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SQSTM1/p62: A Potential Target for Neurodegenerative Disease

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Abstract

Neurodegenerative diseases, characterized by a progressive loss of brain function, affect the lives of millions of individuals worldwide. The complexity of the brain poses a challenge for scientists trying to map the biochemical and physiological pathways to identify areas of pathological errors. Brain samples of patients with neurodegenerative diseases have been shown to contain large amounts of misfolded and abnormally aggregated proteins, resulting in dysfunction in certain brain centers. Removal of these abnormal molecules is essential in maintaining protein homeostasis and overall neuronal health. Macroautophagy is a major route by which cells achieve this. Administration of certain autophagy-enhancing compounds has been shown to provide therapeutic effects for individuals with neurodegenerative conditions. SQSTM1/p62 is a scaffold protein closely involved in the macroautophagy process. p62 functions to anchor the ubiquitinated proteins to the autophagosome membrane, promoting degradation of unwanted molecules. Modulators targeting p62 to induce autophagy and promote its protective pathways for aggregate protein clearance have high potential in the treatment of these conditions. Additionally, causal relationships have been found between errors in regulation of SQSTM1/p62 and the development of a variety of neurodegenerative disorders, including Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis, and frontotemporal lobar degeneration. Furthermore, SQSTM1/p62 also serves as a signaling hub for multiple pathways associated with neurodegeneration, providing a potential therapeutic target in the treatment of neurodegenerative diseases. However, rational design of a p62-oriented autophagy modulator that can balance the negative and positive functions of multiple domains in p62 requires further efforts in the exploration of the protein structure and pathological basis.

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Author Contributions

S.M. and X.X. contributed to conception and design. S.M. performed the literature search and wrote the first draft of the manuscript. S.M. drew all the figures in this review. S.M., I.A., and X.X. participated in revising the manuscript critically for important intellectual content. X.X. supervised the project.

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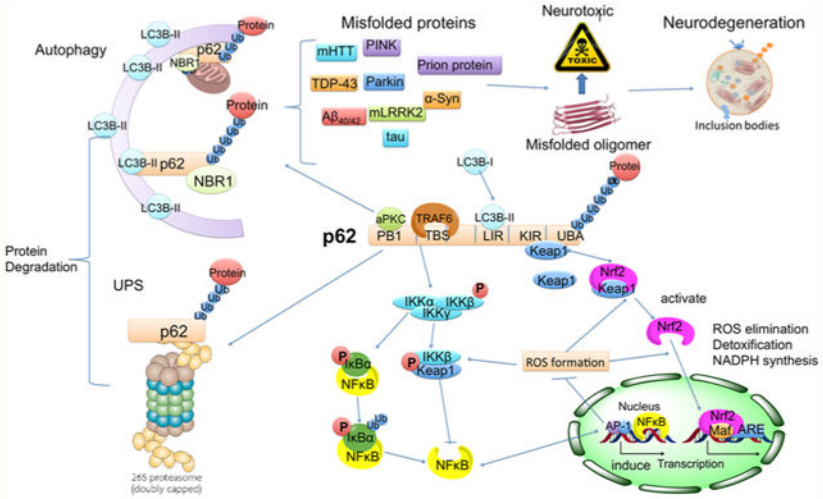
Graphical Abstract



Keywords

SQSTM1/p62; neurodegenerative diseases; autophagy

1. INTRODUCTION

Neurodegenerative diseases result from the progressive loss of function and eventual death of neurons in the central and peripheral nervous systems. Common neurodegenerative conditions include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), motor neuron disease, prion diseases, spinocerebellar ataxia, and spinal muscular atrophy.[1] Millions of people worldwide suffer from neurodegenerative disease, among which at least 500 000 Americans are affected by AD and even more by PD.

These disorders primarily affect neurons. Unlike other cells in the body, neurons lack regenerative capabilities: once damaged or injured, they cannot be repaired, renewed, or replaced. Onset of these conditions results in inevitable progressive neuron dysfunction leading to neuron death, resulting in loss of brain function with corresponding physical or mental symptoms. Current pharmacological treatments are only able to reduce the symptoms associated with neuro-degenerative diseases in an effort to improve the comfort and well-being of the patient. But current methods are unable to prevent, stop, or reverse disease progression.

Researchers are working to understand the genetic and biochemical etiological components, in addition to studying the pathogenesis of common neurodegenerative diseases. Studies show these conditions are likely caused by complex interactions of several factors including genetic, epigenetic, pathogenic, environmental, and other unknown ones. The complexity of these disorders makes it challenging to map the biochemical and physiological pathways in order to better identify areas of potential treatment.

The *SQSTM1* gene codes for p62 and was first identified by Jaekyoon Shin and his colleagues.[2] Also known as seques-tosome-1, p62 is a scaffold protein, crucial in modulating enzyme function through several domain interactions. For example, p62 promotes autophagy degradation by directly binding to an autophagy biomarker, the microtubule light chain 3 (LC3) through a LC3 interacting region (LIR).[3,4] Combined with its ability to bind ubiquitinated proteins at the C-terminal ubiquitin-binding domain,[5] p62 serves as an autophagy receptor in the clearance of unwanted protein molecules and aggregates. In addition to ubiquitin binding domain (UBA) and LIR, which play critical roles in autophagy uptake, other protein-interaction motifs, including an N- terminal Phox-BEM1 domain (PB1), a ZZ-type zinc finger domain,[6] and tumor necrosis factor receptor-associated factor 6 (TRAF6) binding (TBS) domain, are functional domains influential in the regulation of inflammation, oxidative stress, osteoclast genesis, and apoptosis.[7,8] In the past decade, studies have shown that p62 is associated with several diseases including Paget's disease of bone (PDB), PD, AD,[9] HD,[10] liver cancer,[8] breast cancer,[11] obesity, and diabetes.[12] In this review, we will focus on the physiological role of p62 in neuro-degenerative diseases.

2. NEURODEGENERATIVE DISEASES AND MISFOLDED PROTEIN AGGREGATION AND CLEARANCE

The maintenance of protein homeostasis is essential in sustaining a viable neuronal microenvironment to support neuron health and adequate function, especially under metabolic stress.[13] Protein misfolding and aggregation are hallmark signs for the most common forms of neuro-degenerative diseases.[14] For this reason, these conditions are often referred to as "proteinopathies". As shown in Figure 1, under normal conditions, misfolded malfunctioning proteins are removed by protective mechanisms. However, impairment of these mechanisms can lead to accumulation of misfolded peptides, disrupting protein homeostasis and causing neuronal toxicity.[15] Evidence suggests that polypeptide conformational changes can lead to instability of the misfolded intermediates due to interactions between hydrophobic regions and the surrounding aqueous solution. Consequently, the polypeptide forms β-sheets to shield the hydrophobic regions. Aggregation of the β-sheet oligomers can seriously disrupt the neuronal environment, as in the case of β-amyloid buildup into plaques associated with Alzheimer's disease.[14] The conversion of misfolded protein oligomers into insoluble fibrillary species can be directly linked to cell death.[15] The most cytotoxic molecule is considered to be the oligomeric soluble protein, an intermediate in the production of the final amyloid fibril.

As seen in Figure 1, misfolded and aggregated protein molecules are eliminated by three different protective mechanisms, primarily based on molecule size: proteolysis, autophagy, and inclusion body formation. Unfolded peptides and misfolded monomers are eliminated via proteasomal degradation. The majority of misfolded oligomers, in addition to some misfolded monomers, are removed via autophagic clearance. Larger oligomers and insoluble fibrils, which can typically be visualized in cells, will form inclusion bodies. Ubiquitin plays a critical role in all three pathways, as it marks proteins for proteolytic and autophagic degradation and is found in abundance in inclusion bodies. p62 has a ubiquitin binding

domain, which can associate with ubiquitin-modified proteins and shuttle them to the autophagosomal or proteasomal pathways for degradation.

In the case of neurodegenerative conditions, mutations or post-translational alterations lead to protein misfolding. When these misfolded proteins evade degradation, they are then processed into small-misfolded oligomers, at which point they become toxic to the neuronal environment. Examples of these include α-synuclein, β-amyloid, and poly-Qproteins, oligomers known for their pathological roles in Parkinson's, Alzheimer's, and Huntington's diseases, respectively. The toxic oligomeric aggregates are primarily cleared via macroautophagy. Therefore, one of the attractive therapeutic strategies to treat proteinopathies, including those found in neurodegenerative diseases, is to induce the removal of toxic oligomeric molecules by promoting macroautophagy and the ubiquitin proteasome system (UPS) (Figure 1).

As shown in Figure 2, many neurodegenerative diseases share several of the hallmark misfolded protein aggregates, highlighting a common underlying mechanism for neuron dysfunction.[13] AD is characterized by amyloid plaques comprised of Aβ and intracellular neurofibrillary tangles formed by the accumulation of phosphorylated tau protein. The mutations in β-amyloid precursor protein (APP) and presenilin 1, two proteins in Aβ metabolism signaling, are identified as disease related gene changes. Hereditary cystatin C amyloid angiopathy (HCCAA) is a rare but fatal amyloid disease observed in young people in Iceland and caused by a mutation in the *cystatin C* gene. Cystatin C is colocalized with amyloid-β in AD and CAA. Familial amyloidotic polyneuropathy (FAP) is typically caused by the aggregation of mutant transthyretin[16] but is sometimes due to aggregation of the wild-type protein. Familial British disease (FBD) and familial Danish dementias (FDD) are associated with mutations in the BRI2 gene, which are characterized by cerebral deposition of the 34-mer British amyloid (ABri) and Danish amyloid (ADan) peptides, and are accompanied by the observation of neurofibrillary tangles and neuroinflammation.[17,18] The presence of protein deposits called Lewy bodies, formed by aggregated α-synuclein and polyubiquitinated proteins, is the central pathological feature of PD. Lewy bodies have also been linked to the pathological outcomes of multiple system atrophy (MSA) and other Lewy body diseases (LBD). Poly-Q expanded huntingtin, one of the various mutations of the poly-Q protein, is known to cause HD.[10] Other disease-associated mutations of the poly-Q protein have been identified in other neurodegenerative diseases, including dentatorubral-pallidoluysian atrophy (DRPLA), spinal and bulbar muscle atrophy (SBMA), and spinocerebellar ataxia (SCA). TAR DNA-binding protein 43 (TDP-43) was noted as the disease-causing protein for both frontotemporal dementia (FTLD) and ALS. Mutations in TDP-43 cause familial ALS, while cytoplasmic and nuclear inclusions of TDP-43 are found in glial cells and neurons for nearly all anatomical studies of sporadic ALS and FTLD. Prion diseases are a family of rare progressive neurodegenerative disorders characterized by the spongiform changes associated with neuronal loss and failed response to inflammation. Prion disease is caused by a "prion", which refers to a transmissible, pathogenic agent that can trigger misfolding of cellular proteins called prion proteins, most of which are located in the brain. The common types of prion diseases affecting humans include Creutzfeldt–Jakob disease (CJD), variant Creutzfeldt–Jakob disease (vCJD), Gerstmann–Straussler–Scheinker syndrome,[19] fatal familial insomnia,[20] and Kuru disease. In summary, since many of the

misfolded protein aggregates overlap the most commonly known neurodegenerative diseases, it is reasonable to predict that treatment targeting the degradation of these misfolded or aggregated proteins might have therapeutic effects. Macro-autophagy is of importance then, as it is the major cellular clearance mechanism for these toxic protein aggregates.[21]

