Chapter 4

Autophagy-Lysosome Dysfunction in Amyotrophic Lateral Sclerosis and Frontotemporal Lobar Degeneration

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Additional information is available at the end of the chapter

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Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are two devastating neurodegenerative diseases. Several lines of evidence suggest that these diseases are part of a continuum with common genetic factors. As researchers uncover more genes associated with ALS/FTLD, studies have shown that majority of these genes regulate lysosome-related processes. Lysosomes play important roles in clearing damaged organelles and proteins through the autophagy-lysosome pathway and clearing extracellular debris by the endolysosomal pathway. Disruption of both the autophagy and endolysosomal pathways has been implicated in ALS/FTLD pathogenesis.

Keywords: autophagy, lysosome, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), neurodegeneration, progranulin (PGRN), TMEM106B, C9orf72, OPTN, p62, TBK1, ubiquilin2 (UBQLN2), TDP-43, FUS, tau, VCP, CHMP2B

1. Introduction

Proper degradation machinery is necessary for neuronal survival, and disruption of lysosomal function is sufficient to cause neurodegeneration [1–4]. To recycle cellular material, cells use two major pathways: autophagy for damaged organelles and long-lived proteins and the ubiquitin-proteasome system (UPS) for short-lived proteins [5, 6]. Autophagy consists of three pathways and each of them ultimately delivers cellular contents to the lysosome for degradation. The pathways are chaperone-mediated autophagy (CMA), which uses HSC70 to recognize

specific misfolded proteins; microautophagy, which directly invaginates material into the lysosome; and macroautophagy, which is responsible for the degradation of organelles, protein aggregates, and large protein complexes. Macroautophagy (hereafter referred to as autophagy) is the most common pathway. The autophagy pathways and molecular mechanisms have been recently reviewed elsewhere [7, 8]. The presence of protein aggregates in most neurodegenerative diseases suggests common underlying problem in protein degradation systems. Here, we summarize the connection between the autophagy-lysosome pathway and two neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) [9].

ALS is characterized by the loss of upper and lower motor neurons resulting in progressive weakness and ultimately paralysis. Patients survive a median of 3–5 years from disease onset [10]. FTLD is characterized by the degeneration of neurons in the frontal cortex and anterior temporal lobes. This degeneration leads to changes in behavior and language impairment. The subtypes of FTLD can be distinguished by the prominent symptoms, which reflect the area affected by neuron loss [11, 12]. The subtypes are behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and primary nonfluent aphasia (PNFA). Behavioral variant frontotemporal dementia, the most common subtype, is characterized by changes in behavior such as disinhibition, loss of empathy, impaired social skills, and decline in personality. SD is characterized by impaired language comprehension, and PNFA disrupts speech production [9]. These subtypes often overlap and can additionally include Parkinson's disease-like symptoms. Patients survive for a median of 7–11 years after diagnosis. There are no treatments for FTLD [9]. ALS and FTLD symptoms are often present in the same patient with an indication that these diseases have shared etiology [13, 14].

Each disease is also subdivided by molecular pathology depending on the primary components of inclusion bodies, such as Tau, TDP-43 (TAR DNA-Binding Protein 43), FUS (fused in sarcoma), SOD1 (superoxide dismutase 1) and C9 or f72 dipeptide repeats (DPRs) [9, 15]. In 2006, both ALS and FTLD were found to have neuronal inclusions composed largely of TDP-43, an RNA-binding protein, that are also ubiquitin and p62-positive, suggesting that these aggregates were tagged for degradation [16–18]. Additionally, genetic mutations that can lead to the development of both ALS and FTLD have since been discovered. Thus, these two diseases are linked by clinical concurrence, molecular pathology, and genetic overlap [13, 14, 19].

