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Review

Non-cell autonomous autophagy in amyotrophic lateral sclerosis: A new promising target?

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative non-cell-autonomous disease with no cure, thus research is intensely focused on identifying pharmacological targets. Several studies aimed to clarify the pathogenic mechanisms and involvement in various cell types. A crucial factor in ALS is autophagy, which plays a key role in degrading intracellular protein aggregates. The connection between ALS and autophagy is reinforced by the fact that several genes mutated in ALS are linked to fundamental aspects of autophagy. The blockage of the autophagic flux was observed in ALS motor neurons, where it occurs earlier than in glia. However, the inconsistent effects of autophagy modulators in preclinical and clinical studies indicate the need for a deeper understanding of the role of autophagy in other cell types, such as astrocytes, microglia, and oligodendrocytes. Astrocytes and microglia are significantly impacted by autophagy dysregulation, contributing to neurodegeneration in both mouse and human-derived models. Autophagy is overactivated early in the disease, even before symptoms appear. This overactivation is influenced by the timing and specific tissue involved. It can alter cells' immunophenotype, favouring proinflammatory responses and affecting the cellular environment and autophagy in the surrounding cells. In contrast, oligodendrocytes show mild autophagic alterations. Additionally, sex hormones may affect proper autophagy function and ALS progression. The lack of information on how sex influences autophagy in glia highlights the need for more nuanced investigation into this mechanism. Future research should focus on these aspects, paving the way for personalised pharmacological approaches that consider the roles of cell types, time of intervention, and sex.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterised by a progressive neurological decline, which manifests as spasticity, muscle atrophy, and decreased muscle power. Approximately 90 % of ALS cases are classified as sporadic (sALS), whereas the remaining 10 % are familial (fALS) (Feldman et al., 2022). Common pathological features in ALS patients include the loss of both upper and lower motor neurons (MNs), as well as the presence of abnormal cytoplasmic inclusions (Leigh et al., 1988; Lowe et al., 1988). The extent of cytopathology and neuronal loss varies among patients and is closely linked to differences in disease phenotype, complicating the understanding of the underlying processes and hindering the development of effective therapies (Takeda et al., 2020).

ALS typically begins with a focal onset; however, as the disease progresses, it affects other areas of the body, leading to widespread muscle wasting and weakness, with respiratory muscle dysfunction emerging in the later stages (Geevasinga et al., 2016). Approximately 50 % of patients die within 3 years after the onset of symptoms, and up to 20 % within 5 years (Kiernan et al., 2011). This evidence highlights the

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urgent need for a comprehensive understanding of the molecular mechanisms underlying ALS.

The literature identifies several molecular and cellular processes involved in ALS, including oxidative stress, impaired protein degradation, toxic protein aggregation, mitochondrial dysfunction, axonal transport issues, prion-like spreading, neuroinflammation, defects in RNA metabolism, and excitotoxicity (Robberecht and Philips, 2013). More than 25 genes have been associated with fALS (Brown and A.-C. A., 2017; Faller et al., 2025). Among these genes, mutations in the superoxide dismutase type 1 *(SOD1)* have attracted significant attention for two primary reasons: it was the first mutated gene studied in detail (Rosen, 1993), and transgenic mice with the mutated SOD1 exhibit most clinical and neuropathological features of ALS (Gurney et al., 1994; Turner and Talbot, 2008).

While multiple factors contribute to the onset of the disease, current FDA-approved drugs primarily focus on reducing oxidative stress and excitotoxicity. Three pharmaceutical compounds have been shown to slow disease progression and extend survival in ALS patients. They are the glutamate antagonist Riluzole, the reactive oxygen species (ROS) scavenger Edaravone, and the sodium phenylbutyrate/taurursodiol (Relyvrio) combination. All of which have received the Food and Drug Administration (FDA) approval (Ittner et al., 2015; Petrov et al., 2017; Shefner et al., 2022) and can slow down the progression of ALS thus increasing survival by several months. Recently, a novel drug, named Tofersen, an antisense oligonucleotide targeting SOD1 mRNA transcripts, was approved by the FDA. It has shown beneficial effects in both the hSOD1 fALS mouse model and in patients (McCampbell et al., 2018; Miller et al., 2020; Miller et al., 2022; Saini and Chawla, 2024). Despite these treatment advancements, there is currently no cure for other forms of fALS and sALS. In addition to exploring other genetic personalised approaches, which have proven more challenging to implement than initially expected, it is crucial to investigate other pathological mechanisms to identify new and more effective treatments. One significant pathway involved in ALS is autophagy. A functional autophagy system is essential for maintaining the optimal functioning of the central nervous system (CNS) and promoting neuronal survival. Furthermore, evidence indicates a strong correlation between dysregulated autophagy and neurodegeneration, including in ALS (Fleming et al., 2022; Ramesh and Pandey, 2017).

2. Autophagy

Autophagy is an intracellular recycling process in which cytoplasmic material is targeted for lysosomal degradation (Ohsumi, 1999). In mammalian cells, autophagy is traditionally classified into three main types: micro autophagy, chaperone-mediated autophagy (CMA), and macro autophagy (Cristofani et al., 2020). Micro autophagy involves the direct internalisation of smaller portions of cytosol through inward budding vesicles from the lysosomal membrane (Mizushima et al., 2008). In contrast, chaperone-mediated autophagy specifically recognises cytosolic proteins containing the lysosome-targeting motif KFERQ, or other related motifs. These proteins are taken up by the lysosome in a transporter-dependent manner (Kaushik and Cuervo, 2012). Macro autophagy, commonly referred to simply as “autophagy”, entails the engulfing of cytosolic constituents by double-membrane structures, known as autophagosomes, which subsequently fuse with lysosomes (Xie and Klionsky, 2007). After fusion, lysosomal enzymes digest the cargo, and the degradation products are released into the cytosol as new building blocks.

Autophagy can also be categorised based on the nature of the cargo being degraded, distinguishing between non-selective and selective autophagy. Non-selective autophagy is an in-bulk process where cargoes are randomly engulfed in autophagosomes in response to stress factors, such as starvation (Galluzzi et al., 2017). In contrast, selective autophagic degradation pathways help maintain cellular quality and quantity through several receptors that mediate the autophagic engulfment of specific cargoes. However, it remains unclear how different polyubiquitin chains confer specificity for the autophagy receptors (Kanki and Klionsky, 2008).

The process of autophagy is highly regulated and characterised by several steps. The first step, known as induction, involves the formation of the phagophore, which is regulated by a multimeric structure called the phagophore assembly site (PAS). This complex consists of three unc-51 like autophagy activating kinase proteins (ULK1, ULK2 and ULK3), autophagy related proteins (ATG13, ATG101), and retinoblastome coiled-coil protein 1 (RB1CC1/FIP200). Induction is triggered by various stimuli, leading to the dissociation of mTOR from the PAS complex (Hosokawa et al., 2009; Jung et al., 2009; Yang and Klionsky, 2009). The next step is the nucleation of the phagophore, which is orchestrated by a class of III phosphatidylinositol 3-kinase complex (Burman and Ktistakis, 2010). Following this, expansion occurs through the maturation of the phagophore membrane guided by the ATG12-ATG5-ATG16L1 complex. During the sequestration phase, the extended ends of the phagophore fuse around the substrate, encompassing part of the cytoplasm along with its macromolecular and organelle constituents, resulting in the formation of an autophagosome. Then, the autophagosome is transported via microtubules to fuse with the lysosome, which contains hydrolytic proteases, for cargo degradation. This fusion is mediated by the homotypic fusion and vacuole protein sorting (HOPS) complex, consisting of six subunits (VPS11, VPS16, VPS18, VPS33A, VPS39 and VPS41) (Lamb et al., 2013; Liang et al., 2008; Mizushima and Komatsu, 2011; Weidberg et al., 2011; Yorimitsu and Klionsky, 2005).

In summary, autophagy is a highly regulated process. Several studies have identified the transcription factors EB and E3 as the primary positive regulators of this process (Martina et al., 2014; Sardiello et al., 2009; Settembre et al., 2011; Settembre and Ballabio, 2011). Additionally, mammalian target of rapamycin complex 1 (mTORC1) and adenosine monophosphate-activated protein kinase (AMPK) are key players in this field, as they are the two main nutrient-sensing pathways involved in modulating autophagy. These pathways reverse regulate the ULK1 complex through a sequence of phosphorylative events, ultimately leading to the inhibition or activation of autophagy (Chen et al., 2020; Sardiello et al., 2009).

3. Autophagy and neurodegeneration

Several studies suggest that autophagy plays a crucial role in neuroprotection. Since neurons are post-mitotic cells, their autophagic function is essential for preventing proteotoxic events leading to degeneration and for improving cell survival. Unlike other cells, damaged organelles and misfolded proteins in neurons cannot be eliminated through cell division (Levine and Kroemer, 2008; Nikoletopoulou et al., 2013). In addition, synapses require high energy levels and significant protein turnover, which are physiologically supported by autophagy. Abnormal cellular inclusions found in neurodegenerative diseases are often associated with impaired autophagic flux (Son et al., 2012). Analysing mutated genes associated with pathological conditions like Alzheimer’s disease (AD), familial Parkinson’s disease (PD), and ALS reveals that many are directly or indirectly related to autophagy (Blauwendraat et al., 2020; Sakurai and Kuwahara, 2025; Ye et al., 2023), further confirming autophagy’s importance in neuronal homeostasis.