3. AUTOPHAGY IN NEURODEGENERATIVE DISEASES

Autophagy plays a crucial physiological and pathological role in the regulation of cell growth, survival, and death, as well as macromolecule catabolic signaling, aging, inflammation, and immunity. Either a deficiency or overactivation of autophagy will cause neuronal dysfunction, an underlying condition for several brain pathologies.[22] The process of autophagy can be divided into several sequential steps: induction, initiation/vesicle nucleation, autophagosome elongation and completion, maturation and fusion, and degradation (Figure 3). Genetic and pharmacological regulations of many key players in the autophagy process are associated with neurodegeneration, indicating a strong relationship between autophagy and neurodegenerative diseases.[22,23]

3.1. Autophagosome Formation and Autophagic Flux.

As indicated in Figure 3, the autophagosome formation can be induced by inhibition of mammalian target of rapamycin complex 1 (mTORC1) and activation of AMP-activated protein kinase (AMPK), thus suggesting two independent ways that autophagy premature induction could be resolved therapeutically. This will lead to the phosphorylation of serine/threonine-protein kinase ULK1 and the subsequent phosphorylation of all the components in ULK1–Atg1 (autophagy related 1) complex, including Atg13, Atg101, FIP200 (FAK family interacting protein of 200 kDa), ULK1, and ULK2.[23] Phosphorylated serine/threonine-protein kinase ULK1 can also phosphorylate AMBRA in class III phosphatidylinositol 3-kinase (PI3K) CIII complex I, which is composed of phosphatidylinositol 3-kinase Vps34, Vps15, Atg14, and BCL-2-interacting protein (beclin-1), enabling the complex to relocate from the cytoskeleton to the isolation membrane in the preautophagosome structure. In the PI3K CIII complex I, beclin-1 is negatively regulated by Bcl-2 and Bcl-X, which are related to ER (endoplasmic reticulum) stress.[22,23] Then, Vps34 in PI3K CIII complex will generate PI3K, which selectively interacts with the PI3P effector WD repeat domain phosphoinositide-interacting 1 and 2 (WIPIs), catalyzing two reactions that mediate the isolation membrane elongation.[23] The first reaction is a covalent conjunction of Atg5 and Atg12 in the presence of Atg7 and Atg10, followed by Atg5–Atg12–Atg16 complex formation.[23] This complex will translocate to the membrane of early autophagosomes and promote the covalent interaction of microtubule-associated proteins 1A/1B light chain (LC3)-I with phosphatidylethanol-amine (PE). In the process, Atg4 helps pro-LC3 translocate from the cell membrane to the early autophagosomal membrane, thus conjugating with PE and becoming LC3-II. LC3-II can interact with p62 bodies (p62/Next to BRCA1 gene 1 protein (NBR1) complex with ubiquitinated proteins and organelles) and thereby facilitate the elongation and closure of autophagosomal membrane (shown in Figure 3).

Finally, the autophagosome will fuse with the lysosome and its hydrolytic activity, forming an autolysosome where the ubiquitinated proteins and organelle complexes are degraded. Autolysosomes move along microtubule tracks to fuse with the lysosome. Microtubule acetylation, regulated by histone deacetylase 6 (HDAC6), is essential for fusion. Autolysosome formation requires late endosome proteins, such as Ras-related protein Rab-7 (Rab7), several soluble NSF attachment protein receptors (SNAREs), and lysosome-associated membrane glycoproteins (LAMPs).[23] For lysosomal degradation of cargos, lysosomal acidification relies on vATPase, a proton channel on the lysosome membrane. The electrical gradient created is counterbalanced by parallel influx of anions mediated by chloride proton antiporters. Cations, including calcium, can efflux through distinct channels or transporters, including two pore calcium channel protein 2 (TPC2) and transient receptor potential cation channel mucolipin-like protein (TRPML, mucolipin), which may also influence pH.[23] The cargo will be degraded in the autolysosome, and the signaling factors and organelle debris will be removed from the autolysosome (Figure 3).[23]

3.2. Neurodegeneration Caused by Abnormal Gene Regulation of Components in Autophagy.

Many studies have reported that the beclin-1 level is closely associated with neurodegeneration. Reduced beclin-1 level was detected in early stage AD[9] and HD[24]. Impaired beclin-1 expression will increase Aβ accumulation and mutant huntingtin accumulation in AD[9] mice and HD patients.[24] Upregulation of beclin-1 expression can be used to increase the clearance of aggregated proteins and improve neuron functions, thus providing protection against neurodegeneration and prolonging the life span in AD,[9,25] HD,[26,27] PD,[28] and Machado–Joseph disease, a disease characterized by polyglutamine protein accumulation.[24] Interestingly, an enhanced beclin-1 level has been reported in ALS,[20] but reduced beclin-1 expression in ALS patients has been found to increase neural protective activity against the disease.[22,29] It has been reported that heterozygous deletion of beclin-1 caused earlier SOD1 aggregation, onset of symptoms, and motor neuron loss and a markedly shortened survival in ALS mouse models.[30]

Several research studies have indicated that regulating beclin-1 through its interaction with other proteins can also alter the initiation step in autophagy and modulate aggregated protein clearance in neurodegenerative disease models[22]. In PD, both parkin and PTEN induced putative kinase 1 (PINK1) can interact with beclin-1 to alter autophagy function.[31,32] Parkin, PINK1, and mutant leucine-rich repeat kinase 2 (LRRK2) can also regulate the elimination of damaged ubiquitinated mitochondria, thus affecting the mitophagic pathway.[33] For ALS, the mutant SOD1 will interfere with the interaction between beclin-1 and BCL-X, thus influencing the autophagy level.[29] VPS35, a rare mutation observed in PD patients, can also contribute to autophagy dysfunction due to impaired vesicle sequestering.[22,34]

In the autophagosome elongation step, several mutations of the autophagy adaptor protein p62 have been identified in both familial and sporadic ALS patients. Gene expressions of p62 are also related to many neurodegenerative diseases as mentioned above.[35] Mutant huntingtin (mHTT) expression leads to altered cargo recognition and autophagy failure. It is also reported that α-synuclein can bind to Rab1a and inhibit the interaction between Rab1a

and the Atg9 complex, thus hampering the trafficking of autophagy vesicles.[36] The genetic inactivation of Atg5 and Atg7 in the central nervous system of mice will induce autophagy dysfunction and spontaneous neurodegeneration, causing accumulation of aggregated proteins, extensive neuron loss, and death of the mice.[37,38] Metzger et al. reported that the age of onset in HD could be modified by a polymorphism in Atg7.[39]

In the fusion and degradation step, the proteolytic ability of the lysosome depends on the luminal pH in the lysosome.[22] The pH in the lysosome is regulated by ion channels on the lysosomal membrane, including vATPase proton channels, chloride proton antiporters, calcium transporters, and so on. In AD, presenilin-1 can interact with the vATPase subunit, regulating its maturation and function to control the pH level in the lysosome, thereby influencing lysosome function.[40] Other studies showed restored lysosome function can alleviate AD-related symptoms and improve neural function, which is in accordance with the above findings.[41] Mutations in ATPase ATP13A2 in the lysosomal membrane was observed in familial PD,[42] accompanied by impaired lysosome function, altered proteolytic activity, and abnormal accumulation of autophagosome and α-synuclein, indicating that lysosome dysfunction also influences the occurrence of PD.[43]

All these studies indicate a critical role of autophagy in neurodegenerative pathologies in clearing toxic protein aggregates, protecting neurons against degeneration, and prolonging neuronal survival.

3.3. Autophagy-Enhancing Compounds As Therapeutic Agents for Neurodegenerative Diseases.

Since autophagy serves as an efficient approach to selectively degrade abnormal disease-related proteins and damaged organelles in neurodegenerative diseases, several compounds were screened and identified to enhance autophagy in specific steps and have potential therapeutic efficacy to treat different neurodegenerative diseases. Here, we have summarized some of the studies with compounds that can induce autophagy, promote autophagic degradation of disease related protein aggregates, and improve neuron function in cell and animal models (Table 1). Some of the compounds have shown therapeutic efficacy in clinical trials. We will use the mTOR inhibitor rapamycin, an agent widely tested in preclinical models in different neurodegenerative diseases, as an example to illustrate the pharmacological effect of targeting autophagy in neuro-degenerative diseases.

Inhibition of mTOR by rapamycin enhances autophagy in the early stage of AD, improving cognitive function, correlating with reduced levels of amyloid-β and tau phosphorylation as well as delayed formations of plaques and tangles.[44–46] Rubinsztein et al. reported that rapamycin has a protective function against neurodegeneration in fly and mouse HD models, inducing the clearance of mHTT associated with motor activity.[47,48] Rapamycin administration also protects neurons against degeneration and death in both *in vitro* and *in vivo* HD models, accompanied by an ameliorated amount of Lewy bodies and α-synuclein in the brain.[49] Rapamycin increases autophagy in both FTLD-U[50] and SOD mutated mouse models.[51] The rapamycin-induced autophagy alleviated the FTLD symptoms in the mouse models[50] but augmented the motor degeneration in ALS models.[51] It was indicated that rapamycin might exacerbate the ALS pathology via apoptosis, oxidative stress, and other

mechanisms in SOD1^{G93A} mice, according to the severe mitochondrial impairment, higher apoptosis regulator Bax levels, and greater caspase-3 activation.[51]

4. ROLE AND BIOMARKER OF p62/SQSTM1 IN AUTOPHAGY AND DEGRADATION OF UBIQUITINATED PROTEINS

Ubiquitin-enriched misfolded protein inclusions represent an invariant characteristic for almost all the neurodegenerative diseases.[14] p62 serves as a protein adaptor for ubiquitinated substrates and selective macroautophagy.[52] As shown in Figure 4, three domains contribute to the role of p62 to shuttle ubiquitinated proteins to the autophagosome for degradation, including C-terminal UBA domain, LC3B-interaction region domain, and N-terminal Phox-BEM1 (PB1) domain.[52] Misfolded proteins first self-aggregate, are bound to chaperone proteins, and are then ubiquitinated by UPS enzymes. The mono- or polyubiquitinated proteins then recruit p62 via its C-terminal ubiquitin-associated[53] domain, leading to p62-promoted protein aggregation. The UBA domain binds to both mono- and polyubiquitinated proteins, with a preference for the K63 ubiquitinated proteins. Tanji et al. reported that K63-linked polyubiquitin is the most stable enhancer for protein inclusion formation by increasing the protein accumulation and facilitating the formation of intracellular inclusion bodies under normal conditions. Under pathological conditions, cocultured with tau and SOD1 mutations, K63 promotes the accumulation of tau and the formation of SOD1-containing inclusion bodies. K63-linked polyubiquitin acts as a partner with p62 to enhance autophagic clearance of protein inclusions linked to common neurodegenerative diseases.[54] p62 may regulate K63-linked polyubiquitination via interaction with K63 ubiquitinating E3 ligases (TRAF6).[55–57]

