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Chapter 18

Choosing Lunch: The Role of Selective Autophagy Adaptor Proteins

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Abstract

Autophagy (macroautophagy) is a lysosome-dependent catabolic pathway that degrades damaged organelles, protein aggregates, microorganisms, and other cytoplasmic components. Autophagy was previously considered to be nonselective; however, studies have increasingly established that autophagy-mediated degradation is highly regulated. Selective autophagy regulates plenty of specific cellular components through specialized molecules termed autophagy receptors, which include p62, NBR1, NDP52, optineurin, and VCP among others. Autophagy receptors recognize ubiquitinated cargo and interact with the LC3/GABARAP/Gate16 protein on the membrane of nascent phagophore. In this review, we summarize the advances in the molecular mechanisms of selective autophagy adaptor proteins.

Keywords: selective autophagy, adaptor proteins, p62, optineurin, NDP52

1. Introduction

The various functions of eukaryotic organisms depend largely on the existence of highly efficient regulation mechanisms. Each physiologic activity involves the production of several molecules whose half-life must be controlled by degradation system to maintain homeostasis. Up to the present time, two systems of degradation molecules or organelles are known: (a)

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ubiquitin-proteasome system (UPS) and (b) autophagy, a lysosome-dependent degradation system. The precise mechanisms to lead the substrate to UPS or autophagy are not understood completely. However, it is known that ubiquitin is a key protein to regulate the substrate recognition through the conjugation of a single ubiquitin monomer (monoubiquitination) or sequential conjugation of several ubiquitin moieties (polyubiquitination). The conjugation of four ubiquitin monomers is sufficient signal to allow the ubiquitylated target protein to be recognized by UPS [1]. The specificity in the UPS is generated by the ability of ubiquitin to form eight different chain linkages on itself, through its seven lysine residues (K6, K11, K27, K29, K33, K48, and K63). K48 ubiquitin chain is the most well studied and was originally identified as the signal to target proteins to proteasomal degradation [2]. K11 and K63 ubiquitin chains are more related to signal for nonproteolytic functions as DNA repair and cell signaling, but a recent study shows that heterotypic K11/K48-polyUb chains bind to the proteasome and facilitate the degradation of cyclin B1 [3]. Whereas UPS is the major degradation pathway for short-lived and regulatory proteins, autophagy is more linked with the elimination of long-lived proteins and organelles. The selectivity of autophagy degradation is conferred by K63 ubiquitin chains [4, 5] (**Figure 1**). Autophagy was first described as a nonselective bulk degradation system, and now the accumulated evidence indicates that autophagy can be highly selective. Nonselective autophagy is triggered as a response to starvation and implies the random formation of the autophagosomes with the subsequent capture of any organelle or molecule near the autophagosome. In contrast, the selective autophagy is involved in the recruitment of different adaptor proteins that interact with Atg proteins and target organelles or molecules to be degraded [6, 7]. It is possible to distinguish

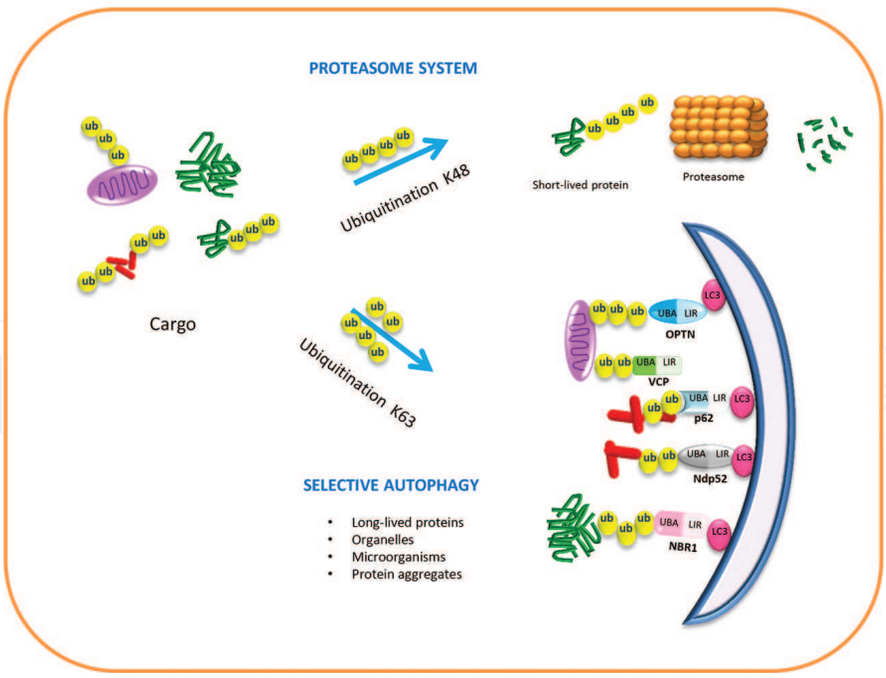

Figure 1. Schematic representation of selective autophagy. The two degradation pathways are shown. Mitochondria, misfolded proteins, and microorganisms are ubiquitinated and selected to proteasome system or autophagy. Selective autophagy involves the participation of adaptor proteins as p62, NDP52, optineurin, NBR1, and VCP, as bridges to cargo and nascent phagophore.

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various types of selective autophagy, depending on the cargo that is captured and degraded: lipid droplets (lipophagy), mitochondria (mitophagy), ER (reticulophagy), pathogens (xenophagy), and aggregation-prone proteins (aggrephagy) [8], among others. Nevertheless, the precise mechanism of cargo recognition remains unclear; the molecular characterization of autophagy receptors, initially SQSTM1/p62 and NBR1, has revealed that ubiquitination is involved in substrate selectivity. Most autophagy receptors have a ubiquitin-binding domain (UBD) and LC3-interacting region (LIR). The UBD domains attach to target molecules or organelles, and LIR domain interacts with LC3/GABARAP/Gate16 protein in autophagy to facilitate autophagosome formation, transport, and/or maturation [8]. The core of LIR consists of D/E, D/E, D/E, F/W/Y, X, X, L/I/V, and D; the phosphorylation of this domain enhances the affinity with LC3/GABARAP/Gate16 protein [7]. In this chapter, we discuss the recent knowledge on autophagy receptors and their role in selective autophagy.

2. SQSTM1/p62

SQSTM1/p62 (referred to hereafter as p62) was initially identified as a phosphotyrosine-independent binding of a 62 kDa (gave p62 its name) to the Src homology 2 (SH2) domain [9]. Subsequently, the term sequestosome-1 (SQSTM1) was assigned for its capacity to sequester polyubiquitinated protein to cytoplasmic storage before its degradation by the proteasome, protecting the cytosol from the toxic effect of misfolded proteins [10]. Currently, p62 has been considered a protein with pleiotropic activities, derived from their multiple domains, which interact with several molecules involved in the cellular death, oxidative stress, inflammatory response, and recognition of molecules to be degraded by UPS or autophagy [10, 11]. Recent studies have reported that mTOR activation depends on p62 as a key regulator of the nutrient-sensing pathway [12].