Autophagy dysfunction is closely related to neurodegenerative diseases (Fleming et al., 2022; Karpova et al., 2025; Nixon and Rubinsztein, 2024). In AD, the accumulation of aberrant protein/peptide aggregates, such as extracellular amyloid plaques, containing amyloid-beta peptides, and intracellular neurofibrillary tangles, composed of hyperphosphorylated tau, is associated with a failure in the proteostasis network, which governs protein synthesis, folding, and degradation. Notably, increased autophagy is associated with a reduction in neurotoxic amyloid-β plaques (Li et al., 2024). Thus, modulating autophagy

has been proposed as a therapeutic strategy for AD due to its potential to clear aggregated proteins (Dhapola et al., 2025; Fernandes et al., 2025). In PD, the impairment of both the autophagy-lysosome pathway and the ubiquitin-proteasome system, two primary mechanisms for degrading misfolded and aggregated α-synuclein (α-Syn) proteins, contributes to a reduced clearance rate of α-Syn aggregates (Senkevich and Gan-Or, 2020). This impairment is further exacerbated by α-Syn aggregates that inhibit their own degradation pathways, creating a vicious cycle of continuous formation, accumulation, and impaired clearance (Park et al., 2023; Yang et al., 2023). Moreover, recent discussions have highlighted the close link between autophagy and oxidative stress, opening new therapeutic implications (Liu et al., 2025).

Interestingly, autophagy has a dual role in neurodegenerative disease. It initially serves as a protective mechanism against toxic cellular debris and prevents protein aggregation, but it can become harmful when dysregulated or overwhelmed, leading to neuronal death. This dual role is influenced by factors as age, disease onset, genetics, environment, and neuronal autophagic flux maintenance (Giorgi et al., 2021). Therefore, there is a need for tailored therapeutic strategies: enhancing autophagy in the early disease stages while normalising or preventing excessive activation later (Bar-Yosef et al., 2019). In many neurodegenerative disease models, including ALS, AD, PD, and Huntington's disease, the modulation of autophagy has been shown to have both neuroprotective and neurodegenerative effects (Giorgi et al., 2021; Labrador et al., 2024). Despite similarities in autophagic dysfunction across these diseases, the role of autophagy varies in each condition (Li et al., 2024), needing a personalised approach when considering autophagy as a therapeutic target (Liu et al., 2023).

The interest in the role of autophagy in neurodegenerative diseases has increased significantly over the years (Rana et al., 2021), particularly in the quest for new therapies (Xu et al., 2021). Different approaches have been used to modulate autophagy, from small molecules that either induce or inhibit this process, such as trehalose and rapamycin, to strategies for manipulating specific autophagy-related proteins or pathways (Rosser et al., 2022), like the inhibition of the phosphoinositide 3-kinase (PI3K) pathway (Razani et al., 2021). Gene therapy approaches using adeno-associated virus (AAV) vectors to deliver autophagy-related genes or RNA interference constructs targeting specific components of the autophagic machinery also face significant challenges (von Jonquieres et al., 2021). Unfortunately, the transition from preclinical neurodegenerative disease models to clinical applications has encountered obstacles, including difficulties in crossing the blood-brain barrier and the occurrence of unfavourable side effects (Carosi and Sargeant, 2019; Mandrioli et al., 2023; Macklin et al., 2025).

4. Autophagy and protein homeostasis in ALS

Since the late 1960s, researchers have reported the presence of protein inclusions in the anterior horn cells in the spinal cord of patients with ALS (Sun et al., 1975). Aggregates of TDP-43 are present in approximately 98 % of the reported sALS cases (Arai et al., 2006; Neumann et al., 2006), while FUS or SOD1 protein inclusions can also be detected in other, less common, ALS cases, particularly those caused by mutations in the respective genes (Gill et al., 2019; Ling et al., 2013; Vance et al., 2009). These inclusions were almost always positive for ubiquitin (Leigh et al., 1991) and for sequestosome-1/ubiquitin-binding protein p62 (SQSTM1/p62) (Matsumoto et al., 2011). Importantly, these misfolded proteins can propagate the disease by transferring from cell to cell (Basso et al., 2013; Sproviero et al., 2018). Their accumulation in intracellular inclusions indicates an imbalance in autophagy and proteosome-mediated protein degradation.

Several genes associated with ALS converge on key aspects of autophagy and *endo*-lysosomal trafficking. Genes encoding chromosome 9 open reading frame (72*C9ORF72),* TANK binding kinase 1 *(TBK1),* ubiquilin-2 (*UBQLN2),* and vesicle-associated membrane protein-associated protein B/C (*VAPB)* produce proteins directly involved in the initiation of autophagy. G4C2 repeat expansions in *C9ORF72* lead to the accumulation of dipeptide repeat proteins (gain of function, GOF) that may disrupt the formation of the ULK1 complex (loss of function, LOF) (DeJesus-Hernandez et al., 2011; Koppers et al., 2015). Mutations in *TBK1* and *VAPB* impair the activation of autophagy receptors and disrupts autophagic flux (LOF) (Brenner et al., 2019; Cozzi and Ferrari, 2022; Duan et al., 2019; Freischmidt et al., 2015; Kuijpers et al., 2013; Ryzhakov and Randow, 2007).

The *UBQLN2*-encoded product regulates both autophagy initiation and lysosomal acidification. Mutations in this gene hinder substrate recognition and degradation (LOF), while promoting protein aggregation (GOF) (Deng et al., 2011; Şentürk et al., 2019; Wu et al., 2020). The autophagy receptors OPTN and SQSTM1/p62 are involved in selective cargo recognition; mutations in their genes impair binding to ubiquitinated substrates and disrupt autophagosome maturation (LOF). Genes encoding proteins involved in autophagosome maturation and fusion include the charged multivesicular body protein 2B (*CHMP2B),* valosin-containing protein *(VCP),* optineurin *(OPTN), SQSTM1*, and *TBK1*. Mutations in *CHMP2B* alter the function of the endosomal sorting complex required for transport-III (ESCRT-III) complex and the autophagosome–lysosome fusion (GOF) (Han et al., 2012; Lee and Gao, 2008; West et al., 2020), while mutations in *VCP* result in aberrant activation of autophagy, impairing autophagosome–lysosome fusion (LOF) (Johnson et al., 2010; Nalbandian et al., 2012; Watts et al., 2004). It is also clear that lysosomal dysfunction, caused by some genetic mutations such as *C9ORF72*, progranulin gene (*GRN*), microtubule-associated protein tau gene (*MAPT*), transmembrane protein 106B (*TMEM106B*), or toxic-gain of function, is a cause of aberrant autophagy and an important pathogenic disease mechanism in ALS (Root et al., 2021). In this context, lysosomal ion homeostasis, maintained by Transient Receptor Potential Channel Mucolipins (TRPMLs), composed of the three members TRPML1, TRPML2, and TRPML3, and the Two-Pore Channels (TPCs), has been found compromised (Tedeschi et al., 2025b).

The regulation of endosomal maturation involves alsin rho guanine nucleotide exchange factor *(ALS2),* polyphosphoinositide phosphatase *(FIG4)*, and *VCP*. Mutations in *ALS2* lead to rapid protein degradation and loss of ras-related protein RAB5 activation (LOF) (Cai et al., 2005; Hadano et al., 2010; Yamanaka et al., 2003), while mutations in *FIG4* disrupt PI(3,5)P2 homeostasis, resulting in enlarged endosomes (LOF) (Bharadwaj et al., 2016; Chow et al., 2007). Additionally, dynactin subunit 1 (DCTN1), kinesin family member 5 A (KIF5A), and tubulin alpha-4 A chain (TUBA4A) are critical for microtubule-based transport. The knockdown of dcn-1 protein reduces the speed and distance of retrograde transport by approximately half and affects the anterograde transport of autophagosomes. Mutations in *DCTN1* impair dynein-mediated retrograde transport and lead to the accumulation of immature autophagosomes (LOF), while the role of GOF mutations remains to be explored. The G59S p150 mutation, which is a GOF mutation, may induce further impairment in axonal transport by either physically blocking the axon or sequestering dynein and dynactin, leading to MN degeneration (Ikenaka et al., 2013; Levy et al., 2006). Mutations in *KIF5A* can disrupt lysosomal transport and autophagic flux (LOF) (Baron et al., 2022; Liu et al., 2021), while mutations in *TUBA4A* can affect microtubule stability, compromising organelle transport (LOF) and potentially causing aggregation (GOF) (Howes et al., 2014; Smith et al., 2014). Notably, dysregulation of the ubiquitin proteosome system (UPS) in ALS patients has been supported by mutations in specific genes, such as *UBQN2* (Teyssou et al., 2017) and *VCP* (Johnson et al., 2010), both of which are related to protein clearance via the UPS (Saeki, 2017). Furthermore, mutations in *OPTN* (Ryan and Tumbarello, 2018; Wen et al., 2025), *SQSTM1/p62* (Katsuragi et al., 2015), *SOD1* (Nishitoh et al., 2008), *VABP* (Chen et al., 2010), *C9ORF72* (Gupta et al., 2017), and Cyclin F (*CCNF*) genes (Tsai et al., 2018) lead to reduced UPS function. This correlation is strongly supported by the observation of ubiquitin-positive inclusions in postmortem neuronal and muscle tissues

of patients with fALS and sALS, particularly in those with C9ORF72 mutations (Leigh et al., 1991). Moreover, UPS LOF has been demonstrated to result from the accumulation of other ALS-related proteins, such as misfolded SOD1 (Sau et al., 2007), and is relevant to the degradation of misfolded TDP-43 (Cascella et al., 2017; Cicardi et al., 2018).