As shown in Figure 4, ubiquitinated protein/p62 aggregates continue growing larger and become p62 bodies, which are then transported to a phagophore-forming location to form an autophagosome. The formation, growth, and transportation of p62 bodies cannot be achieved without the assistance of the N-terminal PB1 domain in p62. The formation of p62 bodies relies on p62 dimerization and further oligomerization. PB1 domain is indispensable and responsible for p62 dimerization; any mutation or variants in this domain will hamper the p62 dimerization. Both p62 homodimerization and heterodimerization with NBR1, both of which are important for the formation of p62 bodies, are regulated by the PB1 domain. Although the underlying mechanism is still unknown, the transportation of p62 bodies to the autophagosome formation location is also dependent on the p62-PB1-mediated homodimerization and heterodimerization.[21,52,56,57]

There are several biological processes related to p62. These processes could be measured by their correlated biomarkers, such as LC3B and beclin-1, biomarkers for macroautophagy. These autophagy biomarkers might also be used as clinical prognostic biomarkers, which can provide information on the likely outcome of diseases in patients and help identify patients for a specific treatment group. For instance, LC3B is one of the best and most commonly used autophagy markers in multiple *in vitro* assays. The expression levels of LC3B protein have also been examined as a useful biomarker by immunohistochemistry (IHC) for the selection of many cancer patients treated with chloroquine (CQ) and other

lysosomal inhibitors. The treatment with lysosomal inhibitors causes the accumulation of p62 due to the blockage of p62 degradation in autolysosomes. In addition to LC3B, other proteins, such as LC3A, beclin-1, ULK1, and VPS34 are also used as autophagy biomarkers to monitor the autophagosome formation and autophagy flux. They might be applied as potential clinical prognostic biomarkers for many cancers as well. The beclin-1–VPS34 complex is a central coordinator for autophagy downstream.[58] Beclin-1 was identified as a potential prognostic biomarker with favorable outcomes for patients with lung cancer, breast cancer, lymphoma, and gastric cancer.[59] Additionally, p62 itself has long served as a biomarker for autophagy flux. Accumulation of p62 protein measured by immunofluorescence and Western blot is usually considered an indication of autophagy inhibition.[58]

The LC3 interaction region is another critical domain in p62 that plays a role in autophagy. The LC3 protein is a key component in autophagy that is necessary for autophagosome elongation and closure as depicted in Figure 4. LC3 protein is cleaved by Atg4 protease to expose its C terminal Gly residue and then conjugates to a phosphatidylethanolamine (PE) group to produce its active form LC3-II. LC3-II directly binds to the autophagosomal membrane and p62 and links them together to form an autophagosome with ubiquitinated protein–p62 aggregates. p62 interacts with LC3-II via its LIR domain (AA332–343). It has been suggested that the LIR domain also binds to key mitophagy components BCL2 interacting protein 3 (BNIP3) and BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like,[23,60,61] as well as the autophagy-dependent cell death mediator tumor protein p53-inducible nuclear protein 1 (TP53INP1).[62] The LIR domain is a short oligomer consisting of about 11 amino acids shared by 10 proteins, including p62. The interaction between p62 and LC3-II anchors the p62 bodies onto the LC3-II-containing autophagosomal membrane, which then continues its maturation and elongation in the autophagy process. Based on the selective interaction between LC3-II and p62, the autophagosome will only contain the ubiquitinated protein aggregates with p62/NBR1, and go through a selective autophagic degradation with lysosome fusion. Therefore, p62 and LC3-II are indispensable regulators for misfolded protein clearance through selective autophagy. Knocking down of LC3 proteins has been shown to induce the accumulation of p62/NBR1-ubiquitinated proteins in the cell plasma. Other studies have shown that ubiquitinated unfolded proteins or organelles could interact with p62/NBR1 and then attach to LC3-II in the autophagosomal membrane, to trigger specific autophagic elimination.[57,63] All these studies demonstrated that p62 is a cargo protein that shuttles the ubiquitinated proteins to autophagic degradation.[56]

5. ROLE OF P62 IN UPS IN NEURODEGENERATIVE DISEASES

The UPS is responsible for the degradation of misfolded proteins via the 26S proteasome and serves as a cellular quality control system. UPS protein clearance has two steps, covalent linkage of polyubiquitin chains to target proteins and degradation of the ubiquitinated proteins by the 26S proteasome complex, releasing free and reusable ubiquitin. Three enzymes take part in ubiquitination of substrates and formation of a bond between the C-terminus of ubiquitin and substrate lysine residues (K6, K11, K27, K33, K29, K48, and K63). “Ubiquitin-activating enzyme (E1) forms a thiol ester with the carboxyl group of Gly76, activating the C terminus of ubiquitin. The activated ubiquitin molecule is carried by

ubiquitin-conjugating enzyme (E2) and transferred to the substrate lysine residue by ubiquitin-ligases (E3).”[63]

As discussed above, the UBA domain in p62 can bind to ubiquitinated proteins, especially those possessing K63-linked polyubiquitin chains. The N-terminus of p62 can directly interact with the 26S proteasome subunit components Rpn10 and Rpt1.[64] Therefore, p62 can shuttle the polyubiquitinated protein via the UBA domain to 26S proteasome via its N-terminus for degradation. In addition, as mentioned above, the PB1 domain of p62 can regulate p62 self-interaction and heterointeraction with PB1 domains of other proteins. It has also been reported that the PB1 domain can assume a ubiquitin fold, which might be favorable for p62 N-terminal interaction with the proteasomal subunit.[64] It has also been reported that p62 associates with polyubiquitinated tau and targets it for proteasomal degradation, supporting the shuttling role of p62 in proteasome-mediated protein degradation.[65] A similar role for p62 has also been reported for TrkA shuttling to the proteasome.[66]

Proteasome inhibitor epoxomicin treatment can enhance levels of ubiquitinated protein and p62 in SK-N-SH cells.[67] p62 overexpression does not affect proteasome catalytic activity but delays UPS substrate delivery to the proteasome’s proteases, leading to their accumulation.[68] Moreover, p62 overexpression along with pharmacological inhibition of UPS or autophagy does not further increase ubiquitin aggregates. It was also observed that soluble p62 colocalized with proteasomes and p62 aggregates contained inactive proteasomes, ubiquitinated proteins, and autophagosomes with epoxomicin treatment.[67] These studies further suggest that p62 plays a critical role in shuttling ubiquitinated proteins for proteasome degradation.

Similar to macroautophagy, UPS, as another intracellular protein clearance system, is also involved in the pathology of neurodegenerative diseases. One possible assessment of UPS function in neurodegenerative diseases is to measure the end point proteolytic activity of the proteasome. Many studies have measured proteasome activities with purified proteasome, different cell lines, animal models, and brain tissues. The results have not been consistent. Some studies have shown reduced proteasome activities in neurodegenerative diseases, including Parkinson’s disease,[40,69–72] Alzheimer’s disease,[73–77] ALS,[78] Huntington’s disease,[79,80] and prion diseases.[81] Some studies reported an unchanged or even increased proteasome activity in neurodegenerative disease models.[81–85] This increase might be due to an induction of immunoproteasomes in inflammatory response[86] or could be an adaptive response to the augmented load of misfolded proteins that occurs in neurodegeneration.[87]

Given the tremendous amount of proteins that are involved in UPS, they might be also associated with neurodegenerative diseases. For example, mutations in the *vcp* gene, which encodes valsolin-containing protein (a ubiquitin binding protein involved in UPS trafficking), were reported to be related to FTLD. A genetic study implied that certain variants in the *ubiquilin 1* gene (UBQLN1), which encodes another shuttling protein that delivers ubiquitinated protein to the proteasome, increase the risk of AD. The deubiquitinating enzyme ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1) removes ubiquitin from proteins and is known to stabilize monomer ubiquitin and facilitate

E3 ligase in UPS. A certain mutation in the *UCHL1* gene has been reported to inhibit the proteasomal degradation of α-synuclein, which makes individuals more susceptible to PD.[88] On the other hand, *UCHL1* overexpression is found to improve memory and restore synaptic functions in AD mouse models.[89]

Parkin, an E3 ligase involved in UPS, is associated with the pathology of both AD and PD and is one of the major components found in Lewy bodies and Lewy neurites, the major pathological features of PD.[90] Parkin overexpression has also been reported to decrease $A\beta$ and restore impaired long-term potentiation (LTP) and behavioral abnormalities in APP/PS1 mouse model.[91–93] The C-terminus of Hsp70-interacting protein (CHIP) is another important E3 ligase in UPS and has been implicated in AD, HD, and PD pathogenesis. CHIP and heat shock protein 70 (Hsp70) are upregulated in the brains of AD model mice.[94] CHIP and Hsp70 can induce the ubiquitination and degradation of p-tau. In addition, over-expression of CHIP or Hsp70 reduces steady-state Aβ levels and promotes Aβ degradation in AD models.[95] Moreover, CHIP can ubiquitinate LRRK2[96] and α-synuclein,[97] promote their degradation, and improve the ligase activity of parkin in PD models.[98] Furthermore, CHIP can suppress the aggregation of polyglutamate proteins and reduce their neuronal toxicity in HD models; while knockdown of CHIP exacerbates the HD process in a transgenic model.[93,99]

6. SEQUESTOSOME 1/P62: A MULTIDOMAIN PROTEIN FUNCTIONING AS A SIGNALING HUB

As shown in Figure 5, sequestosome 1/p62, originally identified in 1996 by Joung, functions as an intracellular signal modulator in multiple signaling pathways. p62 is a multifunctional protein rich in protein-interaction domains, including an N-terminal PB1 domain, ZZ-type zinc finger domain, nuclear localization signal (NLS), TRAF6 binding domain (TBS), export motif (NES), LC3-interacting region, Kelch-like ECH-associated protein 1 (Keapl)-interacting region (KIR), and a C-terminal UBA domain, consistent with its role as a signaling hub.[100] p62 protein acts as a signaling hub for different signaling pathways related to neuronal disease, as shown in Figure 6.[13,101]

Among its multiple motifs, p62 has an N-terminal PB1 domain, which is a protein–protein interaction module present in many other signaling molecules, such as atypical protein kinases Cs (αPKCs) and mitogen-activated protein kinase kinase kinase 3 (MEKK3). These proteins and p62 can bind to each other and themselves through their PB1 domains.[7,102] First, p62 interacts with itself and aggregates via the PB1 domain, facilitating its homo-oligomerization and cellular function.[103] Additionally, hetero-oligomerization can also occur with p62 and other PB1 domain-containing proteins, including αPKCs, dual specificity mitogen-activated protein kinase kinase 5 (MEK5), mitogen-activated protein kinase 3 (MAPK3), MEKK3, and Rpt1, which have critical roles in different signaling pathways that modulate adipogenesis, angiogenesis, neuron survival, cardiovascular pathogenesis, and osteoclastogenesis.[104]

Among them, the interaction between p62 and αPKCs is associated with the activation of the nuclear factor κ-B (NF-κB), which is downstream of cell stimulation by interleukin 1

