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THE ROLE OF AUTOPHAGY IN THE PROGRESSION OF AMYOTROPHIC LATERAL SCLEROSIS (ALS): POTENTIAL TARGETS FOR THERAPEUTIC INTERVENTION AND DISEASE MODULATION

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Abstract

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disorder characterized by the degeneration of motor neurons in a progressive manner. Disturbance in cellular homeostasis, especially by disturbed protein degradation, is vital to the pathogenesis of ALS. Autophagy is an important intracellular degradation mechanism to remove protein aggregates and damaged organelles from neurons. Autophagy dysfunction in ALS has been associated with genetic mutations, mitochondrial dysfunction, and proteostasis failure. We explore the mechanistic importance of autophagy in ALS progression, suggest autophagy-targeting therapeutic approaches, and envisage the future research directions to augment the efficacy of treatment in this review.

Keywords: Amyotrophic Lateral Sclerosis, Autophagy, Neurodegeneration, Therapeutic Targets

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INTRODUCTION

Amyotrophic lateral sclerosis, also known as ALS, is an advanced neurodegenerative disorder which affects motor neurons in the brain and spinal cord, ultimately weakening the muscles, causing paralysis, and causing death. On the average, ALS patients survive between 3 to 5 years from the time they were diagnosed with the illness [1]. While most ALS cases are sporadic (sALS), about 10% are familial (fALS), due to mutations in genes such as SOD1, TARDBP, FUS and C9orf72 [2]. Another hallmark feature of ALS is the accumulation of misfolded proteins in motor neurons leading to cellular toxicity and neurodegeneration [3

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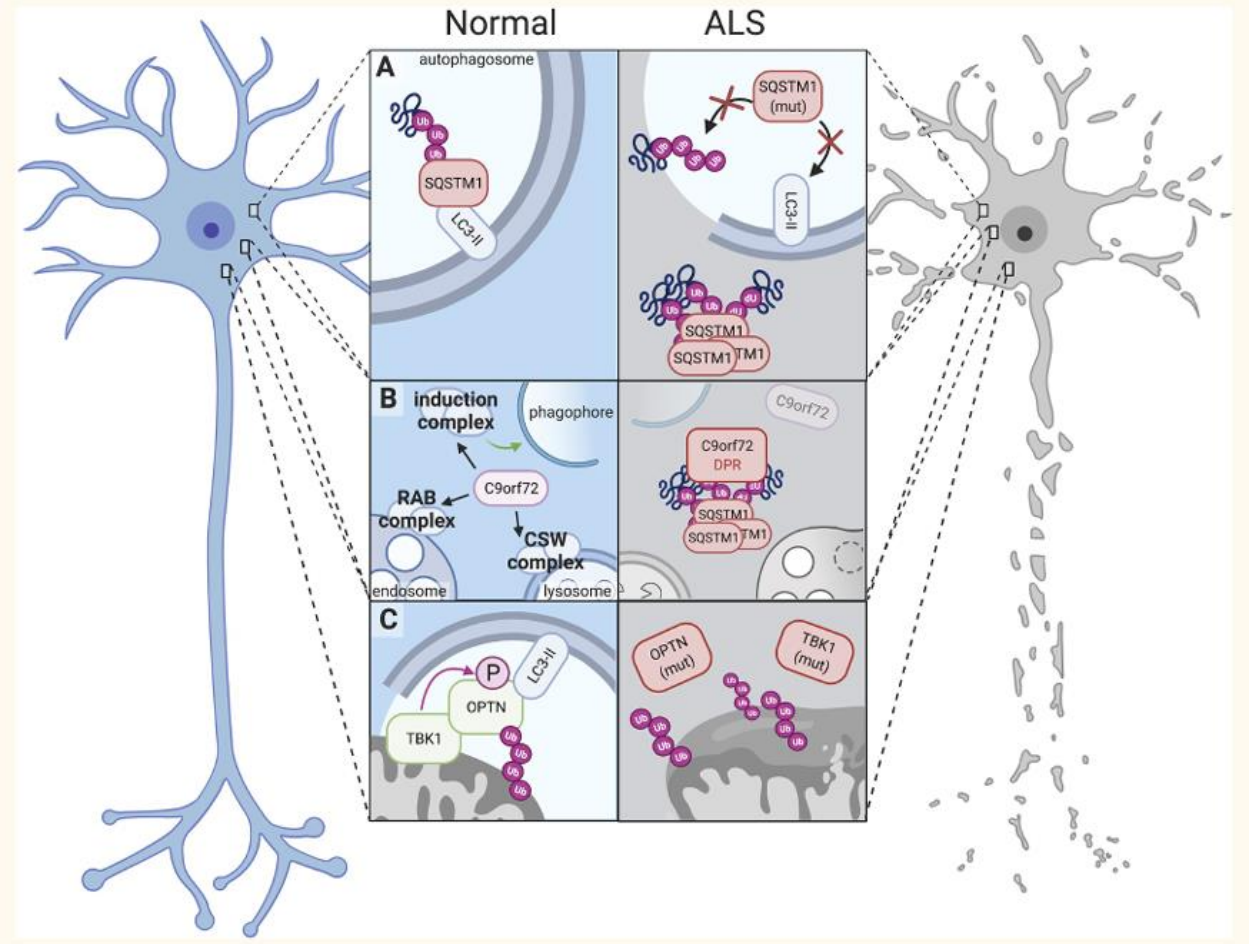