Overall, the mechanisms underlying the disease involve both GOF and LOF mechanisms, with defective autophagy identified as the primary pathway leading to the accumulation of the aberrant inclusions, characteristic of ALS.

The deficiency of the unfolded protein response transcription factor X-box-binding protein-1 (XBP-1) increases autophagy in the CNS. It is associated with heightened autophagic degradation of the SOD1 protein. This process significantly delays the progression of ALS (Hetz et al., 2009). For example, Mitsui et al. confirmed the link between ALS and SQSTM1/p62, demonstrating that the overexpression of SQSTM1 in $SOD1^{H46R}$ mice, a model of ALS, accelerates disease onset by compromising protein degradation pathways (Mitsui et al., 2018). Similarly, progranulin (PGRN) deficiency impairs autophagy, resulting in TDP-43 accumulation (Chang et al., 2017).

A crucial aspect of neurodegeneration, particularly in ALS, is the role of dynein in autophagy. Dyneins are motor proteins that transport cellular cargo along microtubules toward the minus end, playing a fundamental role in the retrograde trafficking of organelles, vesicles, and autophagosomes (Garg and Alisaraie, 2025). There are three main classes of dyneins: cytoplasmic dyneins, including dynein-1, which mediates axonal and vesicular transport, and dynein-2, which is involved in the transport between flagella; and seven forms of axonemal dyneins, which are active in ciliary and flagellar motility (Steinman and Kapoor, 2018). Cytoplasmic dynein-1 operates in concert with the dynactin complex, which stabilises its interaction with microtubules and regulates its motor activity (Singh et al., 2024). Among the dynactin subunits, p150 (also known as DCTN1) is essential for recruiting the dynein complex to microtubules. Notably, p150 is frequently downregulated in MNs of patients with sALS, as shown by post-mortem analyses, suggesting an early impairment of retrograde transport (Jiang et al., 2005; Jiang et al., 2007; Nambiar and Manjithaya, 2024; Reck-Peterson et al., 2018). In this contest, Ikenaka et al. developed a *C. elegans* model that mimics the reduced expression of dynactin-1, observed in ALS patients (Ikenaka et al., 2013). In this model, they identified several pathological features like those seen in human disease, including axonal accumulation of mitochondria, membranous structures, and autophagosomes, as well as MN degeneration. Knocking down *dnc-1*, the *C. elegans* ortholog of *DCTN1*, markedly impaired autophagosome transport, shortened their run length, and caused abnormal accumulation of cellular material, ultimately leading to defective autophagic flux. The role of *DCTN1* in ALS remains unclear. A study of Vilariño-Güell et al. (2009) examines the association between 36 novel DCTN1 variants and various neurodegenerative phenotypes (Vilariño-Güell et al., 2009). Their analysis revealed that all identified variants are rare and do not appear to be associated with disease susceptibility. Additionally, research by Münch et al. (2005) suggests that mutations in DCTN1 may predispose different types of neurons to degeneration. However, other genetic or environmental factors are required to produce the diverse clinical phenotype associated with the disease. Nonetheless, there is insufficient data to determine whether *DCTN1* mutations have functional significance (Münch et al., 2005).

Certain mutations in *DCTN1* are linked to the formation of protein aggregates in rat MNs (Stockmann et al., 2013). However, many of these mutations display uncertain inheritance patterns. They are sometimes found in healthy individuals, suggesting they act as risk modifiers rather than causative mutations. The study by Lai et al. (2007) reveals that the mouse model carrying the G59S substitution in the p150 subunit of dynactin exhibits several symptoms related to ALS. The study indicates that both homozygous *DCTN1* knockout and G59S knock-in mutations are embryonically lethal in mice (Lai et al., 2007). This occurrence suggests that the G59S mutation in p150 may exert a dominant negative effect on the normal function of dynactin, leading to MN degeneration in the heterozygous mutant mice. Another study demonstrates that p150 is essential for maintaining MN function during ageing due to its role in regulating the transport of autophagosomes and lysosomes, thus supporting the notion that its mutations are responsible for a partial blocking of the autophagic flux (Yu et al., 2018). Furthermore, it has been shown that altering dynein-mediated retrograde transport in MNs disrupts autophagosome formation. However, this alteration can also reduce the accumulation of misfolded proteins via UPS, emphasising the critical role of intracellular trafficking in maintaining proteostasis' via autophagy (Cristofani et al., 2017).

In both stressed neurons and ALS models, cyclin-dependent kinase 5 (CDK5) is hyperactivated, which leads to the phosphorylation of nuclear distribution element-like 1 (NDEL1). NDEL1 is a microtubule-associated protein critical for intracellular transport, mitotic spindle assembly, and the regulation of dynein motor function (Niethammer et al., 2000). When CDK5 phosphorylates NDEL1, it promotes the formation of a high-affinity complex formed by LIS1 (Lissencephaly-1)/Ndel/dynein. This complex prevents the ATP-dependent release of dynein from microtubules, thereby inhibiting the processive motility of dynein-driven cargo. This inhibition further compromises the efficiency of the autophagic process, contributing to neuronal dysfunction (Klinman and Holzbaur, 2015; Pandey et al., 2022).

Importantly, all mutations associated with ALS are linked to key autophagic processes in various cell types, thereby reinforcing the connection between ALS and autophagy itself (Fig. 1).

The heat shock protein family B (small) member 8 (HSPB8) has emerged as a crucial regulator of protein quality control system, primarily through its central involvement in chaperone-assisted selective autophagy (CASA). Within this pathway, HSPB8 forms a functional complex with BAG3, HSP70, and STUB1/CHIP, promoting the selective recognition and clearance of misfolded or aggregation-prone proteins (Arndt et al., 2010; Carra et al., 2008; Crippa et al., 2010; Cristofani et al., 2018; Rusmini et al., 2015). This activity is of particular relevance in muscle tissue, where the constant mechanical strain predisposes cytoskeletal components to structural damage. Notably, HSPB8 was first identified in muscle cells as part of the adaptive protein quality control system, underscoring its importance in maintaining cellular proteostasis under conditions of chronic stress (Arndt et al., 2010). The ability of HSPB8 to prevent the accumulation of damaged proteins highlights its essential role in safeguarding muscle integrity and points to its broader significance in disorders characterised by proteotoxic stress.

Crippa et al. (2010) demonstrated that HSPB8 reduces aggregation and enhances the solubility and clearance of mutant SOD1, without affecting its turnover in wild-type SOD1. However, despite its protective role, HSPB8 is insufficient to prevent MN loss, especially at the end-stage of the disease, where its efficiency appears to decline, potentially due to lysosomal impairment or chronic cellular stress (Tan and Finkel, 2023). Interestingly, HSPB8 is predominantly expressed in the spinal cord MNs that survive the pathology, suggesting a selective protective effect that, however, is unable to halt neurodegeneration (Crippa et al., 2010).