(IL-1),[105] tumor necrosis factor receptor superfamily member 11A (RANK) ligand,[106] or nerve growth factor (NGF), to promote neuron survival and to trigger inflammation.[107,108] The downstream signaling cascades will be elevated or suppressed based on the up- or down-regulation of p62 protein expression level. It was reported that knocking out p62 would reduce the αPKC activity, thus increasing MAPK, RAC-α serine/threonine-protein kinase (AKT), and mitogen-activated protein kinase 8–10 (JNK) signaling,[102] which have detrimental effects leading to Aβ pathology and inflammation in neurodegenerative disease. The p62 PB1 domain also binds to MEKK3, thus activating NF-κB signaling.[109] In addition, glycogen synthase kinase-3 β (GSK3β) activity was also enhanced in the p62 knock out mice, leading to tau hyperphosphorylation.[110,111] Normally, p62 will suppress the activity of MAPK, knocking out p62 protein activated MAPK signaling, leading to insulin resistance, impaired plasma glucose levels, and obesity.[112] Insulin resistance has been observed in AD brain samples.[113] It is also reported that the interaction between p62 and MAPK3 will promote adipogenesis.[114]

Next, p62 has a zinc finger[106] domain, which interacts with receptor interaction protein (RIP) to regulate NF-κB signaling and inflammation and necroptosis pathways in conjunction with atypical PIKC.[5,115–117] In addition, p62 possesses a newly reported region located between the ZZ and TB domains that interacts with mTOR regulator Raptor,[118] which makes p62 an integral component for mTORC1 complex. p62 is necessary for mTORC1 activation in response to the uptake of amino acids and the subsequent mTORC1 recruitment to lysosomes.[118] The Xie lab and their collaborators have discovered P62 ZZ domain specific inhibitors and identified them as potential treatments for multiple myeloma and Huntington's disease.[3,119–122] These inhibitors have shown effect to modulate autophagy and proteolysis.[123–125]

Moreover, p62 interacts with TRAF6, a lysine 63 E3 ubiquitin ligase, via its central the TRAF6 binding site (TBS) to regulate several signaling pathways related to neuro-degenerative diseases.[101,105,126] The interaction of p62 and TRAF6 induces p62–TRAF6 oligomerization, followed by K63 polyubiquitination of TRAF6, which leads to the activation of NF-κB.[101,105,107] In 2000, Sanz et al. reported that p62 can interact selectively with TRAF6, thereby activating the NF-κB activation in response to IL-1.[105] NGF interacts with both p75 and tropomyosin receptor kinase A (TrkA), leading to NF-κB activation.[127] In 2001, Wooten and colleagues showed that p62 binds to TrkA but not p75, whereas TRAF6 binds to p75 but not TrkA. They demonstrated that an interaction between p62 and TRAF6 could act as a bridge to link p75 and TrkA signaling and a high affinity-binding site for NGF. They also suggested that p62 serves as a scaffold protein for the activation of NF-κB signaling by NGF, which mediates neuron survival and differentiation responses.[127] Geetha and co-workers found that NGF stimulated TrkA polyubiquitination and this polyubiquitination of TrkA was reduced in p75 knock out mice. Both mutations in ubiquitin (K63R) and an absence of TRAF6 will abolish the polyubiquitination.[128] Moreover, blocking the TBS domain in p62 and mutating the K485 in Trk A with arginine will also eliminate the polyubiquitination of TrkA, and the following NGF activated NF-κB signaling. This work indicated that polyubiquitination serves a role as a common signaling platform for the complex formation and receptor internalization.[128]

In 2005, Wooten showed that p62 facilitated the polyubiquitination of TRAF6.[129] This polyubiquitination will be inhibited or blocked by mutation or deletion of the PB1, UBA, or TBS domain in p62. NGF stimulates the TRAF5 polyubiquitination and p62–TRAF6–IKK–PKC complex formation, which are suppressed by the blocker of p62–TRAF6 interaction.[129] Zheng et al. reported that in PC12 cells, Aβ impaired the TrkA phosphorylation, ubiquitination, and complex formation with TRAF6–p62–p75.[130] They also observed similar impairment of TrkA tyrosine phosphorylation, ubiquitination, and downstream signaling in AD patient brain hippocampus samples compared with the control. A possible explanation is that the nitrotyrosylation of TrkA is increased in the AD hippocampus, which might in turn reduce the TrkA that undergoes ubiquitination and phosphorylation.[55,130] Additionally, they reported a reduced production of matrix metalloproteinase-7 (MMP-7) in AD hippocampus samples, which cleaves proNGF, resulting in an accumulation of proNGF and an attenuated level of active NGF.[130] The accumulated proNGF will activate the p75 (not with TrkA), thereby inducing apoptosis and neuron death. Further analysis showed Aβ and AD lessened not only the ubiquitination and phosphorylation of TrkA but also TrkA regulated downstream signaling, such as NF-κB, p38–MAPK, and PI3K–AKT pathways.[55,101,130] Furthermore, studies showed that deregulation of TrkA/p75 induced neurotrophin signaling caused by lack of p62 or p75 have been linked to cholinergic dysfunction in AD.[131]

Furthermore, the LIR domain and C-terminal UBA domain enable p62 to function as an adaptor between autophagy and ubiquitinated proteins. p62 binds to ubiquitin and ubiquitinated proteins via its UBA domain and then traffics the ubiquitinated protein complex to the autophagosome through LIR interaction with LC3. The detailed description was discussed in the macroautophagy section (section 3).

Additionally, p62 has a KIR domain that directly binds to Keap1 and interferes with the Keap-nuclear factor erythroid 2-related factor 2 (Nrf2) interaction, activating the Nrf2 mediated reactive oxygen species (ROS) elimination. Keap1 is an adaptor for Cullin-3 ubiquitin ligase that senses oxidative stress and binds to Nrf2. Nrf2, a basic leucine zipper protein, is responsible for a series of antioxidant proteins and detoxifying enzymes, which protect cells against oxidative damage triggered by injury and inflammation.[132] Keap1 binds to KIR at the same binding site for Keap1–Nrf2 interaction, thus inhibiting the interaction between Keap1 and Nrf2, leading to the stabilization of Nrf2 and transcriptional hyperactivation of the Nrf2 target gene.[132,133] Given that p62 is closely involved in selective autophagy, the p62–Keap1–Nrf2 axis is also linked to selective autophagy by some post-translational modifications like phosphorylation and ubiquitination.[134] Moreover, since p62 is degraded through autophagy, the lack or deficiency of autophagy in hepatocellular carcinoma cells or liver disease patients will result in p62 accumulation, thereby evoking persistent activation of Nrf2.[135,136] On the other hand, Nrf2 stimulates p62 protein expression, which then produces a positive feedback loop between Nrf2 activation and p62 protein expression. These studies showed that p62 served as a bridge to link the selective autophagy and ubiquitination system to the oxidative stress response system and redox regulation.[137] Maintenance of homeostasis of p62 protein levels is crucial for neuron health. Kanninen et al. showed that the AD symptoms in transgenic AD mice would be improved by elevated Nrf2 expression.[138–140]

In addition to signaling pathways mentioned above, p62 protein also interacts with other proteins and regulates other signaling pathways influential to brain function. For instance, p62 binds to ubiquitinated Dishevelled protein (Dvl2) and mediates its autophagic clearance, so that p62 can inhibit Wnt signaling, which is known to play a role in AD pathogenesis by its ability to control neuron development and maintain synaptic function in the brain.[141] Moreover, two nuclear localization systems (NLS1 and NLS2) and one nuclear export system (NES) were identified in the structure of p62 protein. They are involved in the nucleo-cytoplasmic shuttling for p62 and other scaffold proteins. p62 contains two PEST regions rich in proline (P), glutamic acid (E), serine (S), and threonine (T), which serve as proteolytic signals for rapid degradation.[142] Furthermore, scientists reported that p62 could induce the intracellular aggregation and autophagic clearance of cyclic AMP phosphodiesterase-4A4 (PDE4A4), eliminating the PDE4A4 from its functional sites and thereby augmenting cyclic adenosine monophosphate (cAMP) signaling. So the reduced p62 protein expression will attenuate the cAMP signaling, which plays an important role in the mediation of memory and synaptic plasticity.[143–146]

7. GENETIC REGULATION OF P62/SQSTM1 IN NEURODEGENERATIVE DISEASES

Dysregulation of p62 levels and functions was observed in several neurodegenerative diseases. For example, studies in p62 knockout mice have clearly demonstrated that the lack of p62 protein could result in neuropathological lesions including to the increase of hyperphosphorylated tau and neurofibrillary tangles, anxiety, depression, loss of working memory, and reduced serum brain-derived neurotrophic factor levels and neurodegeneration.[105,147,148] Wooten et al. reported a detectable increase in accumulation of insoluble Lys63 ubiquitinated proteins in the neurons of p62 knockout mice.[149]

7.1. Regulation of p62 in ALS, FTLD, and ALS/FTLD.

Amyotrophic lateral sclerosis is a progressive, invariable fatal neurological disease, which is characterized by the gradual degeneration and depletion of motor neurons in both the brain and spinal cord that are responsible for controlling voluntary muscle movement. Eventually, all voluntary muscles will be affected, and the patient will lose control of muscle movement and strength. Fatality in ALS patients is due to the loss of function of the respiratory muscles. The formations of ubiquitin-immunoreactive inclusions are widely detected in the brains of ALS patients. In 1991, Okamoto et al. examined the brains of 27 amyotrophic lateral sclerosis patients and 50 controls.[150] They found new ubiquitin-positive intraneuronal inclusions in the hippocampal granular cell layer and entorhinal cortex in seven of the ALS patients. Then in 2004, Nakano and colleagues tested p62 immunoreactivity in ubiquitin-positive inclusions in five ALS-D patients and confirmed that the ubiquitin-immunoreactive inclusions are also p62 positive.[151] This suggested that p62 and ubiquitin could play a common role in formation of inclusions and in preventing neuronal death in the ALS degenerative disease process.

Concurrently, mutations in SQSTM1 encoding p62 protein were screened in a large cohort of both familial and sporadic ALS patients. Fecto et al. examined SQSTM1 mutations in a

cohort of 546 patients.[152] They identified 10 novel SQSTM1 mutations in 15 patients. Teyssou and colleagues sequenced SQSTM1 in 74 sporadic ALS cases and 90 familial ALS French patients.[153] They confirmed two mutations in the UBA domain that were previously reported in ALS and Paget's disease patients. They also identified two new missense mutations in sporadic ALS cases, which were not identified in the control group. Further analysis revealed increased p62 levels in the spinal cord and large p62 inclusions in motor neurons. A study from the UK confirmed the presence of the p(Pro392Leu) SQSTM1 mutation in the UBA region in both familial ALS and PDB, indicating a common pathogenic pathway that converges on protein homeostasis.[154] Gal et al. reported that accumulation of p62 can increase formation of polyubiquitinated protein and mutant SOD1 aggregates in G93A mouse spinal cord affected cells.[155] They found that p62 can recognize and bind to an ALS associated SOD1 isoform through its SOD1 mutant interaction region (SMIR), indicating that p62 could link mutant SOD1 to autophagy and proteasome pathways in both ubiquitin-dependent and independent mechanisms.[156] Their findings suggested a direct genetic role for p62 in ALS pathogenesis and a potential therapeutic use for ALS.