As many new genes have been identified for FTLD and ALS in the last decade, studies have revealed a common theme of these genes functioning in the lysosomal network (**Figure 1**). Some mutations, such as *GRN*, *TMEM106B*, *CHMP2B*, and valosin-containing protein (*VCP*) are associated with disrupted lysosomes and multivesicular bodies (MVB). Other mutations, such as in *p62*/*SQSTM1*, *OPTN*, ubiquilin2 (*UBQLN2*), and TANK-binding kinase (*TBK1*) directly disrupt selective autophagy and therefore prevent cargo from being degraded. The rest of the mutations have a more complex relationship with autophagy and lysosome function, such as mutations in the RNA-binding proteins TDP-43 and *FUS*. Here, we will discuss the genetic causes of ALS and FTLD in more detail with specific emphasis on lysosomal and autophagy impairment (**Figure 1**).

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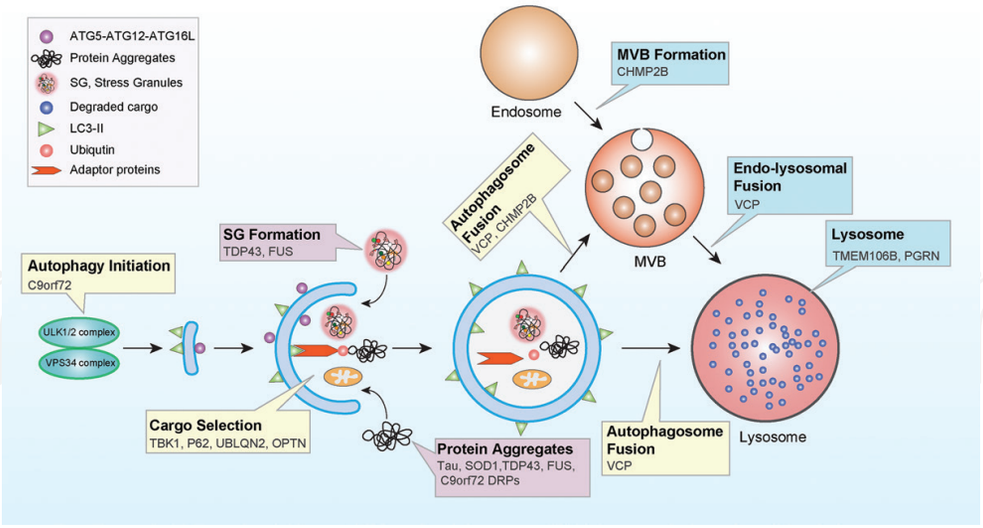

Figure 1. Functions of the ALS/FTLD genes in the autophagy-lysosome pathway. Many genes associated with ALS/FTLD play critical roles in the endosome-lysosomal pathway, regulate lysosomal functions, or affect autophagy pathway directly or indirectly.

2. Mutations affecting the endolysosome pathway: progranulin (PGRN), TMEM106B, CHMP2B, and VCP

2.1. Progranulin

The most common cause of familial FTLD with ubiquitin-positive aggregates is mutation of the *GRN* gene, which accounts for 10% of all FTLD cases and ~25% of familial FTLD [20–22]. About 70 mutations in the *GRN* gene have been linked to FTLD, most of which have been shown or predicted to decrease PGRN protein level or disrupt secretion of PGRN [20–24]. While FTLD is caused by haploinsufficiency of PGRN, a more serve neurodegeneration is caused by homozygous loss of PGRN. This complete loss of PGRN results in neuronal ceroid lipofuscinosis (NCL), a type of lysosome storage disorder (LSD) characterized by the build-up of autofluorescent lipofuscin [25, 26]. These findings suggest that loss of function mutations in the *GRN* gene causes neurodegenerative diseases in a dose-dependent manner and PGRN is important for lysosome function.