Figure 1. Proteostasis instability together with neurotoxicity occurs because autophagy-related proteins become dysfunctional in ALS patients.

SQSTM1 serves as a receptor autophagy protein in its normal form to link through LC3-II and polyubiquitinated proteins thus targeting ubiquitinated substrates to phagophores (left) but mutations in SQSTM1 break its binding capabilities (right top) and create SQSTM1 aggregations into ubiquitin-positive inclusions (right bottom). The C9orf72 protein participates in three autophagy-related complexes that include the ULK1-RAB1A complex for creating autophagosomes and the RAB7-RAB11 complex for endosome maturation and the C9orf72-SMCR8-WDR41 complex for

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autophagic flux regulation (left). A reduction in C9orf72 protein production occurs because of disease-mutated genes (right) and the C9orf72 expansion produces dipeptide repeat proteins which accumulate within SQSTM1 and all of the octapeptide repeat proteins (right). During normal mitophagy processes TBK1 connects with OPTN while phosphorylating the protein for better recognition of polyubiquitinated mitochondria and LC3-II (left). When TBK1 and OPTN suffer mutations their functions become corrupted which leads to defective mitophagy alongside defective mitochondrial clearance of dysfunctional mitochondria.

Autophagy is involved in the breakdown of dysfunctional proteins and organelles via lysosomal pathways as a fundamental cellular function. It serves to keep neurons fit and to resist protein aggregation, a hallmark of neurodegenerative diseases. New evidence suggests, however, that autophagy could be altered in ALS and may lead to the accumulation of toxic proteins and increased cellular stress. Gene mutations such as C9orf72, SOD1, and TARDBP have been associated with dysregulated autophagic flux, which thus appears to hold an important role in shaping the progression of ALS. Furthermore, the involvement of other genes, such as OPTN and TBK1, which govern selective autophagy, offers stronger evidence supporting the concept that impaired autophagy is a major factor in ALS:a pathogenesis that has continued in recent years.