The absence of SQSTM1/p62 was found in childhood-onset neurodegenerative disease patients' fibroblasts and has been linked to defects in mitophagy owing to compromised autophagosome formation following mitochondrial depolarization.[19] The effect of SQSTM1/p62 loss-of-fUnction has been evaluated in zebrafish model of ALS/FTLD, where p62 knockdown led to abnormal motor behavior and shortening of motor neurons, which can be rescued by rapamycin administration.[157,158]

Frontotemporal degeneration (FTD) is the most common cause of dementia under the age of 65 years and the third most common cause of neurodegenerative dementia, after AD and PD.[159,160] The syndrome is also called frontotemporal lobar degeneration (FTLD). However, FTLD refers to a larger group of disorders, FTD being one of its subgroups. The other subgroups of FTLD are progressive nonfluent aphasia (PFNA), and semantic dementia.[61,161] Neuronal cytoplasmic inclusions are pathological hallmarks in several neurodegenerative diseases.[162] For FTLD, cytoplasmic inclusions composed of either the 43-kDa transactive response-DNA-binding protein (TDP-43) or tau are characterized in almost 90% of FTLD.[54] Tanji and colleagues immunoprecipitated p62 in the cerebral cortex from FTLD patients with TDP-43 and found that p62 co-immunoprecipitated several proteins, including TDP-43.[54] p62 can be involved in the degradation of 35 kDa TDP-43, a truncated isoform of TDP-43.[54] The degradation and dysregulation of TDP-43 might play a causative role in ALS and FTLD.[160] Mutations distributed throughout p62 might affect the interaction between p62 and TDP-43 and may participate in the pathogenesis of TDP-43 proteinopathy.[54,56]

In the last two decades, increasing evidence implied that ALS and FTLD share some clinical, neuropathological, and genetic features. A subtype of disease with both ALS and FTLD features is classified as ALS-FTLD. Therefore, we mentioned the regulation of p62 in these two diseases together in one section. FTLD signs can be seen in patients primarily diagnosed with ALS, implying clinical overlap among these two disorders. It is reported that up to 40–50% of ALS patients have FTLD dysfunctions, accessed as frontal dysfunctions or language impairment.[163,164] Additionally, some reports claimed ~50% of FTLD cases developed with ALS signs,[164,165] as subclinical motor neuron degeneration, while others

reported about 10% FTD cases with ALS syndromes. Probably these discrepancies are caused by different disease classifications as well as statistical evaluation methods.[166] In the past decade, pathological investigations and genetic screening have contributed tremendously to elucidating the pathology and genetic variability associated with FTD and ALS. Evidence of shared molecular pathological features was also reported to explain the clinical overlaps between FTD and ALS, such as the ubiquitin-positive neuronal inclusions, its associated TDP-43 aggregate proteinopathy,[166–170] and tau pathology.

Some papers have uncovered the genetic overlap between FTLD and ALS. The most common one is the C9orf72 repeat hexanucleotide expansion coding, which occurs in 10% of all patients. Al-Sarraj et al. identified a new distinctive pathological subtype of C9orf72-ALS/FTLD, which is characterized by p62 positive, phosphorylated TDP-43 (p-TDP-43) negative cytoplasmic and nuclear inclusions.[160] They found that p62 bound to an unknown ubiquitinated protein in a distinctive inclusion, other than p-TDP-43 inclusion, which is the core disease inclusion.[160] Then, Mori et al. found that most of these core inclusions contain poly(Gly-Ala), poly(Gly-Pro), and poly(Gly-Arg) repeat proteins translated from the GGGGCC repeat expansion gene.[171] The genetic mutations in ALS/FTLD and the dominant pathology in C9orf72-ALS/FTLD patients are connected directly by this finding.[171] Later, King et al. also reported a FTLD patient with mixed p62, TDP-43, and tau pathology.[56,172]

P62 is an excellent label to detect the ubiquitinated cytoplasmic inclusion bodies that are important factors in neurodegenerative disease.[162] ALS-FTLD associated L341V mutation in LIR of p62 lead to defective recognition and reductive binding to LC3 and failure in autophagosome formation and aggregated protein degradation. This phenotype was also ameliorated by rapamycin administration, implicating a potential pathogenic role for autophagy in SQSTM1-ALS.[173] Two ALS-FTLD associated KIR mutations of SQSTM1/p62, P348L and G351A, disrupt Keap1 binding, leaving Keap1 to interact with Nrf2, which inactivates the Nrf2 signaling related to oxidative stress response. This suggests that SQSTM1 mutations in KIR reduce Nrf2 signaling activation and partially contribute to etiology of ALS-FTLD through a mechanism of regulation of oxidative response genes.[174]

p62-mediated degradation of SOD1 isoform and TDP-43 via autophagy may provide a therapeutic option to treat a subtype of ALS, FTLD, and ALS/FTLD patients. The mTOR kinase inhibitor rapamycin enhances the autophagy in both FTLD-U[50] and SOD1 mutated mouse models.[51] The rapamycin-induced autophagy alleviates the FTLD symptoms in the mouse models[50] but augments the motor degeneration in ALS models.[51] Wang et al. observed improvement in cognition and memory as well as decreased motor and neuronal function loss in FTLD model mice treated with rapamycin and three additional autophagy enhancers (spermidine, carbamazepine, and tamoxifen).[50] However, autophagy enhancer rapamycin accelerated the motor neuron degeneration, shortening the life span of ALS mice accompanied by severe mitochondrial impairment, higher Bax levels, and greater caspase-3 activation.[51] It is suggested that rapamycin might exacerbate the ALS pathology via apoptosis, oxidative stress, and other mechanisms in $SOD1^{G93A}$ mice.[51] Additionally, other re-searchers suggested that the mTOR-independent autophagy enhancer trehalose could also delay the motor degeneration process and prolong the neuron survival via the activation of autophagy.[175,176]

7.2. Regulation of p62 in Parkinson's Disease (PD).

Parkinson's disease (PD) is the second most common neurodegenerative disorder, following Alzheimer's disease, and the most common neurodegenerative motion disease. It is a progressive disorder in the central nervous system (CNS) that affects movement. Tremors are the most well documented sign of early stage PD; then progressive development of shaking, muscle rigidity, slowed movements, and difficulty walking occurs. Cognitive and mental problems are common in the advanced stages of PD. The cause of the disease is still unknown, but it is suggested to be associated with a combination of genetic, epigenetic, and environmental factors. Intracellular accumulation of Lewy bodies and Lewy neurites, consisting of aggregated proteins, such as α-synuclein, parkin, and ubiquitinated proteins, is one of the major pathological factors of PD.[93] Variants in the gene encoding α-synclein[177,178] are present in autosomal dominant familial PD, while mutations in genes encoding parkin,[179,180] PINK1,[181] UCHL1,[182] and LRRK2[183] result in autosomal recessive familial PD.[93] Among them, PINK1 and parkin are the most common disease-causing genes identified for familial PD. Parkin is an E3 ubiquitin ligase, and PINK1 is a mitochondria-targeted serine-threonine kinase. PINK1 and parkin work together to maintain mitochondrial integrity.[102] PINK1 and parkin mediate mitophagy, the selective degradation of mitochondria by autophagy. Scientists reported that p62/SQSTM1 is indispensable for parkin-induced mitochondrial clustering[184] and plays a role in PINKl/parkin-mediated mitophagy.[185] Parkin and p62 also have an important role in autophagy, loss of which in dopaminergic neurons was recently demonstrated to cause Lewy pathology and motor dysfunction in aged mice.[186] It is also implicated that the dysregulation of parkin/p62 axis may be involved in proteasomal degradation and selective vulnerability of neuronal cells during the onset of PD pathogenesis.[187]

It is reported that the interaction between p62 and LRRK2 regulates LRRK2 toxic biology in PD models.[188] Mutations in LRRK2 lead to autosomal recessive familial PD. p62 physically interacts with LRRK2 as a selective autophagic receptor and modulates antophagic clearance of LRRK2. In turn, LRRK2 indirectly regulates the phosphorylation of p62 and the subsequent interaction between phosphorylated p62 and Keap1.[189] A p62-immunoreactive profile was found in the hypothalamic paraventricular nucleus and the paraventricular nucleus in patients with PD and Lewy body disease.[190] The phosphorylated α-synuclein positive Lewy body was colocalized with p62, but the p62 bodies did not necessarily colocalize with phosphorylated α-synuclein. The average size of p62 bodies was larger in PD patients compared to control ($p < 0.05$), implicating the accumulation of p62 or impairment of autophagy in PD being linked to Lewy body formation.[191]

In addition to parkin/PINK1, p62 was found to colocalize with neuronal and glial ubiquitin-containing inclusions in PD, AD, FTLD, and MSA.[192] The interaction between ubiquitin and p62 participates in the formation of paired helical filament (PHF)-tau and α-synuclein inclusions.[192,193] Moreover, Nakaso suggested that p62 might protect neuronal cells from the toxicity caused by misfolding protein via promoting the aggrege formation under stressful conditions, according to the results of Lewy body formation.[194]

7.3. Regulation of p62 in Huntington's Disease (HD).

Huntington's disease (HD) is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. Today, there are approximately 30 000 symptomatic Americans and more than 200 000 at-risk of inheriting the disease. HD is characterized by progressive neuron dysfunction, which will lead to progressive neuron death in the brain. So far available treatments can only help to alleviate some of the physical or mental symptoms associated with HD but cannot cure the disease. HD is associated with a CAG repeat expansion in the gene encoding huntingtin.[195] Dysfunction of macroautophagy has been proposed to contribute to pathogenesis of Huntington's disease. Inability of autophagic vacuoles to recognize cytosolic cargo was identified in HD cells and could be responsible for the insufficient macro-autophagy in HD cells.[196] It is reported that ULK1 phosphorylates Atg14 and regulates Atg14–Vps34 kinase activity to control macroautophagy level. Atg14 phosphorylation, Vps34 activity, and macroautophagy are reduced in HD mouse models. This reduction of the specific phosphorylation of Atg14 is mediated, in part, by p62-induced sequestration of ULK1 to an insoluble cellular fraction. Increased ULK1 levels and ULK-mediated Atg14 phosphorylation facilitate the clearance of polyQ mutant in cells.[197]

p62 is demonstrated to be associated with HD via mediating autophagy and clearance of aggregated mutant huntingtin often under stress in many reports. In mouse R6/1 Huntington model, p62 level was reduced in all brain regions at an early stage of the disease, it remained reduced as the disease progressed, and accumulated in striatal and hippocampal neurons in the late stage of the disease.[198] SQSTM1/p62 and LC3 form shell proteins surrounding aggregates of mutant huntingtin that are degraded by autophagy to protect neurons. Reduction of p62 protein levels or dysfunction of p62 significantly increased cell death induced by mutant huntingtin in Huntington's disease.[199] The genetic ablation of p62 in three HD model mice (R6/2, HD190QG, and HD120QG) was found to increase cytoplasmic inclusion formation by interrupting autophagic clearance of polyQ inclusions, which decreases polyQ nuclear influx and paradoxically ameliorates disease phenotypes by reducing toxic nuclear inclusions.[200] Ectodermal-neural cortex 1 (ENC1) was reported to bind with p62 in C terminal Kelch domain, which is needed for p62 to interact with ubiquitinated mutant HTT aggregates, thus blocking p62 cargo recognition in macroautophagy. The interaction between p62 and ENC1 is enhanced under ER stress, which inhibits p62 cargo recognition and macro-autophagy, leading to accumulation of neurotoxic mHTT. On the other hand, knockdown of ENC1 will relieve ER-stress induced death of neurons that express mHTT.[201] HD cells are more vulnerable to cell death under proteotoxic stress and during stress recovery. SQSTM1/p62 is upregulated in response to proteotoxic stress, and distinctive subcellular localization of p62 is observed in normal cells and HD cells. The upregulated and abbreviated subcellular localization of p62 might contribute to enhanced vulnerability to proteotoxic stress and its recovery in Huntington's disease.[202]