The function of PGRN is still under investigation: it is known to be a secreted glycoprotein comprised of 7.5 granulin repeats with pleiotropic roles, including protein homeostasis, inflammation, and neuronal survival and outgrowth [27]. Recently, several lines of evidence suggest that it plays a vital role in lysosome function. First, *GRN* has been found to be regulated with other lysosomal genes [28]. Furthermore, *GRN* mRNA and PGRN protein levels are upregulated in response to lysosome or autophagy inhibition [29]. Finally, PGRN was found to be delivered to the lysosome [30, 31]. PGRN reaches the lysosome through at two independent pathways. In one pathway, PGRN's extreme C-terminus binds the sorting receptor sortilin, which carries PGRN to the lysosome [30, 32]. In the second pathway, PGRN binds prosaposin, and they are

transported to the lysosome together by the cation-independent mannose-6-phosphate receptor (CI-M6PR) and low-density lipoprotein receptor-related protein 1 (LRP1) [31].

Mouse models of PGRN deficiency have consistently found increased levels of ubiquitin and p62, an adaptor for delivering cargo to the autophagosome [33], buildup of lipofuscin and its protein components saposin D and SCMAS and electron-dense storage granules, all of which suggest lysosome impairment [34–36]. Several models also found aggregation of TDP-43, similar to what is seen in FTLD patients [34, 37, 38]. Furthermore, PGRN-deficient mouse models also phenocopy FTLD symptoms such as decreased social interaction and mild learning/memory defects [35, 38–40]. The presence of clear lysosomal problems in mouse models and in patients with complete loss of PGRN suggests that PGRN is necessary for lysosome function. FTLD patients with GRN mutations also exhibit typical pathological features of NCL pathology [36], suggesting FTLD and NCL caused by PGRN mutations are pathologically linked and lysosomal dysfunction is one of the underlying disease mechanisms for FTLD-GRN. However, how PGRN regulates lysosomal function remains to be investigated.

2.2. TMEM106B

Another gene associated with FTLD is *TMEM106B*, which is the only identified risk factor for FTLD with *GRN* mutations [41–44]. *TMEM106B* was also found to increase risk in patients with *C9orf72* hexanucleotide repeat expansions [45, 46]. The *TMEM106B* SNP associated with FTLD increases the mRNA and protein levels of TMEM106B [36, 44, 47]. TMEM106B is a single pass, type II transmembrane protein that localizes to the late endosome and lysosome [47–49]. Cellular studies on TMEM106B have pointed to roles in lysosome trafficking and lysosomal stress response [50, 51]. Overexpression of TMEM106B in cells disrupts lysosome morphology and function [47, 48]. Furthermore, when a transgenic TMEM106B mouse line was crossed with a PGRN deficient mouse line, the lysosome abnormalities and lipofuscin accumulation seen in PGRN deficient mice were exacerbated [52]. The connection between TMEM106B's role at the lysosome and a risk factor for FTLD with *GRN* mutations further highlights the importance of the lysosome pathway in FTLD etiology.

2.3. CHMP2B

The sole mutation identified to cause FTLD with ubiquitin-positive aggregates, but tau, TDP-43, and FUS negative inclusions, occurs in the gene *CHMP2B* [53, 54]. *CHMP2B* has also been found to cause rare cases of ALS [55]. CHMP2B functions in the ESCRT-III complex, involved in MVB formation to deliver cargo from endocytic pathway to lysosomes [56, 57]. The mutations identified create an early termination of the protein, resulting in an unregulated CHMP2B truncation that is unable to recruit VPS4 to recycle the ESCRT-III complex to new sites of MVB formation [58, 59]. With ESCRT-III still engaged on the MVB, MVB-lysosome fusion cannot take place [54, 60–62]. Furthermore, *CHMP2B* mutations impair autophagosome maturation, possibly through the disruption of amphisome formation between autophagosome and late endosomes [63–66]. Mouse models of *CHMP2B* mutations replicate both ALS and FTLD pathology, whereas *CHMP2B* knockout mice do not show neurodegenerative

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phenotypes, implicating a gain of function disease mechanism [67–70]. Similar to the PGRN deficiency mouse models, *CHMP2B* mutations cause protein inclusions and accumulation of autofluorescent aggregates in the frontal cortex, reminiscent of lysosome storage disorders [71]. Thus, FTLD-associated mutations in *CHMP2B* impair the endolysosomal pathway, which may cause additional defects in autophagy [66, 69], providing additional evidence that disruption of the autophagy-lysosome pathway may drive ALS and FTLD.

