al., 2011), and chaperone-mediated autophagy (Kaushik and Cuervo, 2012). Among them, macroautophagy (herein referred to as autophagy) is the major pathway to eradicate damaged cell organelles or unused proteins. It is initiated with the sequestration of cytoplasmic components such as the entire organelles, lipid vesicles, or protein aggregates within double-membrane vesicles (so-called autophagosomes). These vesicles are then fused with lysosomes to generate autolysosomes, in which the autophagic cargo is degraded by acidic hydrolases (Galluzzi et al., 2014; Klionsky, 2005). Autophagy can be relatively nonselective, virtually any portion of the cytoplasm can be targeted to lysosomal degradation, triggered by nutrient deprivation. It can also be highly selective, triggered by damaged organelle or intracellular pathogens (Mizushima and Komatsu, 2011). Defects in the autophagic machinery have been associated with diseases, including aging, cancer, neurodegenerative diseases, cardiovascular disorders, and infectious/inflammatory conditions.

The UPS and autophagy were regarded originally as independent and separate pathways, but were found more recently to be closely connected (Wojcik, 2013). The crosstalk between ubiquitination and autophagy is guided by autophagy receptors or adaptors such as multi-domain scaffold/adaptor protein p62/sequestosome-1 (p62/SQSTM-1) and nuclear domain 10 protein 52 (NDP52). These receptors/adaptors can bind both ubiquitin and autophagy-related gene 8 family members microtubule-associated protein 1A/1B-light chain 3/γ-aminobutyric acid receptor-associated protein (LC3/GABARAP) (Wilde et al., 2011) and act as a bridge recognizing selective ubiquitinated proteins or cargoes and bringing them into autophagosomes (Komatsu et al., 2007).

Similar to p62, optineurin has also been shown to be an autophagy receptor or adaptor. In addition, optineurin, upon upregulation or mutation, can induces autophagy and become a substrate for autophagic clearance. Accumulating evidence indicates that optineurin partakes in various cellular functions through autophagy. Herein, we briefly illustrate the multiple connections of optineurin with autophagy.

## 2. Optineurin gene and protein

### 2.1. Gene structure, and mutations in diseases

The human *optineurin* gene (*OPTN*) is located at chromosome 10p13 and spans about a 37 kb genomic region. Its mRNA contains a total of 16 exons. The first 3 exons (exons 1–3) are noncoding sequence and the remaining 13 exons (exons 4–16) code for a 577-amino acid (aa) protein (Rezaie et al., 2005; Ying and Yue, 2012).

The *OPTN* gene was found by Rezaie et al. in 2002 to be a disease-causing gene in NTG, a subtype of primary open angle glaucoma (POAG). Four mutations in *OPTN*, $Glu^{50}\rightarrow Lys$ (E50K), $Met^{98}\rightarrow Lys$ (M98K), $Arg^{545}\rightarrow Gln$ (R545Q), and 691_692insAG (2-bp “AG” insertion), were detected from 54 families with adult-onset POAG in which most displayed normal intraocular pressure (Rezaie et al., 2002). Among the mutations, E50K is seen associated with a more progressive and severe disease (Aung et al., 2005; Hauser et al., 2006). Other *OPTN* alterations observed include $Lys^{322}\rightarrow Glu$ (E322K), $His^{26}\rightarrow Asp$ (H26D), $Glu^{103}\rightarrow Asp$ (E103D), $Val^{148}\rightarrow Val$ (V148V), intron IVS7 + 24G→A, and $His^{486}\rightarrow Arg$ (H486R) (Leung et al., 2003; Willoughby et al., 2004).

*OPTN* mutations were also reported in patients with ALS. Maruyama et al. (2010) identified a homozygous deletion of exon 5, a homozygous nonsense $Gln^{398}\rightarrow$ stop (Q398X) and a heterozygous missense $Glu^{478}\rightarrow Gly$ (E478G) mutations in Japanese ALS patients. Besides exon 5 deletion, exon 1–5 and 3–5 heterozygous *OPTN* deletions were also detected, indicating that the exon might be a hotspot for OPTN deletion in ALS and that OPTN deletions are ALS-specific events (Iida et al., 2012). Other *OPTN* alterations reported in ALS include 382_383insAG (691_692insAG or 2-bp “AG” insertion), $Arg^{96}\rightarrow Leu$ (R96L), $Gln^{165}\rightarrow$ stop (Q165X), $Gln^{454}\rightarrow Glu$ (Q454E), and a heterozygous truncating mutation $p.Lys^{440}\rightarrow Asnfs^{*}8$ (c.1320delA) that causes a frameshift and a premature stop codon ((Weishaupt et al., 2013). The 382_383insAG or 691_692insAG mutation has been previously described in familial POAG (Rezaie et al., 2002). Additionally, 3 POAG alterations (M98K, E322K, and R545Q) were also noted in ALS (Weishaupt et al., 2013).

### 2.2. Protein structure and function

The optineurin protein is expressed in many tissues including the heart, brain, skeletal muscle, liver, and the eye (Li et al., 1998; Rezaie et al., 2005). The protein contains a NF-κB-essential molecule (NEMO)-like domain, leucine zipper and coiled-coil motifs, an ubiquitin-binding domain (UBD), a LC3-interacting region (LIR), and a carboxyl (C)-terminal C2H2 type of zinc finger (Ying and Yue, 2012). The endogenous or ectopically expressed optineurin has been shown to interact with itself to localize in foci and form high molecular weight protein complexes (homo-oligomers) in cells (Gao et al., 2014). It also binds with Ras-related protein 8, huntingtin, myosin VI, transferrin receptor, metabotropic glutamate receptor, transcription factor IIIA, serine/threonine kinase receptor-interacting protein 1, CYLD that is a product of a familial cylindromatosis tumor-suppressor gene (Nagabhushana et al., 2011), LC3/GABARAP (Ying and Yue, 2012), polo-like kinase 1 (Kachaner et al., 2012a), TANK (TRAF-associated NF-kB activator) binding kinase 1 (TBK1), and HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1 (HACE1; Liu et al., 2014). These interactions, shown in Fig. 1, depict basic optineurin functions or