The significance of a proper autophagic process for cell survival has been demonstrated using autophagy inhibitors, such as 3-methyladenine or PI-3-kinase/AKT kinase inhibitors. Under these conditions, neuronal health is deteriorated (Levy et al., 2006; Xiao et al., 2015). Chloroquine prevents proper completion of the autophagic process by neutralising lysosomal acid pH, preventing the digestion of autophagosome cargo and increasing neuronal death (Vakifahmetoglu-Norberg et al., 2015). Notably, recently induced pluripotent stem cell (iPSC)-derived MNs from C9ORF72-ALS patients exhibited disrupted lysosomal homeostasis, abnormal lysosome morphology, inhibited autophagic flux, and accumulation of SQSTM1/p62 compared to isogenic controls, reflecting the toxic GOF mechanisms underlying C9ORF72-ALS. In contrast, the loss of C9ORF72 function had minimal impact on these aspects (Beckers et al., 2023). To further confirm the blockage of the autophagic process in ALS,

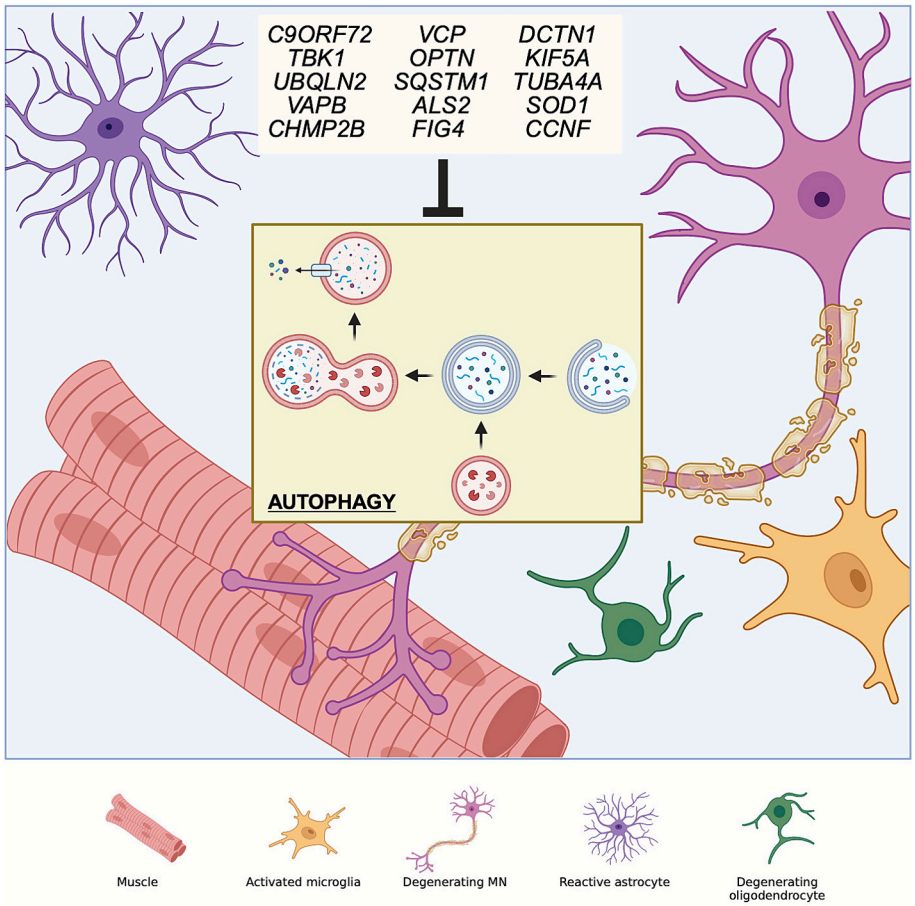

Fig. 1. Selected ALS-mutated genes associated with autophagy. Several genes that are mutated in ALS converge on key aspects of autophagy in both neuronal and non-neuronal cells in the CNS and in muscle fibres. For instance, *C9ORF72*, *TBK1*, *VAPB*, and *UBQLN2* encode proteins that play direct roles in the initiation of autophagy. Mutations in these genes lead to various issues, including the accumulation of dipeptide repeat proteins, reduced activation of the autophagy receptors, disruption of autophagic flux, and impaired regulation of autophagy initiation and lysosomal acidification. The autophagy receptors OPTN and SQSTM1/p6 are crucial for selectively recognizing cargo; mutations in their genes hinder binding to ubiquitinated substrates, thereby disrupting autophagosome maturation. Additionally, genes encoding proteins involved in autophagosome maturation and fusion include *CHMP2B*, *VCP*, and *TBK1*. Mutations in *CHMP2B* affect the function of the ESCRT-III complex and the fusion process between autophagosome and lysosomes. In contrast, mutations in *VCP* cause aberrant activation of autophagy, which also impairs autophagosome–lysosome fusion. The regulation of endosomal maturation involves *ALS2*, *FIG4*, and *VCP*. *DCTN1*, *KIF5A*, and *TUBA4A* are critical for microtubule-based transport. Mutated *SOD1* reduces the efficiency of the ubiquitin proteosome system and the degradation of misfolded TDP-43. As a result, dysfunctional proteins encoded by these genes lead to a blockage of the autophagic pathway, contributing to the accumulation of protein aggregates within MNs, glial cells, and muscle cells. Created in BioRender. Cristofani, R. (2026) https://BioRender.com/awb8cmm

progesterone, a typical female hormone, has been shown, in vitro, to activate autophagy and, consequently, to exert neuroprotective effects, thus delaying, in vivo, ALS progression in $SOD1^{G93A}$ mice (Kim et al., 2013). The mTOR-independent autophagy inducer trehalose attenuates lysosomal fusion deficiency and improves MN function in the $SOD1^{G93A}$ mouse model of ALS. Trehalose treatment significantly delays disease onset, without affecting disease duration. It induces autophagic degradation of aggregated mutant SOD1 protein, thereby protecting MNs from excitotoxicity (Zhang et al., 2014). Similarly, rapamycin activates autophagy by inhibiting mTOR, demonstrating protective effects in several mouse models of neurodegenerative diseases and enhancing the clearance of mutant SOD1 and TDP-43 aggregates in ALS (Hayes and Kalab, 2022). Conversely, rapamycin can have detrimental effects. Zhang et al. (2011) demonstrated that ALS mice treated with rapamycin experienced significantly faster disease progression from onset to death. This finding indicates that while the autophagy pathway is crucial for the degradation mechanism, overactivation may lead to negative effects on neuron viability and mouse survival.

Despite promising preclinical results, these findings have not translated into clinical success, highlighting the complexity of modulating autophagy in human neurodegenerative diseases. A Phase 2/3 randomised, double-blind, placebo-controlled clinical trial of trehalose did not meet its primary efficacy goals in the overall ALS population. Nevertheless, a pre-specified subgroup that excluded patients treated with Relyvrio showed potential slowing of disease progression and respiratory decline, with overall safety being acceptable (Macklin et al., 2025).

Additionally, rapamycin, through a mTOR-dependent mechanism, and colchicine, which stimulates chaperone-assisted selective autophagy, did not reach the primary clinical endpoint in a Phase 2 clinical trial involving ALS patients. However, rapamycin demonstrated promising anti-inflammatory effects by reducing interleukin 18 (IL-18) levels and counteracting the decline in neurofilament levels, which is consistent with ALS pathophysiology (Mandrioli et al., 2023). Colchicine, administered at a lower dose, significantly slowed the decline in motor function, suggesting a potential benefit (Gianferrari et al., 2024; Mandrioli et al., 2023).

Further preclinical research is needed to identify new potential clinical druggable targets to be tested. In this context, dysfunction of lysosomal ionic homeostasis has been considered a potential cause of aberrant autophagy in ALS (Tedeschi et al., 2025b), due to the dysfunction of TRPML1 and TPC2. Interestingly, TRPML1 activation was

able to promote a sort of autophagy reprogramming, leading to a long-lasting effect on MNs exposed to β-methylamino-L-alanine (L-BMAA), a neurotoxin reproducing ALS and Parkinsonism-Dementia Complex (ALS-PDC) (Tedeschi et al., 2019). Moreover, TRPML1 activity stabilization improved ALS progression in vivo in the $SOD1^{G93A}$ mouse model (Tedeschi et al., 2024). Similarly, TPC2 activators, such as the antipsychotic Chlorpromazine (CPZ) and the antidepressant Clomipramine (CMI), boosted autophagy in an in vitro ALS/PDC model by exposing NSC-34, an hybrid cell line produced by the fusion of MN from the spinal cords of mouse embryos with mouse neuroblastoma cells N18TG2 (Cashman et al., 1992), to L-BMAA for 24 h (Tedeschi et al., 2025a). Thus, both TRPML1 and TPC2 activators could be valuable therapeutic options for testing. In the attempts here reported, the strategy to rescue autophagic alterations by drug repurposing is of note.

Overall, the disparity between preclinical and clinical outcomes emphasizes the need for a deeper understanding of autophagy's role in ALS and highlights the importance of careful consideration when developing autophagy-based therapies.

Another stimulating aspect to consider in autophagy is its role in skeletal muscles. Autophagy is essential for maintaining skeletal muscle homeostasis, as it contributes to organelle turnover, protein quality control, and energy balance under both physiological and pathological conditions. In ALS, skeletal muscles undergo early metabolic and structural changes that occur before significant MN loss, including altered autophagy flux (Luo et al., 2013; J. Zhou et al., 2019). In the $SOD1^{G93A}$ transgenic mice, the upregulation of autophagy markers, such as microtubule-associated protein 1A/1B light chain 3B (MAP1LC3-II), SQSTM1/p62, and (HSPB8) has been reported in muscles during the presymptomatic and terminal stages of the disease (Crippa et al., 2013). Notably, unlike in other tissues, autophagy activation in skeletal muscles can persist for extended periods. The activation of autophagy observed at early and late disease stages in $SOD1^{G93A}$ mice may indicate a dysregulation of this process during disease progression, which is likely associated with ALS-related degeneration (Crippa et al., 2013; Dobrowolny et al., 2008; Oliván et al., 2015).