2.4. VCP

Valosin-containing protein (VCP) has been implicated in several diseases including FTLD [22, 72–76], ALS [77], and Charcot Marie Tooth disease, a genetic peripheral nerve disorder [78]. VCP is an AAA^{+}-ATPase that delivers and unfolds ubiquitinated proteins, as well as endoplasmic reticulum–associated protein degradation (ERAD) substrates, at the proteasome [79–83]. Furthermore, VCP binds to clathrin and EEA1 to regulate the size and selectivity of endosomes [83–85]. Pharmacological inactivation of VCP as well as VCP knockdown inhibits MVB formation and blocks autophagosome maturation, resulting in accumulated LC3-II, ubiquitin, and p62 levels along with cytoplasmic TDP-43 aggregation [86–88]. Disease-associated mutants of VCP present similar phenotypes in transgenic mouse models, whereas complete loss of VCP is embryonic lethal [86, 89–91]. Finally, VCP mutants inhibit the autophagic turnover of stress granules, which may be relevant to the accumulation of TDP-43-positive aggregates found in patients with VCP mutations [76, 92, 93]. The precise mechanism that halts autophagosome maturation in VCP mutations remains unclear, though MVB dysfunction may play a role [66]. VCP's role in MVB formation and autophagic flux suggest that loss of VCP function may cause ALS, FTLD, and other related neurodegenerative diseases by impairing the autophagy-lysosome pathway.

3. Autophagy adaptor proteins

Further evidence that ALS and FTLD are linked to autophagy and lysosome disruption comes from mutations that directly affect several autophagy adaptor proteins and their regulation. Genetic mutations in the adaptor proteins *p62/SQSTM1*, *UBQLN2*, and *OPTN* have been shown to contribute to rare cases of ALS [94–99] and FTLD [100, 101]. All these adaptor proteins contain an ubiquitin-associated (UBA) domain, which is able to bind polyubiquitin conjugated proteins that are tagged for degradation by either the UPS or autophagy. The autophagy adaptors then associate with LC3 on the autophagosome to deliver the cargo for degradation through autophagy-lysosome pathway.

3.1. p62/SQSTM1

p62/SQSTM1 (p62)-positive inclusions have been observed in patient tissue samples in both ALS and FTLD [18, 102–104]. The association of p62 with inclusions suggests that the inclusion body has been targeted for degradation and the accumulation of such inclusions suggests defects with their turnover [33, 105, 106]. p62 bridges autophagy substrates to the

autophagosome by interacting with ubiquitinated proteins via its UBA domain [107] and LC3 with its LC3-interacting region (LIR) [33, 108, 109].

p62 is activated by phosphorylation at Ser407 by ULK1, allowing further phosphorylation by casein kinase 2 or TANK-binding kinase 1 (TBK1), which increases p62's affinity for polyubiquitinated cargo [110–113]. p62 acts within the selective autophagy system by aggregating proteins and organelles together for the autophagosome to enclose [106, 114]. These aggregated cargos are then subject to autophagy [115, 116]. While p62 accumulation and association with protein aggregates broadly suggests a defect in autophagy, mutations in p62 directly link selective autophagy impairment to neurodegeneration.

The *p62* mutations identified in ALS and FTLD patients disrupt aggregate formation or decrease the amount of p62 protein produced, leading to loss of function [117–119]. Homozygous mutation of *p62* causes adolescence/childhood-onset neurodegeneration with a defect in mitochondrial depolarization response due to impaired autophagy [120]. Thus, a loss of normal p62 function in autophagy leads to neurodegeneration in a dose-dependent manner, with earlier onset correlating to lower levels of functional p62.