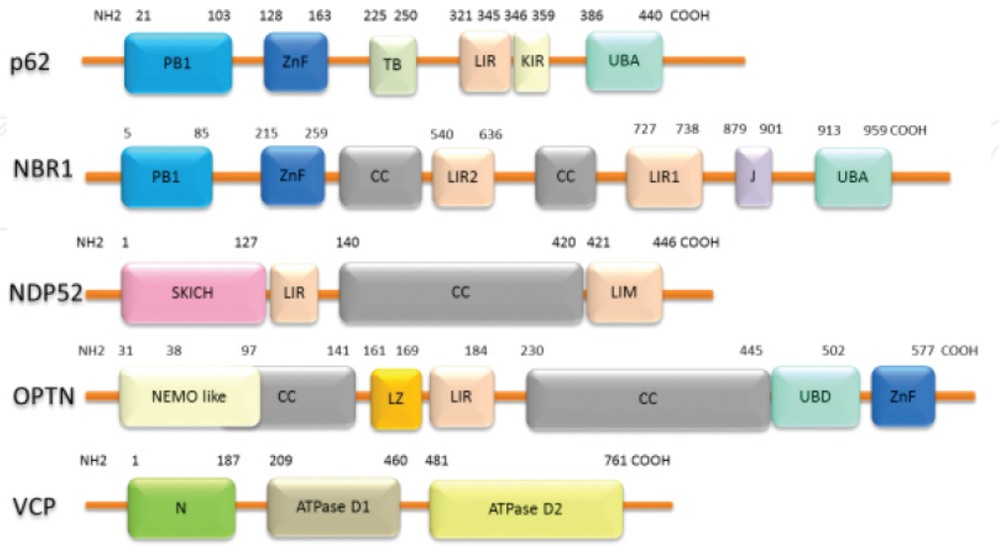

Figure 2. Structure of adaptor proteins involved in selective autophagy.

p62 is a multifunctional protein of 440-amino acids that is conserved in metazoans but not in plants and fungi [13]. Refractory to Sigma P (Ref(2)P) is a homologue protein of mammalian p62 in Drosophila melanogaster, that regulates protein aggregation in adult brain [14]. p62 has six functional domains: the N-terminal Phox/Bem1 domain (PB1, 21–103 aa), a ZZ-type zing finger domain (ZnF, 128–163 aa), TRAF6-binding domain (TB, 225–250 aa), a short LC3-interacting region (LIR, 321–345 aa), KEAP1-interacting region motifs (KIR, 346–359), and ubiquitin-associated domain (UBA, 386–440 aa) which is localized in C-terminal end (**Figure 2**) [11].

PB1 domains, ZZ zinc finger, KIR, and UBA can bind several proteins to participate in inflammatory responses and receptor-mediated signal transduction. PB1 has been associated with atypical protein kinase C (aPKC) to activate NF-kB signaling pathway. The ZZ zinc finger domain is responsible for binding the receptor interacting protein (RIP) to regulate the inflammatory response. The KIR region of this scaffold protein is a regulator for Nrf2, and its activation induces transcription of oxidative stress response genes [11, 15].

p62 provides a link between the degradation of ubiquitin cargo by UPS or autophagy through the UBA domain. The PB1, LIR, and UBA domains are implied in the degradation of ubiquitinated cargo by selective autophagy. UBA domain is responsible for noncovalent binding with polyubiquitinated cargos, through serine 403 phosphorylation by casein kinase 2 (CK2), which increases the affinity for ubiquitinated chains [16, 17]. PB1 domain is involved in self- and heteroligomerization with NBR1 (another receptor of selective autophagy) [18–20], and LIR region is important to LC3 interaction. It has been hypothesized that the activity of p62, in selective autophagy, requires a sequential interaction. Initially, there must be an interaction of p62 with ubiquitin proteins, and then aggregation of complex protein oligomerization to itself or with NBR1, and these aggregates are finally degraded by autolysosomes [7, 21, 22]. This order is altered in defects of autophagy, where firstly accumulations of p62 proteins are present and later are ubiquitinated [23, 24].

Furthermore, p62 is an autophagy receptor that can bind proteins to be degraded by selective autophagy as aggregates of misfolded proteins, damaged mitochondria, peroxisomes, and intracellular bacteria, which are ubiquitinated and targeted for clearance by autophagy [7, 25]. Several works have evidenced that p62 has a critical role in the normal functioning of mitochondria. p62 is localized to mitochondria under physiological conditions and plays an important role in mitochondrial morphology, genome integrity, and mitochondrial import of transcription factors. When p62 is deleted, it leads to mitochondrial fragmentation and mitochondrial dysfunction [26]. The role of p62 as adaptor receptor in mitophagy is currently debated. Geisler and colleagues reported that p62 with PINK1 y Parkin molecules has a key role in the sequential mitophagy process. p62 colocalized with Parkin on clustered mitochondria after the induction of mitophagy by carbonyl cyanide m-chlorophenylhydrazone (CCCP) treatment, and the silence of p62 by siRNA resulted in a significant loss of mitochondrial clearance [27, 28]. In contrast, Narendra and colleagues mentioned that p62 is not indispensable in the mitophagy; in HeLa cells with siRNA directed against p62, no difference was found in lacking mitochondria after the induction of mitophagy but is important in clustering of depolarized mitochondria [29, 30]. Similarly, in pexophagy, the role of p62 is not clear. p62 has

been involved in the clustering of peroxisomes that were labeled with ubiquitin to selective degradation [31], but recent work suggests that p62 is responsible for clustering, and only NBR1 is essential for peroxisome degradation by autophagy [32].

Adaptor p62 protein has an important role in the xenophagy, which is responsible for restriction of the replication of several intracellular microorganisms. The role of p62 has been more explored in infections by intracellular bacteria. Bacteria such as *Shigella flexneri*, a nonmotile actA mutant of *Listeria monocytogenes* [33], *Salmonella enterica* serotype Typhimurium [34], and *Mycobacterium tuberculosis* [25, 35] are targeted selectively through p62 recruitment to deliver into nascent LC3-positive isolation membranes for autophagosomal degradation. Interestingly, p62 has an additional role in antibacterial effect against *M. tuberculosis*, through the delivery of cytosolic proteins to *M. tuberculosis* containing-autolysosomes, where they are processed to convert into new antimicrobial peptides [36]. In viral infections, it has been reported that p62 plays a role in the clearance of viral proteins. Orvedahl and colleagues demonstrate that Sindbis virus capsid protein can interact with p62 in an ubiquitin-independent pathway, suggesting that clearance of viral proteins by autophagy requires p62 and other molecules tag different from ubiquitin [37]. There is little evidence about the role of p62 in infections by parasites. In the infection of *Toxoplasma gondii*, it has been observed that p62 and ubiquitin were recruited to *T. gondii* parasitophorous vacuoles when infected cells were stimulated by INF-γ playing an important role in the antigen presentation to activate specific CD8+T cells [38].

The high relevance of p62 as a signaling hub implies their efficient regulation. When p62 is disregulated or dysfunctional, there are multiple consequences. Several studies have implicated p62 aggregates in cancer, inflammation, neurodegenerative disease, liver disease, and aging [10, 13, 20, 39].

3. NBR1

Neighbor of BRCA1 gene 1 (NBR1) is another cargo receptor that is selectively degraded by autophagy. NBR1 was originally cloned as a candidate gene for the ovarian cancer antigen CA125 [40]. Given the similarity and interaction with p62, NBR1 has been studied in cell signaling and differentiation [41]. In 2009, Kirkin and colleagues have shown that NBR1 was involved in autophagic degradation of ubiquitinated targets [42].