7.4. Regulation of p62 in Alzheimer's Disease (AD).

p62 plays a role in AD pathology. AD is the most common neurodegenerative disease and most common cause of dementia. It is a progressive disorder that slowly destroys memory

and cognitive functions. The pathological mechanism of AD is still unknown. Although no direct mutations in p62 have been detected in AD patients, low expression of p62 has been shown in some AD patients.[35] Genetic inactivation of p62 results in Aβ accumulation, tau hyperphosphorylation, and neurodegeneration.[35] Du et al. observed that the p62 cytosolic level was significantly lower in the frontal cortex of AD patients compared to the control group. They also claimed a lower expression of p62 protein in transgenic (APP-tau-presenilin 1/PS 1) AD mice models due to oxidative stress. The promoter of the p62 gene is in a rich GC repeat region, which is vulnerable to oxidative stress and other environmental factors that might play a role in AD pathology.[102] However, no clear evidence has proven this yet. In addition to GC regions, the p62 gene promoter involves several binding sites for Ets-1 transcription factor family members,[203] which can mediate multiple neuronal functions in the brain, including cognitive development, neuron proliferation, and neuron survival. For example, Ets can regulate PSEN1 gene promoter expression, thus controlling the encoding of presenilin-1 protein, which is an integral part for γ-secretase complex.[204] γ-Secretase is responsible for the cleavage of amyloid protein precursor (APP) to produce amyloid-β (Aβ) peptide. One of the major pathological characteristics of AD is Aβ accumulation that forms amyloid plaques in the brain.[104] It was reported that overexpression of p62 rescues cognitive deficit in APP/PS1 mice, with Aβ level and plaque load decreased and autophagy increased. This reduction in amyloid-β is prevented by administration of an autophagy inhibitor, indicating that p62 regulates Aβ turnover via autophagy.[205]

The PB1 domain in p62 can interact with αPKC and regulate its downstream signaling cascade. Knocking down of p62 will reduce the activity of PKCι/λ, therefore increasing the activities of GSK3β, JNK, MAPK, and AKT signaling,[102] which subsequently leads to tau phosphorylation and detrimental effects on Aβ and inflammation pathology in AD.[110,111] NF-κB signaling, which supports the survival of neurons, can be triggered by p62–TRAF6–TrkA complex[129] via induction by NGF or αPKC activation via interaction with p62.[127] Additionally, lack of p62 results in dysfunction of TrkA/p75-induced neurotrophin signaling, which has been associated with cholinergic dysfunction in AD.[131] p62 also binds to Keap1 by its KIR to interrupt Keap1–Nrf2 mediated antioxidative response. Phosphorylation of S349 in KIR of p62 can be induced by both disruption of the protein degradation system and activation of oxidative stress in AD. The ratio of pS349 p62 to total p62 was significantly increased in the brains of AD patients compared with controls, indicating the occurrence of both sustained activation of Keap1–Nrf2 system and disruption of protein degradation system in the AD brain.[206] Antioxidative capacity of Keap1–Nrf2 oxidative stress response system was reduced along with decrease in p62 level and enhanced autophagy in AD rat brain. This might result in tau hyperphosphorylation and subsequent structural and functional damage to neurons.[207]

8. SUMMARY

p62 is a multidomain signaling scaffold protein that integrates multiple signaling pathways through its functional domains, including PB1, ZZ, TBS, LIR, and KIR. These domains interact with different signaling proteins, involving PKC, RIP1, TRAF6, LC3, and Keap1, to regulate apoptosis, autophagy, oxidative stress response, inflammation, and so on. Additionally, p62 acts in trafficking cargo in the initiation and elongation step of the

macroautophagy process to help remove the abnormal protein aggregates and destroyed organelles from cells and protect neurons against neurodegeneration and death. Additionally, several studies have reported that gene expression regulation and mutations in p62 are correlated with the occurrence of some common neurodegenerative diseases. Pharmacological modulators enhancing autophagy, which is also regulated by p62, showed therapeutic efficacy to treat several neurodegenerative diseases in preclinical models as well as in some clinical trials. All of these studies suggested that p62 played a crucial role in the pathology of neurodegenerative disease. p62, itself, can be identified as a potential therapeutic target against neurodegenerative diseases. However, how to balance the positive and negative effects of p62 modulators for neurodegenerative diseases based on the protein structure remains to be defined.

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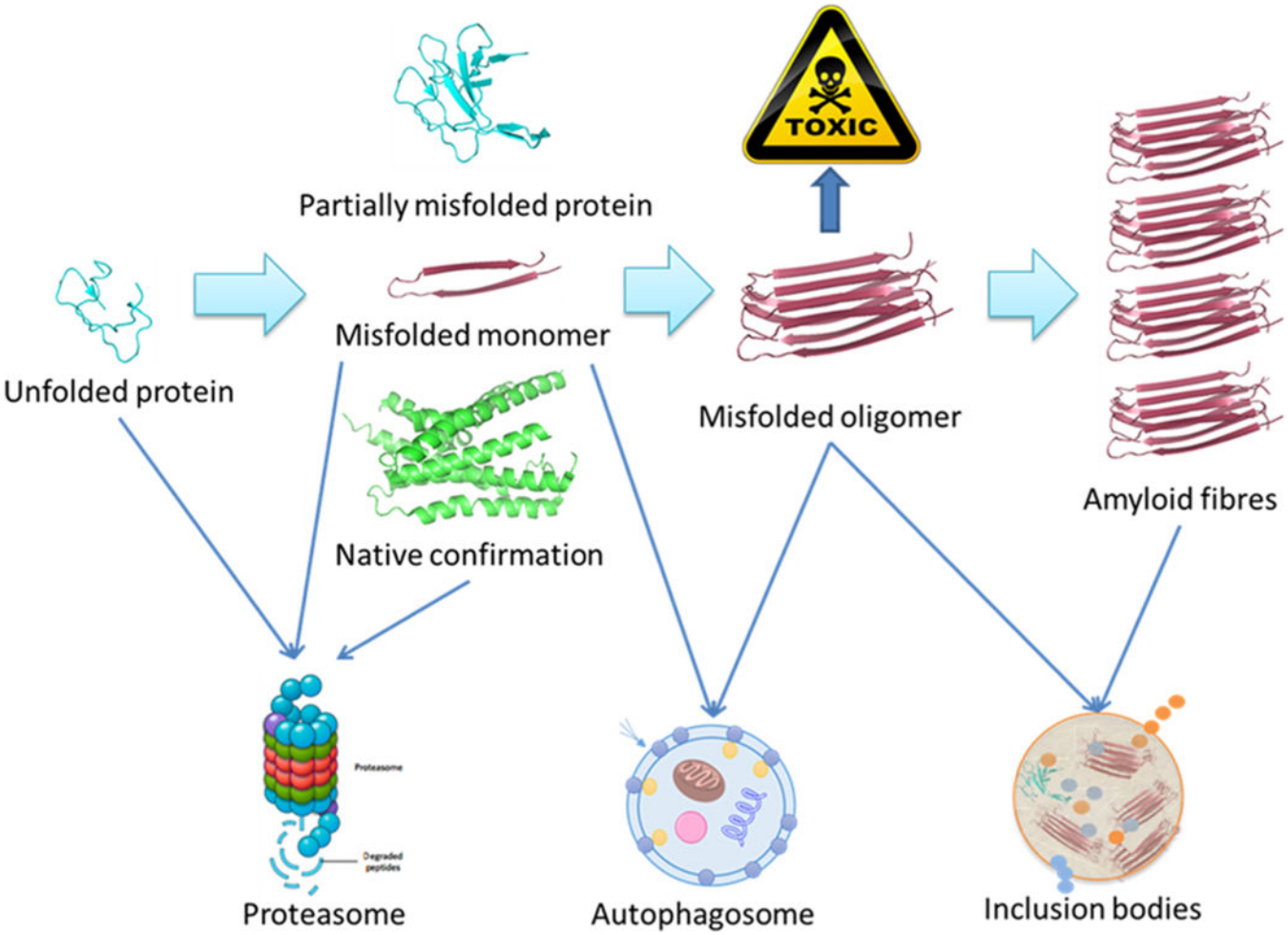


Figure 1.

Schematic representation of misfolded protein degradation processes, using amyloid fibers as an example. As seen above, misfolded and aggregated protein molecules are eliminated by different mechanisms based on molecule size. In the case of neurodegenerative conditions, mutations or alterations lead to protein misfolding. When these misfolded proteins evade degradation, they are then processed into small-misfolded oligomers, at which point they are toxic to the neuronal environment. Examples of these include α-synuclein, β-amyloid, and poly-Q proteins, oligomers known for their pathological roles in Parkinson's, Alzheimer's, and Huntington's diseases, respectively. Cells have three protective mechanisms by which they can remove misfolded and aggregated proteins from the cellular environment: proteolysis, autophagy, and inclusion body formation. Unfolded peptides and misfolded monomers are eliminated via proteasomal degradation. The majority of misfolded oligomers, in addition to some misfolded monomers, are removed via autophagic clearance. Ubiquitin plays a critical role in all three pathways, as it marks proteins for proteolytic and autophagic degradation and is found in abundance in inclusion bodies.