In addition to its role in autophagy, p62 also links ubiquitinated cargo to the proteasome through its UBA domain [106] and mediates the degradation of the protein via the UPS, indicating that p62 plays multiple roles in proteostasis [121].

3.2. Ubiquilin2

Another adaptor protein implicated in ALS and FTLD is ubiquilin2 (UBQLN2) [95, 122]. Similar to p62, UBQLN2 is able to recognize ubiquitinated proteins and bind them via its UBA domain [123]. The UBA domain is also required for UBQLN2 to associate with the autophagosome, though unlike p62 and OPTN, UBQLN2 does not directly recognize LC3 [124, 125].

Knockdown of UBQLN2 in culture reduced autophagosome formation and inhibited lysosomal degradation of mitochondria [124, 125]. This loss of UBQLN2 also sensitizes cells to starvation-induced death in an autophagy-dependent manner [124]. Interestingly, UBQLN2 binds directly to TDP-43 holo-protein and C-terminal fragments and may regulate the levels of TDP-43 in the cell independent of ubiquitin [126]. Indeed, overexpression of UBQLN2 in culture can reduce aggregation of TDP-43 [126].

Many of the disease-associated mutations map to the proline-rich domain in *UBQLN2*, which is important in mediating protein-protein interactions [95, 127]. Furthermore, mutations in *UBQLN2* have a reduced binding to hnRNPA1, a RNA-binding protein associated with stress granules. Interestingly, mutations in hnRNPA1 are also associated with ALS and these mutations also disrupt its interaction with UBQLN2 [128], confirming that the interaction of autophagy adaptors with stress granules is important for neuronal survival.

UBQLN2 knockout in a rodent model showed no neuronal loss, implying that loss of function is not the disease mechanism or that other autophagy adaptors are able to compensate for its loss *in vivo*. Transgenic animals with the ALS/FTLD-associated *UBQLN2* mutations produce ubiquitin, p62, and UBLQN2-positive puncta accompanied by neuronal loss, cognitive defects, and

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motor impairment [129–131]. Increased expression of the wild-type UBQLN2 also causes neurodegeneration in a rodent model [132]. Thus, unlike mutations in *p62*, *UBQLN2* mutations appear to have a gain of function mechanism that impairs proper protein degradation by autophagy.

In addition to its function in the autophagy pathway, UBLQN2 binds to the proteasome through its ubiquitin-like (UBL) domain to deliver polyubiquitinated proteins and ERAD substrates to the proteasome for degradation [133]. A role of UBQLN2 in delivering protein aggregates to proteasome-mediated degradation via HSP70 has been recently demonstrated [134]. UBQLN2 also function together with other ALS/FTLD-related proteins, such as regulating endosome constitution with OPTN [135] and delivering ERAD substrates to the proteasome with VCP [136].

3.3. Optineurin (OPTN)

Rare mutations in *OPTN* are also associated with both ALS [97, 99]as well as FTLD [101]. These mutations are expected to decrease the level of OPTN protein, suggesting a loss of function resulting in disease [101]. In total, 1–4% of familial ALS cases are linked to mutations in OPTN [137]. OPTN, like p62 and UBQLN2, binds to polyubiquitin-labeled proteins via a UBA domain [138]. OPTN also binds LC3 through an LIR to connect cargo to autophagosomes. Damaged mitochondria specifically recruit OPTN to induce mitophagy [139]. In support of a loss of function model for OPTN, depletion of OPTN in zebrafish causes motor defects [140].

OPTN also interacts with several other proteins associated with ALS. The E3 ubiquitin ligase HACE1 ubiquitinates OPTN to promote binding to p62, which forms a complex that enhances autophagic flux [141]. Similarly, phosphorylation of OPTN by TBK1 increases the interaction of OPTN and p62 to the same effect [138, 142]. OPTN also binds directly to SOD1 aggregates independently of ubiquitination. Mutations in *OPTN* do not affect this interaction, but do impair autophagic clearance of SOD1 protein aggregates through an unknown mechanism [138, 140].