5. Autophagy in ALS glial cells

One drawback in the autophagy research field is that most studies have focused primarily on elucidating the underlying pathomechanisms in neurons. However, neurons make up only about half of the brain cells, with glial cells constituting the other most numerous cell type in the CNS. Within the CNS, glial cells include astrocytes, oligodendrocytes, and microglia, each playing a crucial role in maintaining neuronal homeostasis. Given the ubiquitous presence of disease-causing mutations in all CNS cell types, non-neuronal cells likely contribute to the onset and/or progression of ALS. While our understanding of the role of autophagy and its contribution to neurodegeneration in neurons has significantly deepened over the past few years, comparatively little is known about the functions and disease contributions of the autophagy machinery in glial cells (Strohm and Behrends, 2020).

Emerging evidence indicates that dysfunction in each of the glia cell types, as well as abnormal interactions between glia and MNs, contributes to ALS (Patani et al., 2023; Vahsen et al., 2021). Additionally, protein aggregates have been observed in glial cells in individual with ALS (Forsberg et al., 2011; Turner et al., 2004). These findings, along with numerous studies demonstrating non-cell-autonomous mechanisms in ALS, suggest a role for defective glial autophagy in the disease (Filipi et al., 2020; Lee et al., 2016; Pandya and Patani, 2024; Stoklund Dittlau and Freude, 2024; Van Harten et al., 2021). However, the mechanisms by which autophagy is executed in these cells and whether it operates similarly to that in neurons remain elusive.

Research has shown increased autophagic signals in vivo in mice, as well as ex vivo in both spinal MNs and surrounding astrocytes and in microglial cells (Tian et al., 2011). Of note, many neurons exhibit activated autophagy in SOD1 transgenic mice at an early symptomatic stage, around 17 weeks of age; however, this activation is also observed in astrocytes and microglia at the end-stage of disease, around 19 weeks, when the number of surviving MNs decreases (Tian et al., 2011). Therefore, it is crucial to carefully monitor the autophagic process during disease progression to understand its dual role in ALS pathogenesis. To investigate this topic, researchers studied in vivo autophagy dynamics in astrocytes, microglia, and oligodendrocytes at key disease stages by crossing $SOD1^{G93A}$ mice with transgenic RFP-EGFP-LC3 autophagy reporter mice, enabling the quantification of autophagic degradation (Perera et al., 2025). Although oligodendrocytes seemed to mount effective compensatory autophagic responses to counteract mutant SOD1, significantly increased autophagy flux was observed in symptomatic spinal cord microglia and astrocytes compared to control animals. Symptomatic SOD1 astrocytes displayed greater autophagy dysfunction compared to microglia, with subcellular analysis revealing cell compartment-specific, transient autophagy defects that returned to control levels by the end of the disease stage. Interestingly, spinal glia exhibited more pronounced and earlier autophagy dysfunctions compared to motor cortex glia, where issues with autophagy emerged later in the disease's end stage, coinciding with the more severe spinal cord pathology reported in the SOD1 model (Perera et al., 2025).

5.1. Astrocytes

Astrocytes are the largest population of glia in the mammalian CNS, comprising approximately 30 % of the total cell population. They play a crucial role in maintaining the physiological homeostasis of the CNS by participating in synapses with neurons. Astrocytes are involved in K^+ buffering, maintaining the blood-brain barrier maintenance, and regulating neuronal metabolism. They contribute to the structure of tripartite synapses, where they recycle glutamate from the synaptic cleft via the excitatory amino acid transporters EAAT1 and EAAT2. Additionally, astrocytes can release glutamate, GABA, nitric oxide, and ATP (Allen and Lyons, 2018; Hasel and Liddelow, 2021).

In ALS, astrocytes became reactive (Escartin et al., 2021), changing their functions. Although the exact timeline of astrocyte reactivity in ALS remains unclear, evidence suggests that these changes can occur both autonomously within astrocytes and in response to alterations in the surrounding environment. Factors contributing to astrocytes' reactivity include astrocyte-neuron signalling perturbations (Licht-Murava et al., 2023; Tripathi et al., 2017), microglia-mediated activation (Guttenplan et al., 2020; Liddelow et al., 2017), and astrocyte cell-autonomous changes during disease progression (Taha et al., 2022). Although our understanding of autophagy in astrocytes remains limited, eafunctional astrocytes are closely linked to proper autophagic processes. Interest in the role of autophagy in ALS is growing, as several studies have shown the significant contribution of astrocytes to the pathology (Pandya and Patani, 2024; Stoklund Dittlau and Freude, 2024).

Mouse-derived astrocytes with autophagic-lysosomal dysfunction have been shown to directly contribute to neurodegeneration due to their impaired ability to metabolically support neurons (Di Malta et al., 2012). Additionally, a recent report indicates that autophagy is dysregulated in human ALS $SOD1^{G93A}$ astrocytes. In these cells, the insulin-like growth factor 1 receptor (IGF1R) and mTOR pathways were found to be overactivated, which inhibits autophagy, increases cell proliferation, and enhances astrocyte reactivity. Importantly, modulation of this pathway can reduce astrocyte toxicity toward MNs (Granatiero et al., 2021). In a murine model of the disease expressing the mutant $SOD1^{G85R}$ protein inclusions formed earlier and in greater quantities in astrocytes compared to neurons (Bruijn et al., 1997). However, expressing SOD1 mutations exclusively in neurons or astrocytes is insufficient to induce neurodegeneration (Ilieva et al., 2009). Neurodegeneration occurs only when the mutation is present in both cell types, at which point mice develop a pathological phenotype resembling ALS (Gong et al., 2000; Lino et al., 2002; Pramatarova et al., 2001). Of note, reducing or eliminating the accumulation of mutant SOD1 in

astrocytes has been shown to slow disease progression and increase survival in murine models (Yamanaka et al., 2008a; Yamanaka et al., 2008b).

Recently, it was demonstrated that cortical SOD1 astrocytes derived from $SOD1^{G93A}$/RFP-EGFP-LC3 reporter mice did not display significant alterations in autophagy compared to controls during either the pre-symptomatic or symptomatic disease stages. However, they showed local deficits in autophagy flux in cell processes at the end stage of the disease (Perera et al., 2025). Conversely, $SOD1^{G93A}$ spinal cord astrocytes displayed significantly higher autophagy flux at the symptomatic stage, attributed to an increase in autolysosomes. This increase in the autophagy flux was transient, returning to control levels by the end of the disease stage. These findings suggest a compensatory upregulation of autophagy during early symptomatic disease, which may become unsustainable or maladaptive at later stages (Perera et al., 2025).

The relationship between autophagy and neuroinflammation has been documented (Qian et al., 2017). In ALS, inflammation is a predominant feature, supported by the upregulation of inflammatory cytokines, such as the tumour necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1β (IL-1β) in the brain, spinal cord, and body fluids from human patients (Berjaoui et al., 2015; Tortelli et al., 2020). Astrocytes are the primary source of these proinflammatory cytokines (Li et al., 2018; Van Wagoner et al., 1999); however, the cause of aberrant cytokine secretion in ALS astrocytes is still unknown. Autophagy and inflammation mutually influence each other. On one hand, autophagy helps inhibit or remove proteins and fragmented organelles that could trigger an inflammatory response, influencing the development, homeostasis, and survival of inflammatory cells, as well as transcription, processing, and secretion of cytokines (Qian et al., 2017; Shin et al., 2013; Sonninen et al., 2020). On the other hand, inflammatory cytokines interact with the plasma membrane-bound receptors to activate or inhibit the downstream signalling pathways related to autophagy (Wu et al., 2016). The interplay between autophagy and inflammation is evident in ALS. Patient-derived astrocytes from iPSCs have been shown to exhibit increased secretion of the cytokines IL-1β, TNF-α, and IL-6, which can lead to MN toxicity. This release of proinflammatory cytokine is driven by an aberrant mTOR-autophagy pathway (BaofengFeng et al., 2022). In addition, ALS astrocytes exist within an inflammatory environment that disrupts mitochondrial architecture, which requires a functional autophagic process to prevent ROS accumulation (Motori et al., 2013).

SQSTM1/p62, MAP1LC3 I/II, and lisosomal associated membrane protein 1 (LAMP1) were found to be upregulated in astrocytes derived from iPSCs of $SOD1^{L39R}$-expressing patients indicating an active autophagy status compared to the control group. These functional changes in astrocytes negatively impacted MN viability, leading to increased granular stress, oxidative stress, and apoptosis due to an enhancement of ROS production and lysosomal accumulation. Moreover, SQSTM1/p62 and MAP1LC3 I/II expression was significantly increased in MNs after treatment with the secretome derived from $SOD1^{L39R}$ astrocytes, confirming that autophagy plays a critical role in addressing the non-cell autonomous neurotoxicity mediated by astrocytes (Rajpurohit et al., 2020). In contrast, the secretome from normal astrocytes has shown neuroprotection in patient iPSC-derived MNs (Rajpurohit et al., 2020). Reactive astrocytes induce protein aggregation in MNs partly by releasing transforming growth factor β1 (TGF-β1), which disrupts MN autophagy through the mTOR pathway (Tripathi et al., 2017). Likewise, Madill et al. (2017) demonstrated that iPSC-derived MNs, when treated with conditioned medium from patient iPSC-derived astrocytes, exhibited decreased expression of MAP1LC3-II. This key adapter protein is essential for the selective degradation of SQSTM1/p62 and ubiquitinated proteins that are targeted for degradation. Increased accumulation of SQSTM1/p62 was observed in cells treated with conditioned medium from patients' iPSC-derived astrocytes, which was accompanied by a rise in SOD1 expression. Of note, activating autophagic mechanisms with rapamycin reduced the accumulation of SQSTM1/p62-positive puncta in cells treated with patient-conditioned medium. This evidence suggests that astrocytes from ALS patients may modulate MN death by impairing autophagic processes (Madill et al., 2017).