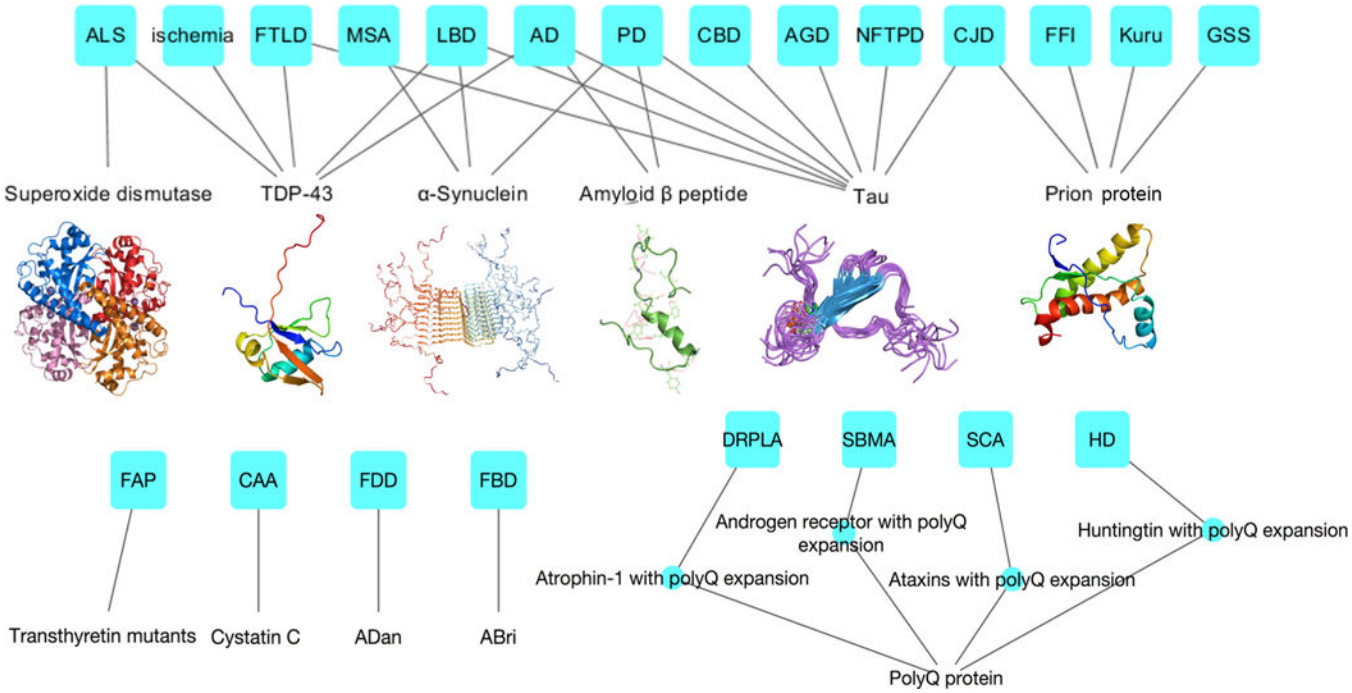


Figure 2.

Misfolded and aggregated proteins related to neurodegenerative diseases. Abbreviations: AGD, amoebic gill disease, CBD, corticobasal degeneration, NFTPD, neurofibrillary tangle predominant dementia.

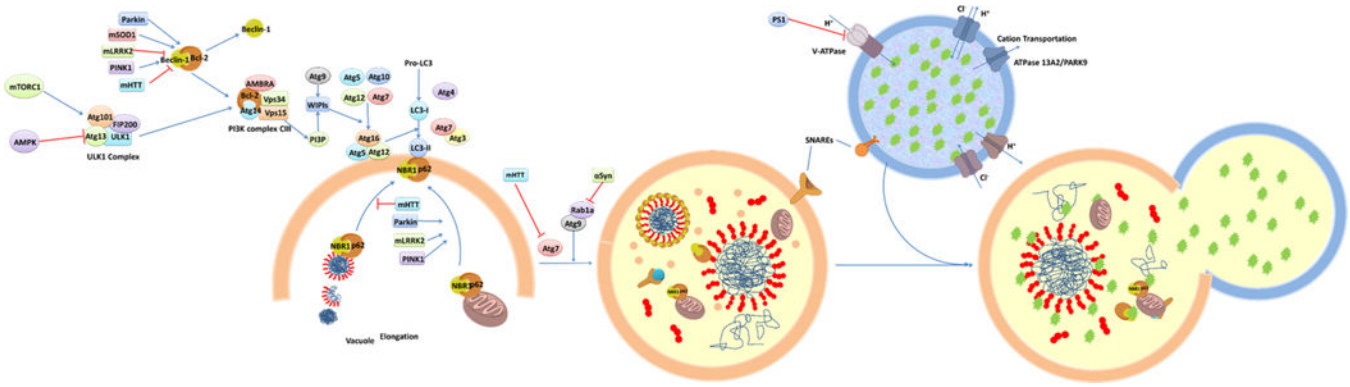


Figure 3.

Key components of the autophagy process. Defective regulation and induction of the autophagy process have been associated with many neurodegenerative diseases. Abnormal interactions of mutant superoxide dismutase 1 (mSODl), LRRK2, Parkin, PINK1, and mutant Huntington (mHTT) with Beclin 1 could alter the initiation steps of autophagy. PINK and Parkin play a key role in the elimination of damaged mitochondria and mutations in these proteins, as seen in Parkinson's disease (PD), and could interfere with overall mitophagy, the selective degradation of mitochondria by autophagy. mHTT expression leads to altered cargo recognition and autophagy failure. α-Synuclein (α-syn) can interfere with autophagy through interaction with Rab1a. Presenilin-1 (PS1) mutations cause impairment in lysosomal acidification and autophagy impairment. In PD, mutations in ATP13A2 could alter the function of lysosomes.

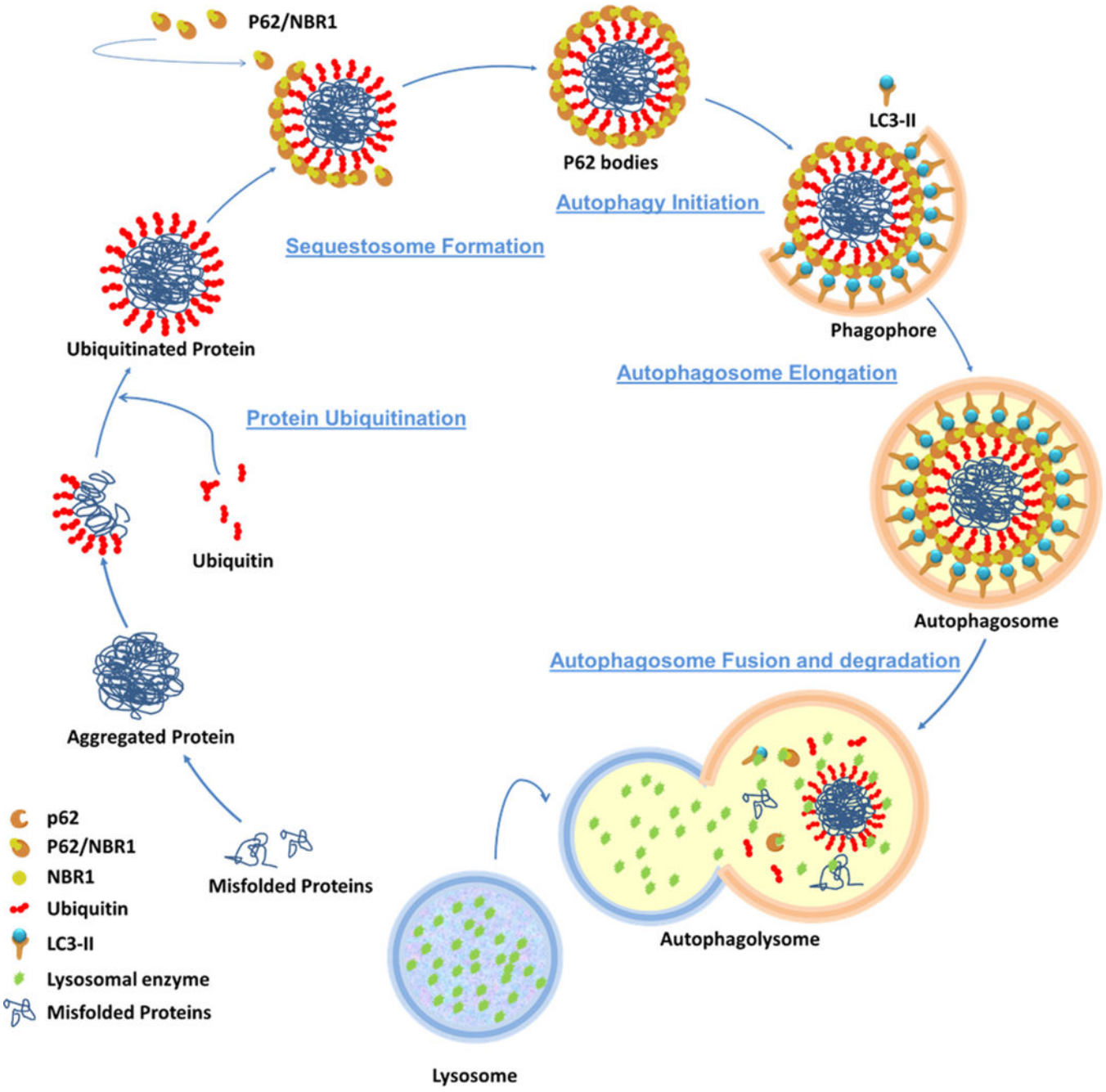


Figure 4.
Trafficking role of p62 in selective macroautophagy.

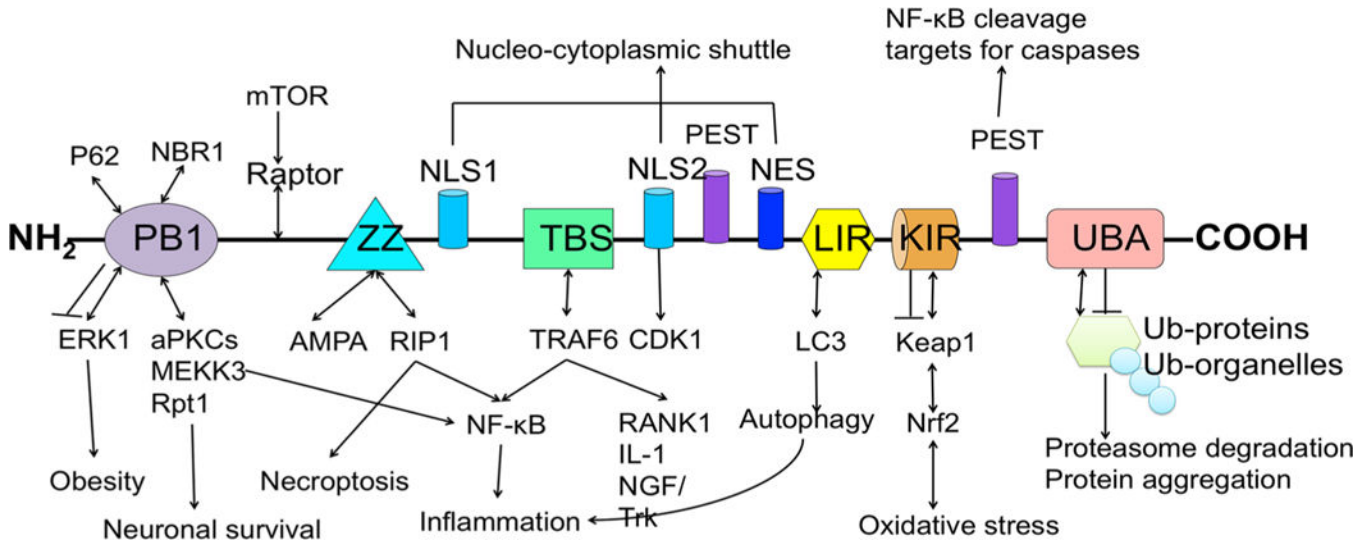


Figure 5.
Functional domains in p62 with their interacting proteins and related pathways.