Mutation in *OPTN* had previously been linked to primary open-angle glaucoma (POAG) where these mutations were shown to decrease basal autophagy and inhibit autophagic flux upon autophagy induction [143]. Thus, mutations in *OPTN* have clear links to multiple neurodegenerative disease with consistent impairment in the autophagy pathway. How mutations in the same gene and similar cellular impairments can lead to distinct clinical outcomes remains unclear.

3.4. TBK1

TBK1 has recently been associated with both ALS and FTLD [96, 98, 101, 110, 111, 144–147]. TBK1 has functions in autophagy and in inflammation [148]. Regarding its function in autophagy, TBK1 phosphorylates p62 and OPTN to increase their binding to LC3 and ubiquitin, respectively [138, 142]. Many of the discovered disease-associated mutations are expected to decrease TBK1 protein level, suggesting a loss of function model [96, 101].

While TBK1 interacts with both p62 and OPTN, TBK1 and OPTN share several additional connections. Like OPTN, some mutations in TBK1 also cause glaucoma [149].

Furthermore, the mutation in OPTN that causes POAG enhances the binding of OPTN to TBK1, which may sequester TBK1 and prevent it from carrying out its normal function [142]. Finally, both TBK1 and OPTN are required specifically for mitophagy, with depletion of either component or expression of an ALS-associated mutant impairing mitophagy [150]. Taken together, mutations in *TBK1* cause decreased protein expression and defects in p62 and OPTN regulation again supporting a role of autophagy in preventing ALS and FTLD.

4. C9orf72

The most common known cause of both ALS and FTLD was discovered to be a hexanucleotide intronic repeat expansion in the gene *C9orf72* [151–153]. This repeat expansion is found in 18–25% of familial FTLD, 40% of familial ALS, and 4–8% of sporadic ALS and FTLD combined [154, 155]. While patients with C9orf72 mutations display TDP-43-positive aggregates, they also have separate inclusions unique to this genetic mutation. These ubiquitin, p62, and occasionally UBQLN2-positive inclusions also contain dipeptide repeats generated from the repeat expansion [156–160]. Three molecular mechanisms of disease have been proposed: toxic gain of function of RNA repeats, gain of function of dipeptide repeats (DPRs) produced by repeat-associated non-ATG translation, and haploinsufficiency of the C9orf72 protein.

RNA-repeats transcribed from the repeat expansion form nuclear foci and sequester many RNA-binding proteins, including several RNA-binding proteins already implicated in ALS and FTLD [151, 161–163]. In addition the RNA foci disrupt nucleocytoplasmic transport [164, 165]. Furthermore, five distinct DPRs are translated and can also alter nucleocytoplasmic transport - [167, 168] as well as disrupt membrane-less, phase-separated organelles such as the nucleolus, nuclear pore, and stress granules [169]. Nuclear translocation of TDP-43 has been shown to be blocked by both RNA repeats and DPRs [166-168] , allowing TDP-43 to accumulate and aggregate in the cytosol, which is observed in ALS/FTLD with C9orf72 mutations.

Haploinsufficiency was also proposed as a disease mechanism [153, 151, 170–172]. Early C9orf72-depletion models in *Caenorhabditis elegans* and zebrafish showed motor dysfunction, supporting this model [173, 174]. However, a neuronal-specific C9orf72 knockout mouse showed no such phenotype [175]. Complete C9orf72 knockout mice also do not show much neurodegeneration, but instead exhibit severe immune problems similar to autoimmune disorders [176–181].

Interestingly, C9orf72 has been reported to play a role in autophagy and lysosome regulation. While many of the reports suggest that C9orf72 and its binding partners, SMCR8 and WDR41, play a role in regulating autophagy initiation or maturation, likely via the FIP200/ULK1 complex, the precise mechanism remains uncertain [179, 182–186]. Other reports suggests that C9orf72 plays a role in mammalian Target of Rapamycin (mTOR) and Transcription Factor EB (TFEB) signaling [186, 187], in stress granule assembly [188], or in actin dynamics [189].