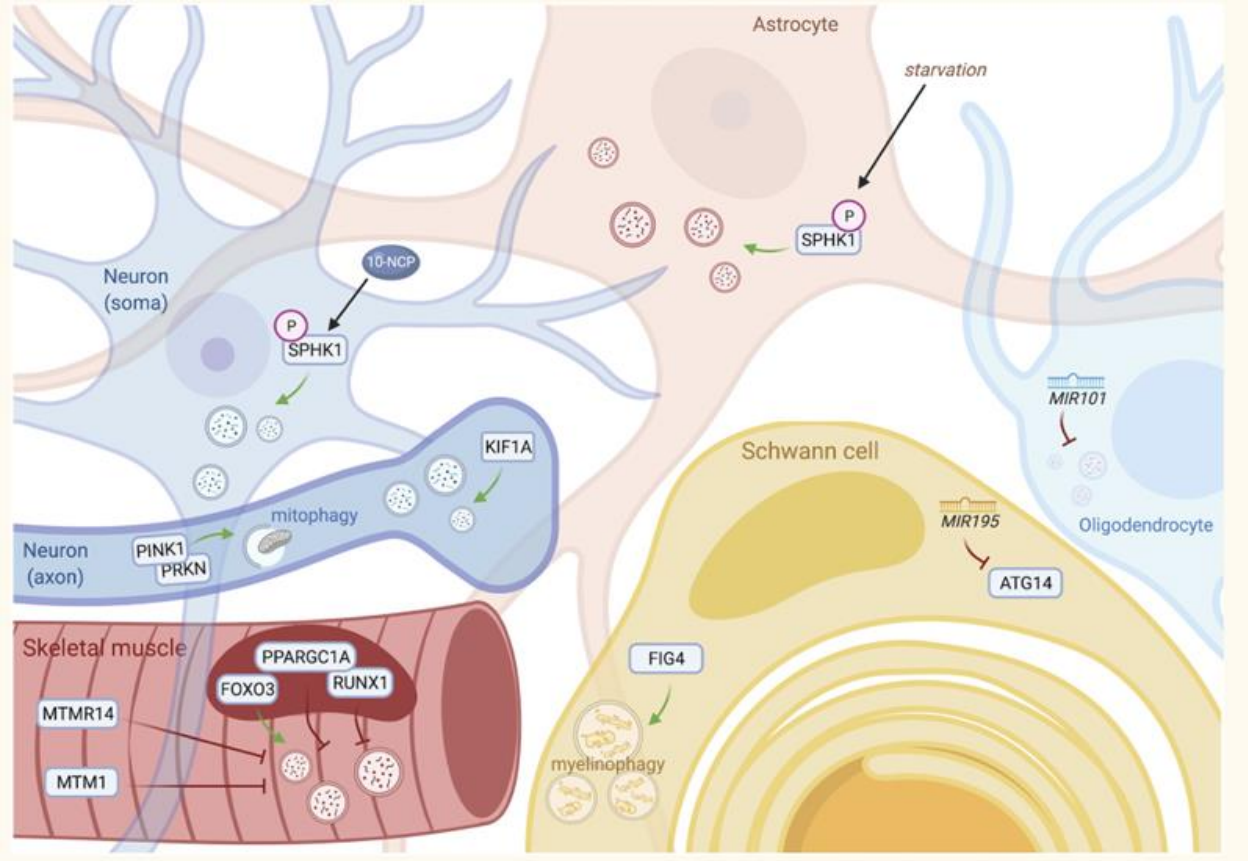

Figure 2. The control of autophagy remains specific to individual cell types inside the nervous system.

Each nervous system cellular component exhibits distinct controllers which affect autophagy expression between CNS and PNS compartments. Primary cells exhibit different autophagic responses

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to 10-NCP and starvation conditions where neurons exclusively respond to phenoxazine compounds yet non-responsive to starvation (top left). Nutrient deprivation within astrocytes (top center) causally activates SPHK1 signaling pathways which results in autophagy development. The activation of autophagic activity in neuron axons occurs through coordination of KIF1A alongside PINK1-PRKN (left, middle). Schwann cells along with oligodendrocytes face blocking of autophagic pathways because of microRNA MIR101 and MIR195 respectively (right). Schwann cells use FIG4-dependent myelinophagy to remove myelin residuals through a specific form of selective autophagy (bottom). The transcription factors FOXO3 cannot activate autophagy in muscle cells because inhibition occurs through PPARGC1A and RUNX1 transcription factors and MTM1 and MTMR14 phosphatases break down necessary phosphoinositides that induce autophagy (bottom left).

ALS impairment also has a causative perspective in mitochondrial dysfunction and aberration in mitophagy. Mutations of CHCHD10 and VCP have been shown to obstruct mitophagy and thereby cause accumulation of injured mitochondria and oxidative stress build-up in neurons [18,19]. Another major attribute of ALS pathology is neuroinflammation, which is connected to impaired autophagic clearance of injured organelles and aggregated proteins, thereby promoting motor neuron degeneration [20]. In view of all these, modulation of autophagy constitutes a promising target for therapeutic intervention in ALS [21].