NBR1 was recognized as a direct binding partner of the autophagosome-specific ATG8/LC3/GABARAP modifiers both in vitro and in vivo. NBR1 has similar domain architecture as p62 and shares several key features with p62 though differs in sequence and size. Both proteins share a very similar overall domain architecture, consisting of an N-terminal PB1(residues 5–85) domain, a ZZ-like zinc finger domain (residues 215–259), a two-domain light-chain-3-interacting regions LRS1 (residues 540–636) and LRS2 (residues 727–738, the LRS2 does not have the core consensus motif W/YXXL/I, most likely representing a novel type of LC3-interacting sequence), and a C-terminal ubiquitin-associated (UBA) domain (**Figure 2**) [43].

NBR1 binds strongly to ubiquitin via its UBA domain with a bias toward the K63-linked polyUb chains [43]. NBR1 undergoes dimerization via the coiled-coil domain. NBR1 can

directly bind to p62, and together they act as cargo receptors for autophagic degradation of polyubiquitylated aggregates and peroxisomes [43–45]. In the absence of p62, NBR1 interacts with misfolded and ubiquitinated proteins for degradation by autophagy [42]. Moreover, it is known that NBR1 promotes cell differentiation, may act as a tumor suppressor, and is also involved in bone remodeling [46, 47]. NBR1 also is involved in protein misfolding disorders such as body myositis sporadic inclusion, and autophagic degradation may have a role in the pathology [48].

4. NDP52

The nuclear dot protein 52 kD (NDP52) also named as calcium binding and coiled-coil domain 2 (CALCOCO2) is a 446-amino acid protein. Discovered in 1995, it was first erroneously found as part of the nuclear domains (ND10) called Kr bodies or PLM-containing oncogenic domains (POD), consisting of protein aggregates detected as dots (approximately 10) by autoimmune sera or monoclonal antibodies. By 1997, Sternsdorf and colleagues found by using polyclonal sera anti-NDP52 that the protein localization is restricted to the cytoplasm but not ND10 and confirmed an increase of NDP52 transcripts when cells were treated with IFN-γ [49].

NDP52 has a predicted molecular mass of 52 kD and exhibits an N-terminal skeletal muscle, and kidney-enriched inositol phosphatase carboxyl homology (SKICH) domain (aa 1–127), a central coil-coiled domain with zipper leucine motifs (aa 140–420) and the C-terminus presents homology with Lin11, Isl-1, and Mec-3 (LIM) domains containing two zinc finger arrangements involved in protein-protein interactions as ubiquitin (**Figure 2**) (aa 421–446) [50–52]. There are two paralogs existing, CoCoA (also known as Calcoco1) and Tax1BP1 (also known TXBP151). The CoCoA paralog comprises SKICH domains and LIM domains as NDP52, but it lacks an ubiquitin-binding domain. Therefore, it did not decorate bacteria when they escaped to the cytosol [53].

First studies linking NDP52 to a physiological process showed that after infection with *S. enterica*, the ubiquitin-coated bacteria in the cytosol are recognized by NDP52, which acts as a receptor. Then, NDP52 interacts with the adaptor proteins, Nap1 or Sintbad (also named TBKBP), and leads to the recruitment of TANK-binding kinase 1 (TBK1), which results in the control of bacterial growth [52]. The authors also found that NDP52 recruits and binds ATG8/LC3, an autophagosomal marker, and the knockdown of NDP52 impairs the autophagy of *Salmonella* [52, 54]. The same effect was observed with *Streptococcus pyogenes*-infected cells but not with *S. flexneri*. They conclude that NDP52 is a receptor that recognizes ubiquitin-coated bacteria and binds ATG8/LC3 leading to the control of bacterial growth by autophagy. Further studies demonstrated that NDP52 has a LC3-interacting region (LIR) domain and the sites of interaction with Nap1 or Sintbad are located at the SKICH domain (**Figure 2**) [55]. Later, Muhlinen and colleagues demonstrated that NDP52 binds all human ATG8/LC3 orthologs (LC3A, LC3B, LC3C, GABARAP, GABARAPL1, GABARAPL2), but only LC3C performs an antibacterial function when binds NDP52 through the LC3C-interacting region (CLIR) [56]. Other studies demonstrated that *S. flexneri* is also targeted by NDP52/P62 to autophagy

pathway dependent upon septin and actin [57]. Additional to the ubiquitin-dependent pathway needed for the recruitment of NDP52, a carbohydrate-dependent galectin-8 pathway also mediates NDP52 recruitment to invading bacteria at early stages of infection, unlike the ubiquitin-dependent pathway which plays a major role at later points [58, 59].

As part of the autophagosome maturation, it was found that NDP52 interacts with myosin VI via RRL motif, and such interaction recruits myosin VI to deliver endosomal membranes to the nascent autophagosome [60, 61]. This function of NDP52 is independent of its function in xenophagy and involves a different binding domain [62].

Recently, it has been demonstrated that NDP52 also plays a role in regulation. The Toll-like receptor (TLR) signaling serves as, an example, the selective autophagic degradation of Toll/interleukin-1 receptor homology domain-containing adaptor-inducing interferon (TRIF), and TRAF6 is mediated by this receptor. The mechanism involves the polyubiquitination of NDP52 by TRAF6 to acquire the ability to form aggregates of polyubiquitinated TRAF6 [63, 64]. The regulation of the miRNA activity is another example; recently, it has been discovered that the miRNA-processing enzyme DICER and the miRNA effector AGO2 are a target by NDP52 for their degradation via autophagy [65]. Another target of NDP52 includes the RNA retrotransposon, and the degradation of this RNA via autophagy helps to maintain the stability of the genome [66]. More recently, Heo and colleagues found that the PINK1-PARKIN mitochondrial ubiquitination pathway promotes mitophagy by recruiting TBK1 kinase which binds to NDP52 and other autophagy receptors to induce autophagy of mitochondria [67, 68].

Some studies with viruses have related autophagy to anti- or pro-viral roles; NDP52 has been involved in promoting viral replication of chikungunya virus (CHIKV) when interacts with the nonstructural protein nsP2 in infected human cells [69].

Although autophagy has a protective role against some intracellular bacteria, some studies indicate that NDP52 has a relation with Crohn's disease, and Ellinghaus and colleagues found an association between the disease and a missense mutation in affected individuals [70, 71]. Additionally, NDP52 has been involved in Alzheimer's disease where it has a protective role in facilitating the clearance of phosphorylated tau [72, 73].

5. Optineurin

Optineurin was first described by Li and colleagues [74]. They were looking for proteins that interact with the early region 3 (E3) 14.7 K protein in the yeast two-hybrid system. E3 14.7 K is synthesized by E3 in group C of adenovirus and is an inhibitor of NF-kB cytolysis. They found a protein with the ability to interact with E3 14.7K and named as FIP-2 (for 14.7K interacting protein), and FIP-2 interacts with E3 14.7K in the cytoplasm and caused redistribution of the protein. Also, FIP-2 reversed the protective effect of E3 14.7K on cell death induced by TNF-α. After, Schwamborn and colleagues described that FIP-2 had a strong homology to NF-kB essential modulator (NEMO) and named as NEMO-related protein (NRP). They found that NRP was associated with Golgi apparatus and is de novo expressed by interferon and

TNF-α [75]. Rezaie and colleagues coined the name optineurin (optic neuropathy-inducing protein) after discovering that this molecule was associated with diseases such as normal tension glaucoma and a subtype of primary open-angle glaucoma [76].