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5. RNA-binding proteins

The RNA-binding proteins TDP-43 and FUS have been closely associated with ALS and FTLD. Pathogenic TDP-43 or FUS aggregates are present in both conditions, though mutations in these genes result primarily in ALS [190]. Both proteins travel between the nucleus and cytoplasm as they regulate gene splicing, mRNA stability and trafficking, and stress granule dynamics [191, 192].

As both TDP-43 and FUS regulate the RNA from thousands of genes, many cellular problems could be anticipated. However, several lines of evidence have pointed out a role in regulating and challenging the autophagy pathway [193].

5.1. TDP-43

The identification of TDP-43 as the main component of protein aggregates in both ALS and FTLD spurred the awareness that ALS and FTLD had some underlying similarities [16, 17]. Interestingly, mutations in *TARDBP* (TAR DNA binding protein), the gene encoding TDP-43, lead overwhelmingly to ALS or ALS/FTLD, but not to FTLD alone [194, 195]. While soluble TDP-43 can be cleared by chaperone-mediated autophagy through its interaction with Hsc70 [196], TDP-43-positive stress granules and aggregates are cleared by macroautophagy [197, 198].

In addition being a substrate of autophagy, TDP-43 may play a direct role in regulating autophagy through its transcriptional regulation of *ATG7* [199]. As TDP-43 is sequestered in protein aggregates, it can no longer regulate *ATG7* transcription, impairing autophagy initiation, and further promoting TDP-43 accumulation [198, 199]. In a similar manner, TDP-43 also regulates the mRNA for Regulatory-Associated Protein of mTOR (RPTOR) and Dynactin subunit 1 (DCTN1) [197]. *RPTOR* encodes a component of the mTOR complex, and loss of *RPTOR* due to TDP-43 loss of function upregulates lysosome and autophagy biogenesis [197]. However, TDP-43 loss of function also results in reduced *DCTN1* mRNA, which encodes dynactin, a key component of autophagosome-lysosome fusion, leading to the accumulation of autophagosomes, preventing the turnover of aggregated TDP-43 [197].

TDP-43 additionally plays an important role in stress granule dynamics and mutations in *TARDBP* have been shown to increase the stability of stress granules, possibly allowing them to become irreversible protein aggregates [198, 200–203]. In support of this prolonged stress granule hypothesis, mutations in VCP decrease stress granule turnover by autophagy, leading to TDP-43-positive inclusion [92].

The interaction of TDP-43 with autophagy suggests a complex regulatory balance between the two under normal conditions. In disease states, a feedforward mechanism of TDP-43 sequestration into stress granules and aggregates followed by impaired autophagy could drive pathogenesis of ALS and FTLD [9, 202].

5.2. FUS

Like *TARDBP*, mutations in *FUS* have been linked more closely to ALS, though positive protein aggregates for FUS appear in both ALS and FTLD [9]. FUS-positive inclusions account for about 5–10% of FTLD cases [9] and 1% of ALS cases [15]. Several proposed mechanisms link FUS to disruption of the autophagy-lysosome pathway. First, the presence of FUS-positive aggregates in both familial and sporadic cases of ALS and FTLD suggests FUS may be particularly susceptible to aggregation. FUS is also involved in autoregulation, which could allow for a feedforward cycle of increased FUS production followed by cytosolic accumulation and aggregation [198, 204].

Additionally, mutations in *FUS* have been linked to altered stress granule dynamics [205, 206]. FUS-positive stress granules were found to be degraded by autophagy; however, stress granules containing mutant FUS were more stable and prevented stress granules disassembly [198]. As with TDP-43, stabilized stress granules may promote insoluble aggregate formation [202, 207–209]. This increases the burden on the autophagy pathway and may drive further cell damage. A recent study also found that ALS-associated mutant *FUS* was able to inhibit the early steps of autophagosome formation, leading to impaired autophagy flux [210]. Many of these studies found that enhancing autophagy, genetically or pharmaceutically, was able to reduce FUS-positive inclusions and prevent cellular toxicity [198, 205, 210]. While less well understood than TDP-43, the RNA-binding protein FUS seems to play a similar cellular role as TDP-43, including regulating the dynamics of stress granules. Besides increased burden on autophagy due to stabilized stress granules, FUS may also play a more direct role in autophagy impairment.