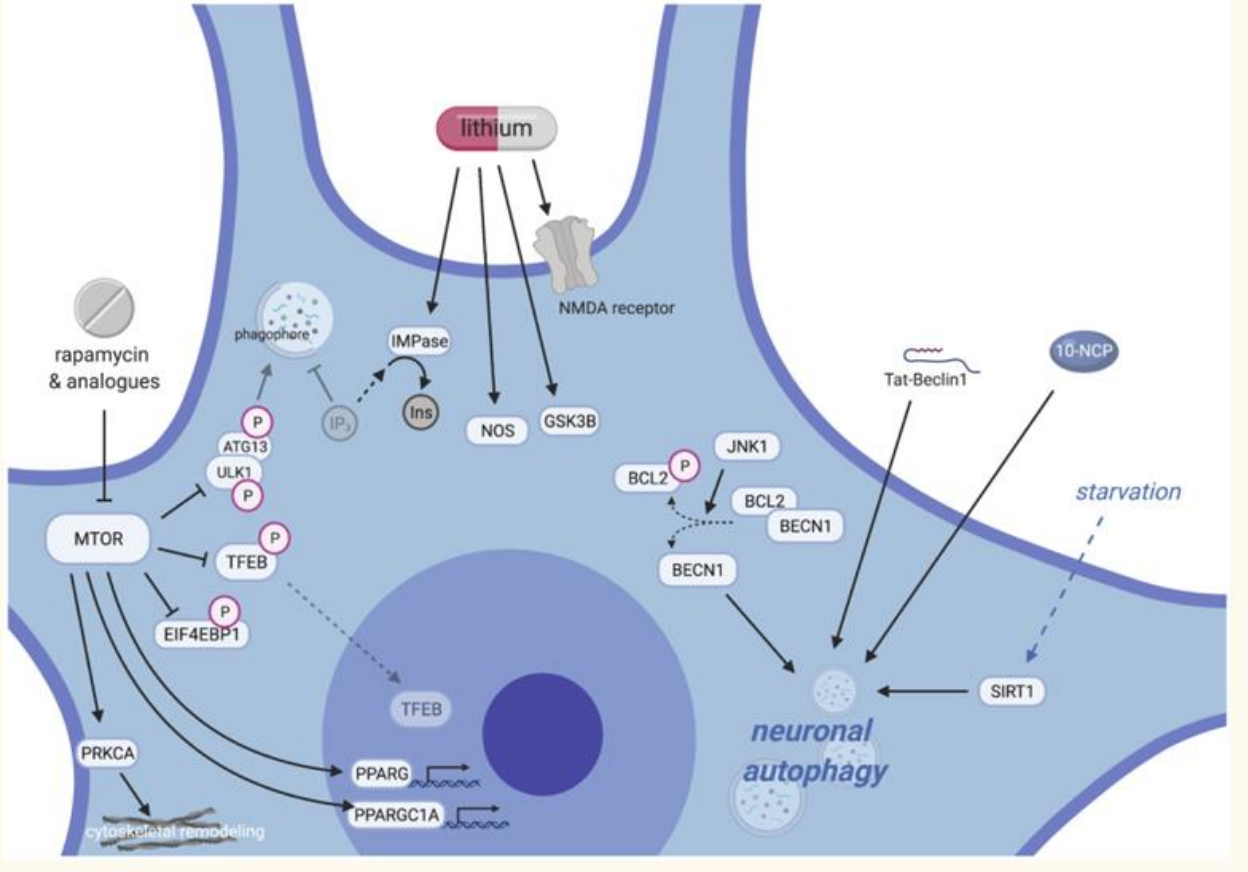

Figure 3. Mechanisms of neuronal autophagy and associated consequences on the therapeutic design of ALS.

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Pharmacodynamic evaluations of drugs employed during current treatment interventions determine factors that regulate autophagy modulation. MTOR inhibitor rapalogs set off minimal autophagy reactions in neuronal cells whereas their approval triggers an array of cellular functions from growth signaling to translation and stress management along with transcription regulation and cytoskeletal rearrangements (left). The diverse effects of rapalog drugs cause widespread documented toxicities throughout multiple body systems during extended administration; nevertheless, newer-generation rapalogs show potential in targeting autophagy specifically and selectively. The various action points of lithium include targeting IPC 3 through IMPase-mediated depletion and NMDA receptor stimulation with augmented glutamatergic signaling as well as activating nitric oxide synthase and GSK3B inhibition together with other effects (middle). Lithium has a restricted medicinal range due to its multiple effects that reduces its protective potential in the nervous system.