Optineurin is a 67 KDa intracellular protein found in different tissues [77], and optineurin gene encodes an 884-amino acid protein and contains three noncoding exons and 13 exons that code for a 577-amino acid protein [78]. The mRNA can be found in 3 isoforms as a result of alternative splicing [74]. Optineurin has been described in different tissues such as spleen, kidney, skeletal muscle, brain, heart, lung, pancreas, and eyes of various species: human, mouse, and chicken [74, 78, 79]. The UPS is a very important pathway to recycle optineurin, but in situations where optineurin is upregulated, the UPS is compromised and autophagy is induced to control the optineurin levels [80].

Optineurin has different domains through which it can interact with different proteins. It contains putative domains such as C-terminal zinc finger, leucine zipper domain [74], a LIR domain [81], a NEMO-like domain [75], UBD domain [82], and various coiled-coil motifs [83]. In **Figure 2**, optineurin is shown and compared with other adaptor proteins involved in selective autophagy.

Optineurin can participate in different biological activities because it has multiple domains, which mediate the interaction with other proteins. For example, optineurin can interact with Rab8 [83–85], transferrin receptor [86], serine/threonine kinase receptor-interacting protein 1 (RIP) [87], ubiquitin [88], and Myosin VI [61, 84], among others. The interaction of optineurin with myosin VI [84, 89] is mediated by the UBD domain, and this interaction is important in the fusion of secretory vesicles with the plasma membrane [90]. Also, it has been described that macrophages from patients with Crohn's disease where optineurin was under-expressed fail to secrete pro-inflammatory cytokines [91], which suggest that optineurin can also be involved in the vesicular transport of the autophagosomes.

As it was mentioned, the importance of optineurin in selective autophagy relies on their UBD and LIR domains, through their interaction with specific cargo and the autophagy machinery respectively. However, it has been reported that optineurin can recognize a target like a superoxide dismutase 1 and huntingtin protein by an ubiquitin-independent pathway and degrade protein aggregates through autophagy [92], and this recognition was related to the C-terminal coiled-coil domain of optineurin.

LIR domain mediates the interaction of optineurin with autophagy machinery. The phosphorylation of serine 177 on LIR domain by TANK-binding kinase 1 (TBK1) increases the affinity of optineurin to LC3/GABARAP proteins [81, 93]. After the dominant phosphorylation at serine 177, optineurin forms a strand with the beta-strand 2 of LC3B and phenylalanine 178 and isoleucine 181 are inserted into a hydrophobic pocket on the LC3B [93]. On the other hand, the isomers of LC3 and the proteins of the GABARAP family interact with the machinery involved in autophagosome elongation, which is recruited to LC3/GABARAP-optineurin. Then, autophagy-related protein ATG4 is recruited to cleavage at the C-terminal of LC3/GABARAP and exhibits phenylalanine and glycine amino acids, which participate in the

conjugation of LC3/GABARAP with phosphatidylethanolamine (PE) [94] to complete autophagosome formation finally.

Mitochondria are important and dynamic organelles, depending on energetic requirements of the cells, mitochondria can undergo cycles of fusion and fission [95]. When mitochondria are damaged, they suffer an increase in the rate of fission, and this results in their fragmentation. Damaged and fragmented mitochondria are removed via mitophagy [28, 96]. The role of optineurin in mitophagy has been recently studied. Mitophagy requires the interaction with other proteins. First, damaged mitochondria are marked with ubiquitin by Parkin and PINK1. Both proteins act in the ubiquitination of Mitofusin 1 and Mitofusin 2 when mitochondrial depolarization was induced by carbonyl cyanide-m-chlorophenylhydrazone (CCCP) treatment [97]. When mitochondria become depolarized, PINK1 accumulates on the mitochondrial outer membrane and phosphorylates to Mitofusin 2, this allows their interaction with inactive Parkin, and the subsequent activation of Parkin by PINK1 activates the Parkin ubiquitin ligase activity [98]. This ubiquitination allows the interaction of optineurin with ubiquitinated mitochondria through its UBD domain, and this recognition is similar to p62 and NIX [28]. After this initial recognition, optineurin recruits autophagy machinery around damaged mitochondria to capture it into the autophagosome [96].

Xenophagy has been considered as an innate immune response against intracellular infections. Xenophagy guided by optineurin has been poorly described, so it represents an interesting and wide field of study. It has been described that xenophagy mediated by optineurin participates in the intracellular control of *S. enterica*. For this activity, optineurin requires UBD and LIR domains. It has been reported than when UBD domain was mutated, optineurin failed to colocalize with *S. enterica* and when LIR domain was mutated, optineurin colocalized with *S. enterica* but not with LC3. Also, TBK1 activity was necessary for the xenophagy mediated by optineurin [81]. Tumbarello and colleagues found that optineurin, TAX1BP1, and NDP52 are important in xenophagy response against *Salmonella typhimurium*. Also, they found that Myosin VI is necessary to restrict the replication of *S. typhimurium*, highlighting the role of Myosin VI in the vesicular transport of autophagosomes containing *S. typhimurium* to lysosomes [99].

Due to the role of optineurin in the capture of unnecessary or damaged organelles, the lack or the deficiency of optineurin has been associated with different pathologies such as amyotrophic lateral sclerosis [100], Paget's disease of bone [101], normal tension glaucoma, and primary open-angle glaucoma [102].

6. VCP/p97

Valosin-containing protein (VCP/97)—also called Cdc48p in yeast, p97 in Xenopus, CDC-48 in *Caenorhabditis elegans*, or TER94 in *Drosophila*—belongs to the hexameric AAA (ATPases associated with diverse cellular activities) family of proteins with two ATPase domains, D1 and D2. The structure of VCP/97 molecule includes N (1–187), D1 (209–460), D2 (481–761), and C (762–806) domains, with two linkers: N-D1 linker (188–208) and D1–D2 linker (461–480)

(**Figure 2**). VCP proteins form a barrel-like structure that comprises two ring-shaped layers made of D1 and D2 AAA modules [103]. The diversity of cellular functions and the activity of VCP/p97 are mediated by their interaction with a large number of protein cofactors. p97 forms core complexes with the major cofactors, which include the proteins ubiquitin-X (UBX) domain, the Ufd1 (ubiquitin fusion degradation 1)-Npl4 (nuclear protein localization homolog 4) heterodimer, and p47 [104]. Several works have established p97 as a principal element in emerging functions of the UPS as was described in a review by Meyer et al. [104]. Nevertheless, p97 lacks a LIR domain; recent reports now link to p97 with the autophagy. The first findings of the involvement of p97 with autophagy were reported in studies of the multisystem degenerative disorder characterized by inclusion body myopathy, frontotemporal dementia, and Paget's disease of bone (also known as IBMPFD) [105] which is associated with VCP mutations. This disorder is characterized by the extensive accumulation of ubiquitin conjugates in affected tissues, and in IBMPFD patients the VCP mutations cause no damage in ubiquitin-dependent degradation by the proteasome, but do impair maturation of ubiquitin-containing autophagosomes. Further, the myoblasts derived from IBMPFD patients showed accumulation of LAMP-1, LAMP-2, and LC3-II-positive vacuoles indicating that VCP/p97 is essential to autophagosome maturation [106]. Additional work has provided evidence about the role of Cdc48/p97 in the regulation of autophagosome biogenesis. In *Saccharomyces cerevisiae*, it has been demonstrated that the participation of Cdc48/p77 in autophagy is mediated by direct interaction of Shp1/Ubx1 cofactor with Atg8 PE-conjugated form [107]. Recently, it has been recognized the role of VCP/p97 in mitochondrial maintenance. On the one hand, VCP/p97 was accepted as part of outer mitochondrial membrane-associated degradation (OMMAD), functioning as retrotranslocase of ubiquitinated mitochondrial proteins for degradation by UPS [108]. On the other hand, Tanaka and colleges showed that p97 and proteasome activity are required to mitophagy mediated by Parkin protein [109]. The role of VCP/p97 in xenophagy remains unexplored, which opens a new window to investigate.