6. Microtubule-associated protein tau

Thirty percent of familial FTLD cases are caused by mutations in Microtubule-Associated Protein Tau (MAPT), encoding the protein tau [211]. These cases are characterized by the presence of tau aggregates positive for ubiquitin and p62, suggesting impaired degradation of accumulated tau [121, 212]. Genetic disruption of autophagy cargo selection is sufficient to cause aggregation of pathogenic tau [213]. The tau protein is mostly well-known for its association with Alzheimer's disease, when it also forms aggregates and is accompanied by neurodegeneration of the hippocampus [214]. How Alzheimer's disease and FTLD patients have overlapping cellular pathology but develop different clinical symptoms remains unclear.

Full length tau can be degraded by the UPS in an ubiquitin-dependent and independent manner [121, 215, 216], whereas misfolded or phosphorylated tau is sent to the autophagy pathway [217]. Generally, tau aggregation and toxicity correlates with autophagy activity, where enhanced autophagy rescues neurodegeneration and impairment exacerbates the symptoms [218–221]. Likewise, modulating TFEB to increase lysosome biogenesis prevents the accumulation of tau [222].

Tau is a microtubule-binding protein that helps to stabilize axonal microtubules [223, 224]. Small increases in unbound tau induces aggregation, suggesting that even mild impairment

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of the UPS or autophagy-lysosome pathway could lead to pathological tau accumulation [225, 226]. In support of this idea, Niemann-Pick disease, another lysosome storage disorder, also develops tau aggregates [227, 228]. These studies suggest that tau clearance is highly dependent on autophagy and lysosome function and disruption of this pathway may drive tau aggregation. Furthermore, tau has a role in microtubule stability and disrupted cytoskeletal dynamics and trafficking have also been proposed as a disease mechanism. Since lysosomes, endosomes, MVB, and autophagosomes all move along microtubules, any disruptions would affect their ability to maintain proteostasis [229].

7. Discussion

ALS and FTLD are distinct clinical disorders that share overlapping symptoms, pathology, and genetics. Many of the causative genetic mutations and risk factors result in disruption of the lysosome-autophagy pathway (**Figure 1**). Some disease-associated mutants or alleles directly impact lysosomal function through yet unknown mechanisms, such as *PGRN* and *TMEM106B*, or through disruption of the late stages of the endolysosome pathway, as *VCP* and *CHMP2B* mutations are proposed to do. Beyond the lysosome, there are also many mutations in adaptor proteins that impair selective autophagy, including *p62*/*SQSTM1*, *OPTN*, and *UBQLN2*. The misregulation of these adaptors is sufficient to induce neurodegeneration, as seen with *TBK1* mutants. Finally, some mutations have a more intricate relationship to the autophagy-lysosome pathway that future research will have to address, including C9orf72 protein, repeat-associated RNA foci, and dipeptide repeats, as well as the microtubule-binding protein tau and the RNA-binding proteins TDP-43 and FUS.

Identifying the underlying cellular problems that lead to disease is an important step in being able to distinguish disorders and subtypes that may ultimately require distinct diagnosis and treatment. The genetic analysis of ALS and FTLD has improved our understanding of this disease spectrum and may inform us of the broad problems that underlie both familial and sporadic ALS and FTLD. The consistent impairment of cellular clearance pathways by ALS and FTLD-associated mutations points to a disease mechanism that is likely to be shared in undiscovered genetic causes, as well as environmental risk factors, that account for the cases of ALS and FTLD that have no known cause.

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