The effects in human trials for neurodegenerative disease to date. To reduce off-target effects, recent efforts have focused on MTOR-independent strategies for stimulating autophagy, including By upregulating SIRT1, applying phenoxazine compounds such as 10-NCP, or using synthetic peptides such as Tat-Beclin 1, triggering the selective p62 phosphorylation by ULK1.

protein clearance of aggregates, especially with an emphasis on neuronal homeostasis[34]. Disregulations of the PI3K/AKT/mTOR pathway aggravate the condition of this ladder further, as it plays a vital role in the compromise between the mechanisms of autophagic removal and cellular metabolism [23]. Defective operations of this pathway inhibit autophagic function, thereby enhancing neuronal damage and aggregation of proteins in ABN [24]. Pharmacological interference with these pathways might provide for suitable therapeutic intervention [25].

Oligodendrocyte dysfunction, recent evidence postulates, plays a fundamental role in ALS pathology, second only to axonal apoptosis in affected white matter regions of patient brain tissue [27]. Autophagic impairment of oligodendrocytes contributes to disease progression with an emphasis on the need to target various cellular systems in the hopes of combating ALS [28]. Neuroinflammation as a result of astrocyte and microglia autophagic impairment worsens the loss of neurons in patients with ALS [29].

All of these factors suggest that inducing the process of autophagy might be an avenue of therapeutic intervention in ALS. Activation of the celldefense protein TFEB with the ability to pharmacologically induce autophagy was shown to restore autophagic clearance and reduce neurodegeneration in ALS models [30,31]. Small molecules enhancing autophagy, such as rapamycin and other mTOR inhibitors, have been studied for their neuroprotective effect. [32,33].

Recent data indicate that disturbed autophagy reduces the turnover of stress granules in ALS pathology [35,36]. Stress granules contain RNA-binding proteins such as TDP-43 and FUS, known to generate cytoplasmic aggregates [37] in ALS. Autophagy impairment would therefore impact the clearance of these stress granules, leading to accumulation of toxic protein aggregates [38,39].

The latest insights from transcriptomics and proteomics revealed that the expression of autophagy-related genes was altered in ALS patients [40]. The development of targeted therapies to

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modulate autophagy and restore cellular homeostasis in ALS is therefore imperative.

METHODOLOGY

On the basis of extensive reading, this review presents an exhaustive analysis of peer-reviewed articles retrieved from databases such as PubMed, Scopus, and Web of Science. The keywords included in this literature search were: "ALS," "autophagy," "protein aggregation," "neurodegeneration," and "therapeutic targets". The studies included in this review are based on relevance, recentness, and contributions to understanding autophagy in ALS with both experimental and clinical studies analyzed to offer a comprehensive understanding of the mechanisms underlying autophagy dysfunction in ALS and potential therapeutic strategies.

FUTURE DIRECTIONS

Autophagy modulation is a promising therapeutic approach for ALS; however, some hurdles remain. Future research should strive to theseduce the specific mechanism by which autophagy is perturbed with mutation of genes caused by the disease ALS. Longitudinal studies in the future on autophagy biomarkers may facilitate early diagnosis and therapeutic monitoring [7-14]. Further, selective therapeutic candidates may also prove useful in application to clinics [22-25]. For example, combinatorial contributions of an agent enhancing autophagy together with a neuroprotective agent may give synergy for benefits to ALS treatment. It is indeed possible to obtain targets that regulate autophagy and also optimize their precision medicine approaches through advanced multi-omics technologies such as transcriptomics and proteomics [26,27-40].

CONCLUSION

Autophagy is a crucial determinant for ALS pathogenesis since it drives protein clearance and cellular homeostasis. Dysfunctional autophagy, therefore, is aggravated by neurodegeneration via protein aggregation and mitochondrial impairment. Targeting the autophagic pathways offers a very promising way for ALS treatment, and several pharmacological agents are being studied. However, further studies must refine the autophagy-based therapies, develop reliable biomarkers, and facilitate clinical translation. Meeting these challenges would make modulation of autophagy a potential treatment option to modify disease progression and improve clinical outcome in ALS.

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