A recent study has linked the C9ORF72 mutation to changes in autophagy (Webster et al., 2016) and to altered secretion of inflammatory cytokines as well as extracellular vesicles containing microRNAs (miRNAs) from astrocytes derived from iPSCs of C9ORF72 human patients (Varcianna et al., 2019; Webster et al., 2016). Notably, miR-494-3p, which negatively regulates semaphorin 3A (SEMA3A) and other targets involved in axonal maintenance, was found downregulated in vesicles released by C9ORF72 astrocytes. Restoring the level of this miRNA, MN survival was rescued. Since miRNAs can also regulate autophagy (Shah et al., 2018), it would be valuable to explore the potential non-autonomous control of neuronal autophagy mediated by mutant C9ORF72 astrocytes.

Furthermore, autophagy dysregulation is a relevant aspect of astrocyte function in ALS, as evidenced by distinct transcriptional and proteostasis disturbances observed in astroglia, including the early accumulation of the autophagy signalling protein SQSTM1/p62 in long-term human cortical organoids, which recapitulate the early molecular pathology of ALS/frontotemporal dementia (FTD) (Szebényi et al., 2021).

Overall, the autophagic pathway may be a promising target in the development of novel therapeutics. Focusing on this target can ameliorate the functionality of non-neuronal cells themselves, while also positively influencing MN viability. Molecules that stimulate autophagy, promoting TDP-43 clearance, enhanced survival both in primary murine neurons and human stem cell-derived neurons and astrocytes harbouring mutant TDP-43 (Barmada et al., 2014). Although it remains unclear whether TDP-43 elimination occurs specifically through UPS or autophagy, the activation of this process in neurons, muscle cells and astrocytes appears promising. This is relevant, considering that human astrocytes with TDP-43 mutations exhibit autonomous toxicity (Cicardi et al., 2018; Serio et al., 2013).

5.2. *Microglia*

Microglia represent about 15 % of all cells in the CNS. They are the most abundant type of mononuclear phagocytes in this area and are responsible for phagocytosis, helping to eliminate microbes, dead cells, protein aggregates, and other harmful particulate and soluble antigens that can endanger the CNS (Colonna and Butovsky, 2017). In addition, microglia secrete numerous soluble factors, including chemoattractants, cytokines, and neurotrophic factors that contribute to various aspects of the immune response and tissue repair within the CNS (Colonna and Butovsky, 2017). Microglial cells are involved in neuroinflammation and can induce or modulate many cellular responses. Due to their plasticity, their role can be beneficial or detrimental, depending on the context (Colonna and Butovsky, 2017). As resident immune cells of the CNS, microglia continuously monitor the neural environment and can rapidly respond to pathological changes by altering their phenotype (Prinz et al., 2019). In response to different stimuli, microglia can adopt a spectrum of activation states, ranging from neurotoxic to neuroprotective phenotypes, and are identified as disease-associated microglia, depending on the specific pathological scenario (Guo et al., 2022; Keren-Shaul et al., 2017).The functional properties of microglia change in the context of neurodegenerative diseases. In these conditions, microglia can exhibit increased production of inflammatory mediators and altered phagocytic behaviours, which can lead to neurotoxicity (Hickman et al., 2018). However, the extent to which microglial dysfunction arises from the diseased CNS environment versus cell-autonomous factors is not yet fully understood.

Recent studies highlighted the crucial role of autophagy in the immune functions of microglia (Y. Chen et al., 2024; Quick et al., 2023). Both canonical and non-canonical autophagy processes occur in these cells (Jülg et al., 2020). Impaired autophagy in microglia may contribute

to neurodegeneration, as seen in ALS (Gao et al., 2023; Jin et al., 2018; Plaza-Zabala et al., 2017). Notably, Massenzio et al. (2018) demonstrated that the intracellular accumulation of mutant $SOD1^{G93A}$ and $SOD1^{A4V}$ occurs not only in neurons but also in microglia, albeit to a lesser extent, leading to neurotoxicity (Massenzio et al., 2018). Recently, Perera et al. (2025) identified a localised autophagy defect in the soma of $SOD1^{G93A}$ cortical microglia, characterised by an accumulation of autophagosomes, at both the pre-symptomatic and symptomatic stages of the disease, while no changes in overall cell autophagic flux were observed. At the symptomatic disease stage, there was i) a significant increase in the number of autolysosomes in the soma of cortical microglia, paralleled by a decrease in their processes reflecting a response to the increment of the autophagosomes, and ii) an augmentation of the cell autophagy flux, which persisted until the end stage (Perera et al., 2025). In contrast, at the symptomatic stage, $SOD1^{G93A}$ spinal microglia contained a significantly higher number of autolysosomes compared to controls, reflecting an increased autophagy flux as an adaptive response to the accumulation of misfolded SOD1 inclusions and the surrounding MN death (McLeod et al., 2022; Vinsant et al., 2013). By the end stage of the disease, a depletion of autophagosomes was observed in $SOD1^{G93A}$ spinal cord microglia, potentially due to a transient increase in autophagy degradation capacity. However, autophagy flux at this stage was comparable to that of the control group. Interestingly, healthy mice exhibit an age-dependent increase in microglial autophagosome size, a phenomenon that is absent in $SOD1^{G93A}$ mice. This studies suggest that $SOD1^{G93A}$ mice do not achieve the age-dependent expansion of autophagosomes until late in the disease, which may lead to impaired clearance and accumulation of $SOD1^{G93A}$ inclusions. Alternatively, the autophagosome pool in $SOD1^{G93A}$ microglia may remain smaller due to the rapid fusion with lysosomes, a consequence of increased autophagy flux in symptomatic microglia. Once the flux normalises at the end stage of the disease, age-related autophagosome expansion becomes evident (Perera et al., 2025).

The critical role of autophagy in microglia function and its impact on MNs in ALS has been recently pointed out. iPSC-derived microglia carrying a profilin 1 (PNF1) mutation, which is penetrant and accounts for 1-2 % of inheritable ALS (Brown and Al-Chalabi, 2017; Wu et al., 2012), exhibited differentially expressed proteins and genes related to lipid metabolism, autophagy, and phagocytosis. Mutant ALS-PFN1 iPSC-derived microglia also showed evidence of autophagy dysregulation, accompanied by an accumulation of lipid droplets, that should typically be cleared through the autophagy pathway. While WT iPSC-derived microglia were able to engulf synaptosomes and other substrates, mutant ALS-PFN1 iPSC-derived microglia were deficient in processing phagocytosed material through the endo-lysosomal pathway (Funes et al., 2024). Overall, these authors demonstrated a gain-of-toxic mutant PFN1 function in the context of microglial vesicular degradation, which could be pharmacologically ameliorated with the use of rapamycin. Interestingly, iPSC-derived microglia with reduced C9ORF72 protein levels are associated with impaired phagocytosis, an exaggerated immune response when stimulated with lipopolysaccharide, and a failure to initiate autophagy. Of note, co-culture studies with MNs demonstrated that the autophagy deficit in C9ORF72-iPSC-derived microglia drives increased vulnerability of C9ORF72-iPSC-derived MNs to excitotoxic stimulus. Activation of autophagy ameliorated both cell-autonomous functional deficits (Banerjee et al., 2023).

Inflammation can also affect microglia autophagy, with evidence suggesting that TDP-43 aggregation is influenced by inflammation (Correia et al., 2015). Optineurin truncation, specifically the $Optn^{470T}$ variant, which resembles ALS mutations found in patients, leads to increased levels of TDP-43 protein in microglia. In cells lacking functional optineurin, TDP-43 levels could not be increased further by an inflammatory stimulus, indicating a potential plateau effect (Prtenjaca et al., 2022). Additionally, primary microglial cells overexpressing $SOD1^{G93A}$ mutations, particularly $SOD1^{A4V}$, exhibited significantly greater intracellular accumulation of SOD1 and co-localisation of SOD1 with the lysosomal vesicle marker LAMP-1 when compared to microglial cells overexpressing the WT human SOD1. This accumulation was associated with the activation of inflammatory responses in these cells and extensive neurotoxicity. Of note, a reduction in MAP1LC3B levels was observed along an increase in SQSTM1/p62 expression in microglial cells overexpressing mutant SOD1, supporting the idea that autophagy impairment corresponds with protein accumulation and suggesting a reduction in microglial autophagy, which may reflect differences between in vitro and in vivo conditions (Perera et al., 2025). Furthermore, treatment with trehalose was found to rescue the autophagic flux, preventing protein accumulation and promoting a non-neurotoxic microglia phenotype (Massenzio et al., 2018).