7. Conclusion

Currently, autophagy is an attractive area of investigation. It has been recognized the participation of autophagy in homeostatic cellular functions, such as clearance of damaged organelles, misfolded proteins, and microorganism, among others. Scientists have focused on describing the molecular mechanisms responsible for the autophagy. Now, we know that autophagy, far from beginning a random pathway, is a mechanism that elegantly regulates and is highly orchestrated by several proteins. Some proteins have been identified as bridges between the cargo and nascent phagophore, and recently studies are in process to know how these proteins are working and how to interact with the complex autophagy machinery. Several of these proteins share some structural characteristics, such as LIR domain, which allow the direct interaction with LC3 protein. However, recently, studies have identified new proteins that participate in selective autophagy but lack LIR domain, for example, VCP/p97 and Alfy. The studies to know the precise mechanisms of interaction of these proteins are in process. The understanding of the molecular mechanism that governs the autophagy represents an

interesting field because many of these molecules could be manipulated to recover the cellular homeostasis in several pathologies, where autophagy is involved.

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References

[1] Thrower JS, Hoffman L, Rechsteiner M, Pickart CM. Recognition of the polyubiquitin proteolytic signal. EMBO J. 2000;19:94–102. doi:10.1093/emboj/19.1.94

[2] Hershko A, Ciechanover A. The ubiquitin system. Annu Rev Biochem. 1998;67:425–79. doi:10.1146/annurev.biochem.67.1.425

[3] Grice GL, Lobb IT, Weekes MP, Gygi SP, Antrobus R, Nathan JA. The proteasome distinguishes between heterotypic and homotypic lysine-11-Linked polyubiquitin chains. Cell Rep. 2015;12:545–53. doi:10.1016/j.celrep.2015.06.061

[4] Erpapazoglou Z, Walker O, Haguenauer-Tsapis R. Versatile roles of k63-linked ubiquitin chains in trafficking. Cells. 2014;3:1027–88. doi:10.3390/cells3041027

[5] Vasco Ferreira J, Rosa Soares A, Silva Ramalho J, Pereira P, Girao H. K63 linked ubiquitin chain formation is a signal for HIF1A degradation by Chaperone-Mediated Autophagy. Sci Rep. 2015;5:10210. doi:10.1038/srep10210

[6] He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet. 2009;43:67–93. doi:10.1146/annurev-genet-102808–114910

[7] Johansen T, Lamark T. Selective autophagy mediated by autophagic adapter proteins. Autophagy. 2011;7:279–96. doi:10.4161/auto.7.3.14487

[8] Isakson P, Holland P, Simonsen A. The role of ALFY in selective autophagy. Cell Death Differ. 2013;20:12–20. doi:10.1038/cdd.2012.66

[9] Park I, Chung J, Walsh CT, Yun Y, Strominger JL, Shin J. Phosphotyrosine-independent binding of a 62-kDa protein to the src homology 2 (SH2) domain of p56lck and its regulation by phosphorylation of Ser-59 in the lck unique N-terminal region. Proc Natl Acad Sci USA. 1995;92:12338–42. doi:10.1073/pnas.92.26.12338

[10] Komatsu M, Kageyama S, Ichimura Y. P62/SQSTM1/A170: Physiology and pathology. Pharmacol Res. 2012;66:457–62. doi:10.1016/j.phrs.2012.07.004

[11] Katsuragi Y, Ichimura Y, Komatsu M. p62/SQSTM1 functions as a signaling hub and an autophagy adaptor. FEBS J. 2015;282(24):4672–8. doi:10.1111/febs.13540

[12] Sahani MH, Itakura E, Mizushima N. Expression of the autophagy substrate SQSTM1/p62 is restored during prolonged starvation depending on transcriptional upregulation and autophagy-derived amino acids. Autophagy. 2014;10:431–41. doi:10.4161/auto.27344

[13] Bitto A, Lerner CA, Nacarelli T, Crowe E, Torres C, Sell C. p62/SQSTM1 at the interface of aging, autophagy, and disease. Age (Omaha). 2014;36:1123–37. doi:10.1007/s11357-014-9626-3

[14] Nezis IP, Simonsen A, Sagona AP, Finley K, Gaumer S, Contamine D, et al. Ref(2)P, the Drosophila melanogaster homologue of mammalian p62, is required for the formation of protein aggregates in adult brain. J Cell Biol. 2008;180:1065–71. doi:10.1083/jcb.200711108

[15] Geetha T, Wooten MW. Structure and functional properties of the ubiquitin binding protein p62. FEBS Lett. 2002;512:19–24. doi:10.1016/S0014-5793(02)02286-X

[16] Matsumoto G, Wada K, Okuno M, Kurosawa M, Nukina N. Serine 403 phosphorylation of p62/SQSTM1 regulates selective autophagic clearance of ubiquitinated proteins. Mol Cell. 2011;44:279–89. doi:10.1016/j.molcel.2011.07.039

[17] Vadlamudi RK, Joung I, Strominger JL, Shin J. p62, a phosphotyrosine-independent ligand of the SH2 domain of p56(lck), belongs to a new class of ubiquitin-binding proteins. J Biol Chem. 1996;271:20235–7. doi:10.1074/jbc.271.34.20235

[18] Wooten MW, Hu X, Babu JR, Seibenhener ML, Geetha T, Paine MG, et al. Signaling, polyubiquitination, trafficking, and inclusions: Sequestosome 1/p62's role in neurodegenerative disease. J Biomed Biotechnol. 2006;2006:62079. doi:10.1155/JBB/2006/62079

[19] Seibenhener ML, Geetha T, Wooten MW. Sequestosome 1/p62–more than just a scaffold. FEBS Lett. 2007;581:175–9. doi:10.1016/j.febslet.2006.12.027

[20] Salminen A, Kaarniranta K, Haapasalo A, Hiltunen M, Soininen H, Alafuzoff I. Emerging role of p62/sequestosome-1 in the pathogenesis of Alzheimer's disease. Prog Neurobiol. 2011;96:87–95. doi:10.1016/j.pneurobio.2011.11.005

[21] Ichimura Y, Komatsu M. Selective degradation of p62 by autophagy. Semin Immunopathol. 2010;32:431–6. doi:10.1007/s00281-010-0220-1

[22] Pankiv S, Clausen TH, Lamark T, Brech A, Bruun JA, Outzen H, et al. p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. J Biol Chem. 2007;282:24131–45. doi:10.1074/jbc.M702824200

[23] Du Y, Wooten MC, Wooten MW. Oxidative damage to the promoter region of SQSTM1/p62 is common to neurodegenerative disease. Neurobiol Dis. 2009;35:302–10. doi:10.1016/j.nbd.2009.05.015

[24] Rusten TE, Stenmark H. P62, an autophagy hero or culprit? Nat Cell Biol. 2010;12:207–9. doi:10.1038/ncb0310-207

[25] Jo EK. Autophagy as an innate defense against mycobacteria. Pathog Dis. 2013;67:108–18. doi:10.1111/2049-632X.12023