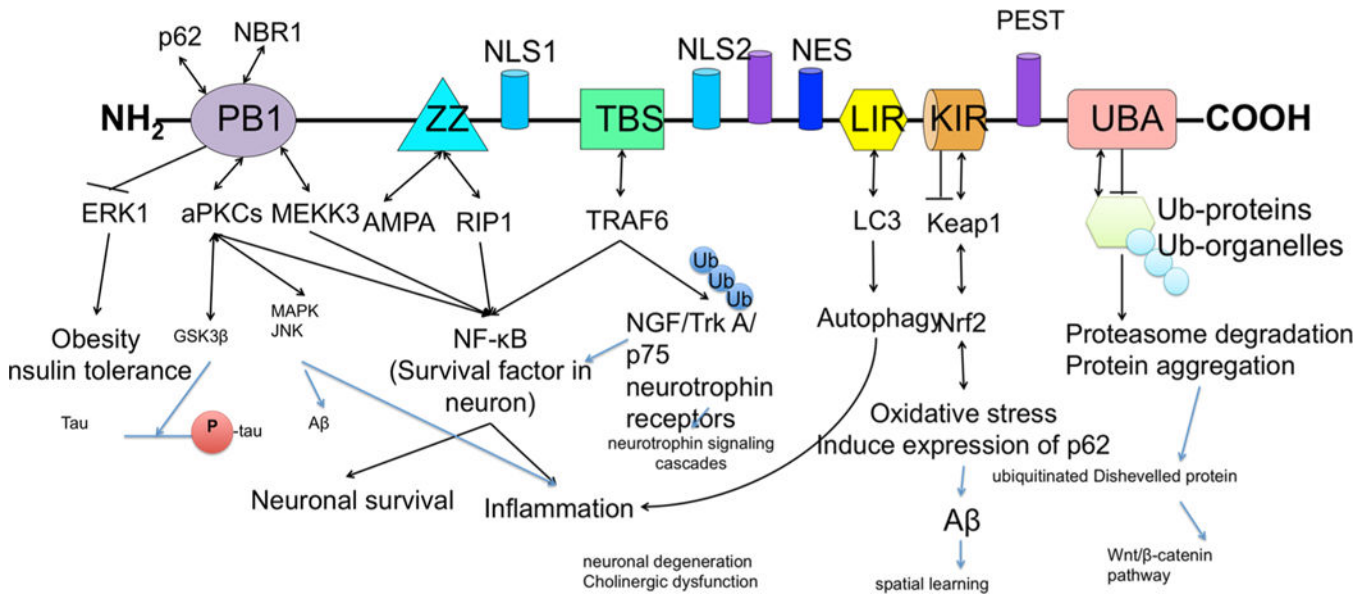
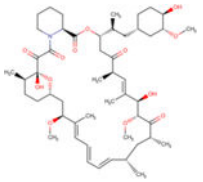
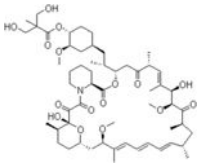
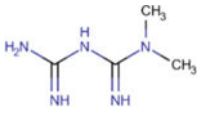
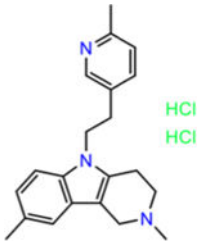
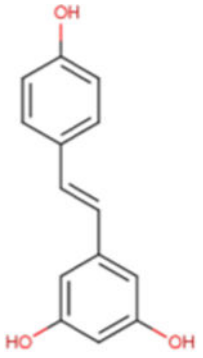
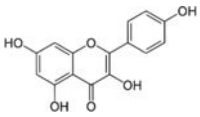
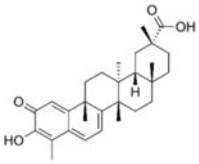
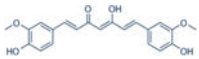
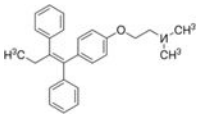
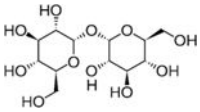
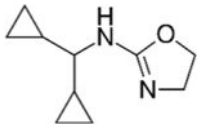
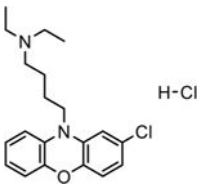
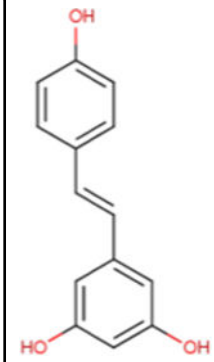
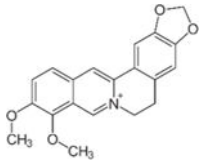
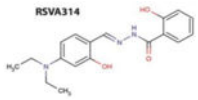
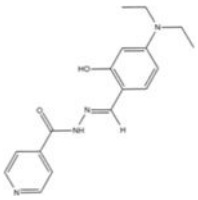
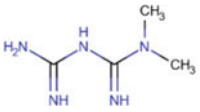
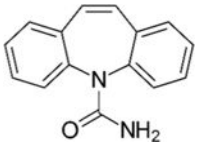


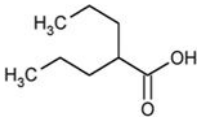
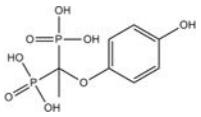
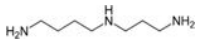
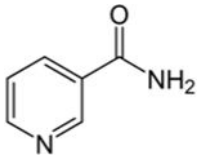
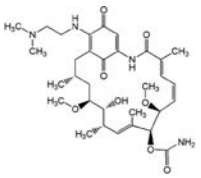
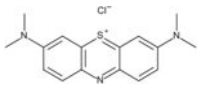
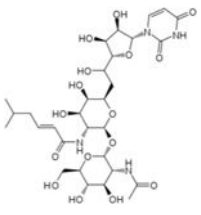
Figure 6.
Multiple domains of p62 and its functions related to neurodegenerative diseases.

Table 1

Autophagy step	Target	Compound	Structure	Disease	References	Effect
Induction	mTOR ihibition	Rapamycin		AD, PD, HD, ALS, FTLD-U	Caccamo et al. 2010, J. Biol. Chem., 285(17), 13107–13120.; Caccamo et al. 2011, J. Biol. Chem. 286(11), 8924–8932. Spilman et al. 2010, PloS one, 5(4), e9979. Malagelada et al. 2010, Journal of Neuroscience, 30(3), 1166–1175. Ravikumar et al. 2004, Nature genetics, 36(6), 585–595; Zhang et al. 2011, *Autophagy*, 7(4), 412–425. Cortes et al. 2012, Journal of Neuroscience, 32(36), 12396–12405.	
		CCI-779		PD, HD	Ravikumar et al., 2004, Nature genetics, 36(6), 585–595.	
		Metformin		AD	Kickstein et al., 2010, Proceedings of the National Academy of Sciences, 107(50), 21830–21835.	Clinical trial phase II
		Latrepirdine		AD, HD	Steele and Gandy, 2013, Autophagy, 9(4), 617–618.	Clinical trial phase III
		Resveratrol		AD	Vingtdeux et al., 2010, Journal of Biological Chemistry, 285(12), 9100–9113.	Clinical trial phase III

Autophagy step	Target	Compound	Structure	Disease	References	Effect
		Kaempferol		PD	Filomenin et al., 2012, Neurobiology of aging, 33(4), 767–785.	
		Celastrol		PD	Deng et al., 2013, Neurochemistry international, 63(1), 1–9.	
		Curcumin		PD	Jiang et al., 2013, Journal of Neurolmmune Pharmacology, 8(1), 356–369.	
		Tamoxifen		FTLD-U		
	AMPK activation	Lithium	Li	AD, ALS	Forlenza et al., 2012, Drugs & aging, 29(5), 335–342; Fornai et al., 2008, Autophagy, 4(4), 527–530.	Clinical trial phase II inositol monophosphatase (IMPase) inhibitors
		Trehalose		FTLD-U, ALS, HD	Zhang et al., 2014, Autophagy, 10(4), 588–602. Tanaka et al., 2004, Nature medicine, 10(2), 148–154	
		Rilmenidine		HD	Rose et al., 2010, Human molecular genetics, 19(11), 2144–2153.	Imidazoline-1 receptors (11R) agonists
		10-NCP		HD	Tsvetkov et al., 2010, Proceedings of the National Academy of Sciences, 107(39), 16982–16987.	AKT inhibitor

Autophagy step	Target	Compound	Structure	Disease	References	Effect
		Resveratrol		PD	Khan, et al., 2010, Brain research, 1328, 139–151; Chen, et al., 2009, Proceedings of the National Academy of Sciences, 106(10), 3907–3912; Jin et al., 2008, European journal of pharmacology, 600(1), 78–82.	
		Berberine		Krabbe's disease	Arzamastsev et al., 2013, US patent, US8440683B2, US20130226133A1	
		RSVA314		AD	Vingtdeux et al., 2011, Journal of Biological Chemistry, 285(12), 9100–9113.	
		RSVA405		AD	Vingtdeux et al., 2011, Journal of Biological Chemistry, 285(12), 9100–9113.	
		Metformin		HD,AD	Ma et al., 2007, Neuroscience letters, 411(2), 98–103. Gupta et al., 2011, Neuropharmacology, 60(6), 910–920.	
Initiation	BECN1	Beclin-1 expression regulation		PD	Spencer et al., 2009, J Neurosci. 28; 29(43): 13578–13588.	
		Beclin-1 biomimetics		AD	Shoji-Kawata et al., 2013, Nature, 494(7436), 201–206.	
	IP3 level and inositol level regulation	Carbamazepine		FTLD-U, ALS	Sarkar, et al., 2006, Autophagy, 2(2), 132–134.	

Autophagy step	Target	Compound	Structure	Disease	References	Effect
		Valproic Acid		FTLD-U, ALS	Sarkar et al., 2006, Autophagy, 2(2), 132–134; Duarte-Silva et al., 2014, The Cerebellum, 13(6), 713–727.	
	inositol monophosphatase (IMPase) inhibitors	L-690,330		FTLD-U, ALS	Sarkar, et al., 2006, Autophagy, 2(2), 132–134.	
Fusion and degradation	Histone Acetyl-Transferase	Spermidine		FTLD-U	Yamashima et al., 2012, The Journal of clinical investigation, 118(8), 2796–2807.	
	lysosomal function	Nicotinamide		AD	Liu et al., 2013, Neurobiology of aging, 34(6), 1564–1580.	Clinical trial phase I
	TFEB	TFEB expression regulation		PD	Decressac et al., 2013, Proceedings of the National Academy of Sciences, 110(19), El817-El826.	
	calpain inhibitors	calpastatin	protein	AD	Trínchese et al., 2008, The Journal of clinical investigation, 118(8), 2796–2807.	
	Hsp 90 inhibitor	17-DMAG		SCA3	Silva-Fernandes et al., 2014, Neurotherapeutics, 11(2), 433–449	clear Mutant ataxin-3
	Nitric oxide synthase, brain (NOSI), Guanylate cyclase soluble subunit alpha-2 (GUCY1A2)	Methylthioninium chloride		AD	Congdon et al., 2012, Autophagy, 8(4), 609–622.	clear Tau
	glycosylation of newly synthesized insulin receptor	Tunicamycin		PD	Fouillet et al., 2012, Autophagy, 8(6), 915–926	Protects dopaminergic neuron on a toxicological model