The essential role of a proper autophagy in microglia is supported by the fact that impaired autophagic flux can disrupt synaptic pruning and cause social behavioural defects (Kim et al., 2017). Thus, impaired autophagy may contribute to the synaptic abnormalities observed in MNs of ALS patients.

Overall, autophagy dysfunction in microglia can exacerbate neuroinflammation associated with sustained microglial activation, characterised by increased production of pro-inflammatory cytokines and reduced phagocytosis of apoptotic cells. This chronic inflammatory state can amplify MN damage and accelerate disease progression (Bonilla et al., 2013).

5.3. Oligodendrocytes

Oligodendrocytes (OLs) are glial cells in the CNS responsible for myelinating axons. They provide electrical insulation, as well as metabolic and trophic support to axons (Butt et al., 2025). In addition, to facilitating faster nerve signal conduction, oligodendrocytes provide metabolic support to axons, which is essential to compact myelin. Cytoplasmic channels within the myelin allow the transport of substances between the OL cell body and the inner part of the myelin sheath (Snaidero et al., 2017). This makes OLs and myelinated axons metabolically connected. Recently, the implications of OL dysfunction and myelin damage have gained increased attention. They are now considered as significant contributors to neurodegeneration in various neurological diseases, including ALS. Research has documented OL dysfunction, defective maturation of the oligodendrocyte precursor cells (OPCs), and impairment in supplying energy to MNs in ALS (Raffaele et al., 2021).

The role of autophagy in oligodendrocyte lineage cells remains unclear. Under physiological conditions, autophagy is required for maintaining the correct OPCs and mature OLs populations, as well as ensuring myelin integrity, particularly during brain ageing (Chen et al., 2025). Inactivation of autophagy in OLs leads to an increased number of OPCs and OLs, in the developing brain. Still, it also exacerbates the loss of these cells. Additionally, when autophagy is inhibited in OLs, it impairs the turnover of myelin basic protein (MBP), causing this protein to accumulate in the cytoplasm as multimeric aggregates. This accumulation prevents MBP from being incorporated into the structural myelin, which results in attenuated endocytic recycling and ultimately in compromised myelin integrity and demyelination (Chen et al., 2025). Notably, autophagy induces apoptosis in premyelinating OLs during development, acting in a cell-autonomous manner. Furthermore, autophagy interacts genetically with the transcription factor EB (TFEB) pathway to limit the OL number across different brain regions (Zhang et al., 2023b). Autophagy and apoptosis work together in OLs to control the specificity and functionality of myelination (Zhang et al., 2023a). In the context of glial cells, OLs' autophagy is essential for their proper cellular functioning. In fact, enhancing autophagy in OLs helps alleviate white matter injury and cognitive impairment caused by chronic cerebral hypoperfusion (Wang et al., 2023).

To date, research has identified FUS and TDP-43 inclusions in OLs from post-mortem tissue of fALS and sALS patients (Mackenzie et al., 2011), additionally, with or without SOD1 mutation, as well as in cases

of ALS with dementia (Mackenzie et al., 2007, 2011). In addition, a high burden of glial inclusions, labelled with p62 and TDP43, were found in prefrontal cortex, precentral gyrus, and spinal cord, specifically located in OLs (Pons et al., 2020). Although this evidence suggests that there may be impaired autophagy in OLs in ALS, further analysis is needed to confirm this hypothesis.

Recently, Perera et al. (2025) mapped autophagy in OLs in both the cortex and the spinal cord of double mutant SOD1^{G93A}/CAG-RFP-GFP-LC3 reporter mice. Their findings indicate that OLs were somewhat preserved from autophagy dysfunction. In double mutant SOD1 mice, OLs efficiently manage autophagy without significant dysfunction to overall cell flux. However, several subcellular defects were observed precociously in the motor cortex in mature, myelinating APC/CC1^{+} OL processes, as well as in the spinal cord soma of pan Olig2+ progenitor and mature OLs. These changes suggest that there may be compensatory mechanisms or adaptations in response to a pathological environment, indicating that localised efforts to cope with early stress might have been successful. Furthermore, the absence of significant defects in the overall cell flux, despite the observed changes in cell compartments, supports the idea that OLs can manage autophagy in response to mutant SOD1, at least up to the late disease stage examined.

Overall, the dysregulation of non-cell autonomous autophagy can affect the surrounding environment and also microglia, astrocytes, and oligodendrocytes, themselves. This dysregulation increases the reactive and proinflammatory status of these cells, which exacerbates their autophagy function, and ultimately impacts the viability of MNs (Fig. 2).

6. Possible correlations between sex and autophagy

The cell-specific response to changes in autophagy alterations highlights the need to further investigate these aspects to identify the most affected cell types and the therapies that could have a positive impact. Additionally, factors such as sex, could significantly influence how cells respond to autophagy impairments during disease progression

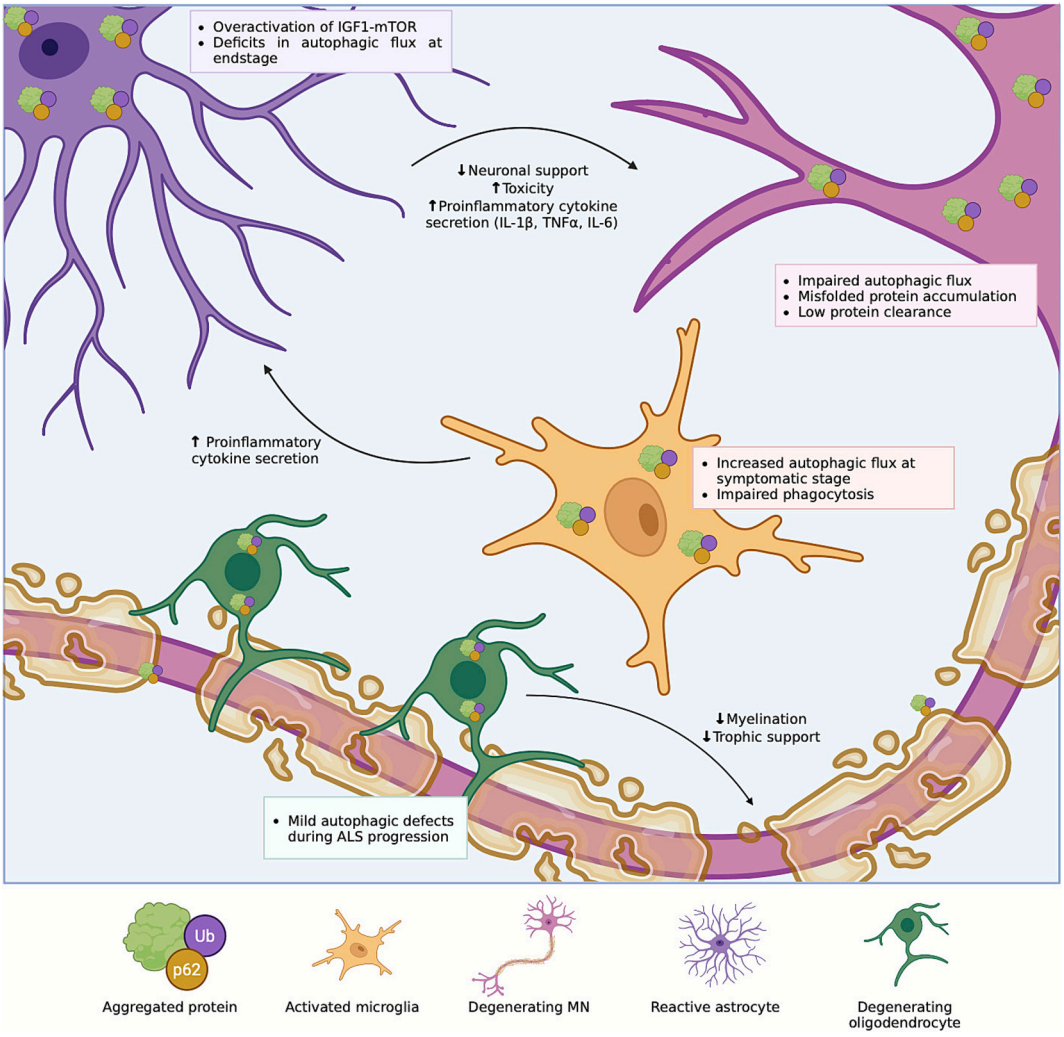

Fig. 2. Cell and non-cell autonomous dysfunctions during ALS progression. In the degenerating CNS, ubiquitinated, SQSTM1/p62-positive misfolded protein aggregates have been observed, resulting from different gene mutations associated with ALS. These aggregates are found not only in neurons but also in glial cell, including microglia, astrocytes, and oligodendrocytes. To date, in ALS, impaired autophagic flux and reduced protein clearance have been strictly associated with MNs. In the case of microglia, studies have shown an increase in autophagy accompanied by a decrease in phagocytosis. Moreover, the presence of different gene mutations favours the activation of microglia, leading to elevated secretion of proinflammatory cytokines into the extracellular space. This inflammatory environment induces a reactive state in astrocytes, characterised by the overactivation of the IGF-mTOR pathway, which results in decreased autophagic flux. At the same time, reactive astrocytes show reduced support for neurons and an increased release of toxic molecules and inflammatory cytokines, all of which negatively impact MN viability. Altough only mild autophagic defects have been observed in oligodendrocytes, the presence of ALS-related mutations adversely impacts their functions, leading to reduced trophic support and myelination of MN axons, contributing to neuronal degeneration. Created in BioRender. Magdalena, R. (2026) https://BioRender.com/pn52mxd

(Vegeto et al., 2020; Villa et al., 2016).