[26] Seibenhener ML, Du Y, Diaz-Meco MT, Moscat J, Wooten MC, Wooten MW. A role for sequestosome 1/p62 in mitochondrial dynamics, Import and genome integrity. Biochim Biophys Acta—Mol Cell Res. 2013;1833:452–9. doi:10.1016/j.bbamcr.2012.11.004

[27] Geisler S, Holmström KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ, et al. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat Cell Biol. 2010;12:119–31. doi:10.1038/ncb2012

[28] Ding WX, Ni HM, Li M, Liao Y, Chen X, Stolz DB, et al. Nix is critical to two distinct phases of mitophagy, reactive oxygen species-mediated autophagy induction and Parkin-ubiquitin-p62-mediated mitochondrial priming. J Biol Chem. 2010;285:27879–90. doi:10.1074/jbc.M110.119537

[29] Narendra DP, Kane LA, Hauser DN, Fearnley IM, Youle RJ. p62/SQSTM1 is required for Parkin-induced mitochondrial clustering but not mitophagy; VDAC1 is dispensable for both. Autophagy. 2010;6:1090–106. doi:10.4161/auto.6.8.13426

[30] Okatsu K, Saisho K, Shimanuki M, Nakada K, Shitara H, Sou YS, et al. P62/SQSTM1 cooperates with Parkin for perinuclear clustering of depolarized mitochondria. Gene Cell. 2010;15:887–900. doi:10.1111/j.1365-2443.2010.01426.x

[31] Kim PK, Hailey DW, Mullen RT, Lippincott-Schwartz J. Ubiquitin signals autophagic degradation of cytosolic proteins and peroxisomes. Proc Natl Acad Sci USA. 2008;105:20567–74. doi:10.1073/pnas.0810611105

[32] Yamashita S ichi, Abe K, Tatemichi Y, Fujiki Y. The membrane peroxin PEX3 induces peroxisome-ubiquitination-linked pexophagy. Autophagy. 2014;10:1549–64. doi: 10.4161/auto.29329

[33] Dupont N, Lacas-Gervais S, Bertout J, Paz I, Freche B, Van Nhieu GT, et al. Shigella Phagocytic vacuolar membrane remnants participate in the cellular response to pathogen invasion and are regulated by autophagy. Cell Host Microbe. 2009;6:137–49. doi:10.1016/j.chom.2009.07.005

[34] Zheng YT, Shahnazari S, Brech A, Lamark T, Johansen T, Brumell JH. The adaptor protein p62/SQSTM1 targets invading bacteria to the autophagy pathway. J Immunol. 2009;183:5909–16. doi:10.4049/jimmunol.0900441

[35] Seto S, Tsujimura K, Horii T, Koide Y. Autophagy adaptor protein p62/SQSTM1 and autophagy-related gene Atg5 mediate autophagosome formation in response to Mycobacterium tuberculosis infection in dendritic cells. PLoS One. 2013;8. doi:10.1371/journal.pone.0086017

[36] Ponpuak M, Davis AS, Roberts EA, Delgado MA, Dinkins C, Zhao Z, et al. Delivery of cytosolic components by autophagic adaptor protein p62 endows autophagosomes with unique antimicrobial properties. Immunity. 2010;32:329–41. doi:10.1016/j.immuni.2010.02.009

[37] Orvedahl A, MacPherson S, Sumpter R, Tallóczy Z, Zou Z, Levine B. Autophagy protects against Sindbis virus infection of the central nervous system. Cell Host Microbe. 2010;7:115–27. doi:10.1016/j.chom.2010.01.007

[38] Lee Y, Sasai M, Ma JS, Sakaguchi N, Ohshima J, Bando H, et al. P62 plays a specific role in interferon-γ-induced presentation of a toxoplasma vacuolar antigen. Cell Rep. 2015;13:223–33. doi:10.1016/j.celrep.2015.09.005

[39] Manley S, Williams JA, Ding W-X. Role of p62/SQSTM1 in liver physiology and pathogenesis. Exp Biol Med (Maywood). 2013;238:525–38. doi: 10.1177/1535370213489446

[40] Campbell IG, Nicolai HM, Foulkes WD, Senger G, Stamp GW, Allan G, et al. A novel gene encoding a B-Box protein within the BRCA1 region at 17q21.1. Hum Mol Genet. 1994;3:589–94. doi:10.1093/hmg/3.4.589

[41] Lange S, Xiang F, Yakovenko A, Vihola A, Hackman P, Rostkova E, et al. The kinase domain of titin controls muscle gene expression and protein turnover. Science. 2005;308:1599–603. doi:10.1126/science.1110463

[42] Kirkin V, Lamark T, Sou YS, Bjørkøy G, Nunn JL, Bruun JA, et al. A role for NBR1 in autophagosomal degradation of ubiquitinated substrates. Mol Cell. 2009;33:505–16. doi:10.1016/j.molcel.2009.01.020

[43] Kirkin V, McEwan DG, Novak I, Dikic I. A role for ubiquitin in selective autophagy. Mol Cell. 2009;34:259–69. doi:10.1016/j.molcel.2009.04.026

[44] Odagiri S, Tanji K, Mori F, Kakita A, Takahashi H, Wakabayashi K. Autophagic adapter protein NBR1 is localized in Lewy bodies and glial cytoplasmic inclusions and is involved in aggregate formation in α-synucleinopathy. Acta Neuropathol. 2012;124:173–86. doi:10.1007/s00401-012-0975-7

[45] Deosaran E, Larsen KB, Hua R, Sargent G, Wang Y, Kim S, et al. NBR1 acts as an autophagy receptor for peroxisomes. J Cell Sci. 2013;126:939–52. doi:10.1242/jcs.114819

[46] Kuo T-C, Chen C-T, Baron D, Onder TT, Loewer S, Almeida S, et al. Midbody accumulation through evasion of autophagy contributes to cellular reprogramming and tumorigenicity. Nat Cell Biol. 2011;13:1214–23. doi:10.1038/ncb2332

[47] Waters S, Marchbank K, Solomon E, Whitehouse CA. Autophagic receptors Nbr1 and p62 coregulate skeletal remodeling. Autophagy. 2010;6:981–3. doi:10.4161/auto.6.7.13155

[48] D´Agostino C, Nogalska A, Cacciottolo M, King Engel W, Askanas V. Abnormalities of NBR1, a novel autophagy-associated protein, in muscle fibers of sporadic inclusion-body myositis. Acta Neuropathol. 2011;122:627–36. doi:10.1007/s00401-011-0874-3

[49] Sternsdorf T, Jensen K, Züchner D, Will H. Cellular localization, expression, and structure of the nuclear dot protein 52. J Cell Biol. 1997;138:435–48. doi:10.1083/jcb.138.2.435

[50] Korioth F, Gieffers C, Maul GG, Frey J. Molecular characterization of NDP52, a novel protein of the nuclear domain 10, which is redistributed upon virus infection and interferon treatment. J Cell Biol. 1995;130:1–13. doi:10.1083/jcb.130.1.1

[51] Di Y, Li J, Zhang Y, He X, Lu H, Xu D, et al. HCC-associated protein HCAP1, a variant of GEMIN4, interacts with zinc-finger proteins. J Biochem. 2003;133:713–8. doi:10.1093/jb/mvg091

[52] Thurston TLM, Ryzhakov G, Bloor S, von Muhlinen N, Randow F. The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. Nat Immunol. 2009;10:1215–21. doi:10.1038/ni.1800