The role of sex is now well-established in ALS, influencing disease onset, progression, prevention, therapeutic success, and prognosis (Bonifacino et al., 2017, 2019; Milanese et al., 2021; Nicoletti et al., 2023; Raffaele et al., 2024; Trojsi et al., 2020; Zamani et al., 2024). Understanding these sex-specific differences is of paramount importance in developing precision medicine approaches.

In ALS, women appear to be less susceptible to developing the disease, and disease progression in female patients tends to be slower (Couratier et al., 2016; McCombe and Henderson, 2010; Talbott et al., 2016; Zarei et al., 2015). However, sex-dependent differences become less pronounced with age, leading to the hypothesis that sex hormones may play a role in this process (Manjaly et al., 2010). Supporting this idea, studies have demonstrated that a deficiency in endogenous estrogen negatively affect female SOD1 transgenic mice, accelerating disease progression and making their lifespan comparable to that of male mice (Choi et al., 2008; Groeneveld et al., 2004; Yan et al., 2018).

Moreover, bilaterally ovariectomised SOD1 mice exhibited accelerated disease progression, which was reversed by estrogen therapy (Choi et al., 2008; Groeneveld et al., 2004; Heitzer et al., 2017). Heitzer et al. (2017) found that the treatment with 17β-estradiol in male $SOD1^{G93A}$ mice increased MN survival, potentially due to the downregulation of several components of the inflammatory response (e.g., NLRP3, IL-1β, and activated caspase-1) that were abnormally elevated in the spinal cord of affected mice (Heitzer et al., 2017).

Thus, it is now clear that sex influences the progression of ALS; however, the specific mechanisms by which sex affects specific non-cell autonomous features causally linked to the pathology are still unknown. A study in $SOD1^{G93A}$ mice revealed that allopregnanolone (PG) slowed disease progression and prolonged lifespan in males, without delaying symptom onset (Kim et al., 2013). PG may delay the neurodegenerative process by activating the autophagic degradation of mutant SOD1 mice. This female sex hormone PG is synthesised in the brain, spinal cord, and peripheral nervous system, where it serves as a precursor to various neurosteroids. In the CNS, PG and neurosteroids can exert diverse physiological functions, including modulating GABAergic and glutamatergic transmission (Maitra and Reynolds, 1998). Since autophagy may play a role in ALS pathogenesis or could be targeted for treatment, Kim et al. (2012) aimed to determine whether PG activates autophagy in spinal cord astrocytes and in ALS mice, as well as its impact on the neurodegenerative process in the $SOD1^{G93A}$ mouse model (Kim et al., 2012). They demonstrated that exposing cultured murine astrocytes to 250 or 500 nM PG led to the appearance of cytosolic vacuoles within hours of treatment initiation. Confocal live-cell microscopy of astrocytes transfected with red fluorescent protein-conjugated MAP1LC3 (RFP-LC3), a marker for autophagic vacuoles, as well as transmission electron microscopy, revealed that these vacuoles were autophagic. Moreover, western blot analyses showed increased levels of MAP1LC3-II (Kim et al., 2012). Thus, PG appears to activate autophagy in cultured murine astrocytes, potentially slowing neurodegeneration by degrading mutant SOD1. The estrogen estradiol (E2) is considered a potential therapeutic agent for ALS but may have undesirable effects that increase the risk of breast and uterine cancers or stroke. Raloxifene (Ral) has mixed estrogenic and antiestrogenic properties, depending on the targeted cell and tissue type, and it does not exhibit the above adverse effects. Like E2, Ral enhances autophagy and suppresses apoptosis to limit MN death by binding to ERα/β or GPR30 in NSC-34 cell model of ALS that stably expresses the 25-kDa C-terminal fragment of TDP-43 (i.e. TDP-25 cells), a model of ALS. Therefore, being both a promising replacement for estrogen and a therapeutic strategy for ALS (Zhou et al., 2018).

Since the progression of ALS appears to differ based on sex, it is worthwhile to investigate also potential differences in the regulation of skeletal muscle autophagy. Recent studies, suggest that specific markers of autophagic and lysosomal activity, such as cathepsins and MAP1LC3, are sensitive to fluctuations of testosterone levels and tend to increase following animal castration (Serra et al., 2013), supporting the hypothesis that male sex hormones act as negative regulators of autophagy in skeletal muscles. Additionally, the study conducted by Olivan and colleagues (2014) examined sex-specific differences in autophagy in the muscle tissue of wild-type (WT) mice by monitoring the transcriptional and the protein expression levels of the two autophagy markers MAP1LC3 and SQSTM1/p62 revealing significant variations between sexes (Oliván et al., 2014). These results underscore the importance of considering sex in the evaluation of disease models to minimise potential negative consequences of sex-related biases.

In in vivo models of cancer cachexia, such as AH-130 tumour-bearing rats, treatment with megestrol acetate, a synthetic PG analogue, produced significant protective effects on skeletal muscle, reducing the activation of the specific autophagy markers MAP1LC3-II, BECN1, and SQSTM1/p62 and improving both survival and muscle mass (Musolino et al., 2016). However, these findings cannot be directly extrapolated to endogenous or natural PG, given the distinct pharmacodynamics of synthetic progestins. Crippa et al. (2013) have identified sex-related differences in autophagy within the muscle and spinal cord of $SOD1^{G93A}$ mice. Specifically, SQSTM1/p62 expression was significantly increased in the skeletal muscle of female $SOD1^{G93A}$ mice. In contrast, HSPB8 expression was significantly elevated in the spinal cord of $SOD1^{G93A}$ male mice.

Overall, the role of sex hormones in the regulation of skeletal muscle autophagy remains poorly understood. Further targeted studies are needed to determine the conditions under which PG may act as a modulator of this process.

7. Conclusions

The findings presented in this review suggest that dysfunctions in autophagy in ALS vary based on timing and cell type, which is crucial for developing effective therapeutic strategies. The different responses among various cell types, along with their unique roles in autophagy dysregulation throughout ALS progression, emphasise the importance of clarifying the specific function of each cell lineage in the autophagic process. Additionally, it is essential to consider sex as a potential modifying factor.

Overall, the autophagic pathway may be a promising target in the development of novel therapeutics. Focussing on this target can ameliorate the functionality of non-neuronal cells themselves, while also positively influencing MN viability. Molecules that stimulate autophagy, promoting TDP-43 clearance, enhanced survival both in primary murine neurons and human stem cell-derived neurons and astrocytes harbouring mutant TDP-43 (Barmada et al., 2014). Although it remains unclear whether TDP-43 elimination occurs specifically through UPS or autophagy, the activation of this process in neurons, muscle cells and astrocytes appears promising. This is relevant, considering that human astrocytes with TDP-43 mutations exhibit autonomous toxicity (Cicardi et al., 2018; Serio et al., 2013).

The involvement of different cell types in autophagic impairment during ALS may explain the diverse outcomes observed when attempting to enhance this process in vivo (Perera et al., 2018, 2021; Zhang et al., 2011, 2014, 2019). A generalised approach to stimulating autophagy, without considering either the specific cell type or the disease stages, may not be the most effective therapeutic strategy for ALS. Of note, sex may play a significant role in this context. Recent Phase 2/3 clinical trials of rapamycin (Mandrioli et al., 2023) and trehalose (Macklin et al., 2025) have been completed. While these treatments were well tolerated, they did not achieve their primary or some secondary outcomes in ALS patients. This challenge might be overcome by specifically targeting CNS cell types, possibly using loaded nanoparticles (Zhang et al., 2011). Additionally, strategies in mouse models that translate specific findings, including the use of the Cre-LoxP recombination system for time-specific deletion of essential autophagy genes in astrocytes or microglia could be beneficial. Alternatively, using adeno-associated viral vectors with glial-specific promoters (O'Carroll et al.,

2021) to deliver microRNAs targeting autophagy genes selectively to astrocytes, Ols, or microglia may also help. While we are making progress toward personalised therapies that consider timing and sex, along with being cell-targeted, further efforts are needed to refine these approaches.

CRediT authorship contribution statement

Francesca Rosso: Writing – review & editing, Writing – original draft. **Rocio Magdalena:** Writing – review & editing, Writing – original draft. **Carola Torazza:** Writing – review & editing, Writing – original draft. **Francesca Bacchetti:** Writing – original draft. **Marco Milanese:** Supervision, Funding acquisition. **Angelo Poletti:** Supervision, Project administration, Funding acquisition, Conceptualization. **Giambattista Bonanno:** Supervision, Conceptualization. **Riccardo Cristofani:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Tiziana Bonifacino:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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