[53] Ivanov S, Roy CR. NDP52: The missing link between ubiquitinated bacteria and autophagy. Nat Immunol. 2009;10:1137–9. doi:10.1038/ni1109-1137

[54] Von Muhlinen N, Thurston T, Ryzhakov G, Bloor S, Randow F. NDP52, a novel autophagy receptor for ubiquitin-decorated cytosolic bacteria. Autophagy. 2010;6:288–9. doi:10.4161/auto.6.2.11118

[55] Randow F. How cells deploy ubiquitin and autophagy to defend their cytosol from bacterial invasion. Autophagy. 2011;7:304–9. doi:10.4161/auto.7.3.14539

[56] von Muhlinen N, Akutsu M, Ravenhill BJ, Foeglein Á, Bloor S, Rutherford TJ, et al. LC3C, Bound selectively by a Noncanonical LIR motif in NDP52, is required for antibacterial autophagy. Mol Cell. 2012;48:329–42. doi:10.1016/j.molcel.2012.08.024

[57] Mostowy S, Sancho-Shimizu V, Hamon MA, Simeone R, Brosch R, Johansen T, et al. p62 and NDP52 proteins target intracytosolic Shigella and Listeria to different autophagy pathways. J Biol Chem. 2011;286:26987–95. doi:10.1074/jbc.M111.223610

[58] Thurston TLM, Wandel MP, von Muhlinen N, Foeglein Á, Randow F. Galectin 8 targets damaged vesicles for autophagy to defend cells against bacterial invasion. Nature. 2012;482:414–8. doi:10.1038/nature10744

[59] Li S, Wandel MP, Li F, Liu Z, He C, Wu J, et al. Sterical hindrance promotes selectivity of the autophagy cargo receptor NDP52 for the danger receptor galectin-8 in antibacterial autophagy. Sci Signal. 2013;6:ra9. doi:10.1126/scisignal.2003730

[60] Morriswood B, Ryzhakov G, Puri C, Arden SD, Roberts R, Dendrou C, et al. T6BP and NDP52 are myosin VI binding partners with potential roles in cytokine signalling and cell adhesion. J Cell Sci. 2007;120:2574–85. doi:10.1242/jcs.007005

[61] Tumbarello DA, Waxse BJ, Arden SD, Bright NA, Kendrick-Jones J, Buss F. Autophagy receptors link myosin VI to autophagosomes to mediate Tom1-dependent autophagosome maturation and fusion with the lysosome. Nat Cell Biol. 2012;14:1024–35. doi:10.1038/ncb2589

[62] Verlhac P, Grégoire IP, Azocar O, Petkova DS, Baguet J, Viret C, et al. Autophagy receptor NDP52 regulates pathogen-containing autophagosome maturation. Cell Host Microbe. 2015;17:515–25. doi:10.1016/j.chom.2015.02.008

[63] Inomata M, Niida S, Shibata KI, Into T. Regulation of toll-like receptor signaling by NDP52-mediated selective autophagy is normally inactivated by A20. Cell Mol Life Sci. 2012;69:963–79. doi:10.1007/s00018-011-0819-y

[64] Into T, Inomata M, Takayama E, Takigawa T. Autophagy in regulation of toll-like receptor signaling. Cell Signal. 2012;24:1150–62. doi:10.1016/j.cellsig.2012.01.020

[65] Gibbings D, Mostowy S, Jay F, Schwab Y, Cossart P, Voinnet O. Selective autophagy degrades DICER and AGO2 and regulates miRNA activity. Nat Cell Biol. 2012;14:1314–21. doi:10.1038/ncb2611

[66] Guo H, Chitiprolu M, Gagnon D, Meng L, Perez-Iratxeta C, Lagace D, et al. Autophagy supports genomic stability by degrading retrotransposon RNA. Nat Commun. 2014;5:5276. doi:10.1038/ncomms6276

[67] Heo JM, Ordureau A, Paulo JA, Rinehart J, Harper JW. The PINK1-PARKIN mitochondrial ubiquitylation pathway drives a program of OPTN/NDP52 recruitment and TBK1 activation to promote mitophagy. Mol Cell. 2015;60:7–20. doi:10.1016/j.molcel.2015.08.016

[68] Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature. 2015;524:309–14. doi:10.1038/nature14893

[69] Judith D, Mostowy S, Bourai M, Gangneux N, Lelek M, Lucas-Hourani M, et al. Species-specific impact of the autophagy machinery on chikungunya virus infection. EMBO Rep. 2013;14:534–44. doi:10.1038/embor.2013.51

[70] Ellinghaus D, Zhang H, Zeissig S, Lipinski S, Till A, Jiang T, et al. Association between variants of PRDM1 and NDP52 and Crohn's disease, based on exome sequencing and functional studies. Gastroenterology. 2013;145:339–47. doi:10.1053/j.gastro.2013.04.040

[71] Till A, Lipinski S, Ellinghaus D, Mayr G, Subramani S, Rosenstiel P, et al. Autophagy receptor CALCOCO2/NDP52 takes center stage in Crohn's disease. Autophagy. 2013;9:1256–7. doi:10.4161/auto.25483

[72] Jo C, Gundemir S, Pritchard S, Jin YN, Rahman I, Johnson GVW. Nrf2 reduces levels of phosphorylated tau protein by inducing autophagy adaptor protein NDP52. Nat Commun. 2014;5:3496. doi:10.1038/ncomms4496

[73] Kim S, Lee D, Song JC, Cho SJ, Yun SM, Koh JH, et al. NDP52 associated with phosphorylated tau in brains of an Alzheimer disease mouse model. Biochem Biophys Res Commun. 2014; 454:196–201. doi:10.1016/j.bbrc.2014.10.066

[74] Li Y, Kang J, Horwitz MS. Interaction of an adenovirus E3 14.7-kilodalton protein with a novel tumor necrosis factor alpha-inducible cellular protein containing leucine zipper domains. Mol Cell Biol. 1998;18:1601–10. doi:10.1128/MCB.18.3.1601

[75] Schwamborn K, Weil R, Courtois G, Whiteside ST, Israël A. Phorbol esters and cytokines regulate the expression of the NEMO-related protein, a molecule involved in a NF-kB-independent pathway. J Biol Chem. 2000;275:22780–9. doi:10.1074/jbc.M001500200

[76] Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science. 2002;295:1077–9. doi:10.1126/science.1066901

[77] Ying H, Shen X, Park B, Yue BYJT. Posttranslational modifications, localization, and protein interactions of optineurin, the product of a glaucoma gene. PLoS One. 2010;5. doi:10.1371/journal.pone.0009168

[78] Rezaie T, Sarfarazi M. Molecular cloning, genomic structure, and protein characterization of mouse optineurin. Genomics. 2005;85:131–8. doi:10.1016/j.ygeno.2004.10.011

[79] Stroissnigg H, Repitz M, Miloloza A, Linhartova I, Beug H, Wiche G, et al. FIP-2, an IkappaB-kinase-gamma-related protein, is associated with the Golgi apparatus and translocates to the marginal band during chicken erythroblast differentiation. Exp Cell Res. 2002;278:133–45. doi:10.1006/excr.2002.5567

[80] Shen X, Ying H, Qiu Y, Park JS, Shyam R, Chi ZL, et al. Processing of optineurin in neuronal cells. J Biol Chem. 2011;286:3618–29. doi:10.1074/jbc.M110.175810

[81] Wild P, Farhan H, McEwan DG, Wagner S, Rogov VV, Brady NR, et al. Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth. Science. 2011;333:228–33. doi:10.1126/science.1205405

[82] Shen WC, Li HY, Chen GC, Chern Y, Tu PH. Mutations in the ubiquitin-binding domain of OPTN/optineurin interfere with autophagy- mediated degradation of misfolded proteins by a dominant-negative mechanism. Autophagy. 2015;11:685–700. doi:10.4161/auto.36098

[83] Hattula K, Peränen J. FIP-2, a coiled-coil protein, links Huntingtin to Rab8 and modulates, cellular morphogenesis. Curr Biol. 2000;10:1603–6. doi:10.1016/S0960-9822(00)00864-2

[84] Sahlender DA, Roberts RC, Arden SD, Spudich G, Taylor MJ, Luzio JP, et al. Optineurin links myosin VI to the Golgi complex and is involved in Golgi organization and exocytosis. J Cell Biol. 2005;169:285–95. doi:10.1083/jcb.200501162

[85] Vaibhava V, Nagabhushana A, Chalasani MLS, Sudhakar C, Kumari A, Swarup G. Optineurin mediates a negative regulation of Rab8 by the GTPase-activating protein TBC1D17. J Cell Sci. 2012;125:5026–39. doi:10.1242/jcs.102327

[86] Park B, Ying H, Shen X, Park JS, Qiu Y, Shyam R, et al. Impairment of protein trafficking upon overexpression and mutation of optineurin. PLoS One. 2010;5. doi:10.1371/journal.pone.0011547

[87] Zhu G, Wu CJ, Zhao Y, Ashwell JD. Optineurin negatively regulates TNFα-induced NF-kB activation by competing with NEMO for ubiquitinated RIP. Curr Biol. 2007;17:1438–43. doi:10.1016/j.cub.2007.07.041

[88] Gleason CE, Ordureau A, Gourlay R, Arthur JSC, Cohen P. Polyubiquitin binding to optineurin is required for optimal activation of TANK-binding kinase 1 and production of interferon β. J Biol Chem. 2011;286:35663–74. doi:10.1074/jbc.M111.267567

[89] Chibalina MV, Poliakov A, Kendrick-Jones J, Buss F. Myosin VI and optineurin are required for polarized EGFR delivery and directed migration. Traffic. 2010;11:1290–303. doi:10.1111/j.1600-0854.2010.01101.x

[90] Bond LM, Peden AA, Kendrick-Jones J, Sellers JR, Buss F. Myosin VI and its binding partner optineurin are involved in secretory vesicle fusion at the plasma membrane. Mol Biol Cell. 2011;22:54–65. doi:10.1091/mbc.E10-06-0553

[91] Smith AM, Sewell GW, Levine AP, Chew TS, Dunne J, O'Shea NR, et al. Disruption of macrophage pro-inflammatory cytokine release in Crohn's disease is associated with reduced optineurin expression in a subset of patients. Immunology. 2015;144:45–55. doi:10.1111/imm.12338

[92] Korac J, Schaeffer V, Kovacevic I, Clement AM, Jungblut B, Behl C, et al. Ubiquitin-independent function of optineurin in autophagic clearance of protein aggregates. J Cell Sci. 2013;126:580–92. doi:10.1242/jcs.114926

[93] Rogov VV, Suzuki H, Fiskin E, Wild P, Kniss A, Rozenknop A, et al. Structural basis for phosphorylation-triggered autophagic clearance of Salmonella. Biochem J. 2013;454:459–66. doi:10.1042/BJ20121907

[94] Klionsky DJ, Schulman BA. Dynamic regulation of macroautophagy by distinctive ubiquitin-like proteins. Nat Struct Mol Biol. 2014;21:336–45. doi:10.1038/nsmb.2787

[95] Mishra P, Chan DC. Mitochondrial dynamics and inheritance during cell division, development and disease. Nat Rev Mol Cell Biol. 2014;15:634–46. doi:10.1038/nrm3877

[96] Wong YC, Holzbaur EL. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proc Natl Acad Sci USA. 2014;111:E4439–48. doi:10.1073/pnas.1405752111

[97] Gegg ME, Cooper JM, Chau KY, Rojo M, Schapira AH V, Taanman JW. Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Hum Mol Genet. 2010;19:4861–70. doi:10.1093/hmg/ddq419

[98] Pallanck L. Mitophagy: Mitofusin recruits a mitochondrial killer. Curr Biol. 2013;23:R570–2. DOI: http://dx.doi.org/10.1016/j.cub.2013.05.032

[99] Tumbarello DA, Manna PT, Allen M, Bycroft M, Arden SD, Kendrick-Jones J, et al. The autophagy receptor TAX1BP1 and the molecular motor myosin VI are required for clearance of salmonella typhimurium by autophagy. PLoS Pathog. 2015;11:e1005174. doi:10.1371/journal.ppat.1005174

[100] Maruyama H, Morino H, Ito H, Izumi Y, Kato H, Watanabe Y, et al. Mutations of optineurin in amyotrophic lateral sclerosis. Nature. 2010;465:223–6. doi:10.1038/nature08971

[101] Ying H, Yue BYJT. Cellular and molecular biology of optineurin. Int Rev Cell Mol Biol. 2012;294:223–58. doi:10.1016/B978-0-12-394305-7.00005-7

[102] Ying H, Turturro S, Nguyen T, Shen X, Zelkha R, Johnson EC, et al. Induction of autophagy in rats upon overexpression of wild-type and mutant optineurin gene. BMC Cell Biol. 2015;16:1–13. doi:10.1186/s12860-015-0060-x

[103] Wang Q, Song C, Li CCH. Molecular perspectives on p97-VCP: Progress in understanding its structure and diverse biological functions. J Struct Biol. 2004;146:44–57. doi:10.1016/j.jsb.2003.11.014

[104] Meyer H, Bug M, Bremer S. Emerging functions of the VCP/p97 AAA-ATPase in the ubiquitin system. Nat Cell Biol. 2012;14:117–23. doi:10.1038/ncb2407

[105] Kimonis VE, Mehta SG, Fulchiero EC, Thomasova D, Pasquali M, Boycott K, et al. Clinical studies in familial VCP myopathy associated with Paget's disease of bone and frontotemporal dementia. Am J Med Genet Part A. 2008;146:745–57. doi:10.1002/ajmg.a.31862

[106] Tresse E, Salomons FA, Vesa J, Bott LC, Kimonis V, Yao TP, et al. VCP/p97 is essential for maturation of ubiquitin-containing autophagosomes and this function is impaired

by mutations that cause IBMPFD. Autophagy. 2010;6:217–27. doi:10.4161/auto.6.2.11014

[107] Krick R, Bremer S, Welter E, Schlotterhose P, Muehe Y, Eskelinen EL, et al. Cdc48/p97 and Shp1/p47 regulate autophagosome biogenesis in concert with ubiquitin-like Atg8. J Cell Biol. 2010;190:965–73. doi:10.1083/jcb.201002075

[108] Fang L, Hemion C, Pinho Ferreira Bento AC, Bippes CC, Flammer J, Neutzner A. Mitochondrial function in neuronal cells depends on p97/VCP/Cdc48-mediated quality control. Front Cell Neurosci. 2015;9:16. doi:10.3389/fncel.2015.00016

[109] Tanaka A, Cleland MM, Xu S, Narendra DP, Suen DF, Karbowski M, et al. Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. J Cell Biol. 2010;191:1367–80. doi:10.1083/jcb.201007013

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