Caenorhabditis elegans Models Established for Amyotrophic Lateral Sclerosis

Subjects: Biochemistry & Molecular Biology

Contributor: Yingjie Wu, Yining Chen, Xiaochun Yu, Minxing Zhang, Zhaoyu Li

Amyotrophic lateral sclerosis (ALS) is a lethal motor neuron disease characterised by the selective and gradual loss of motor neurons in the spinal, bulbar and cortical regions. *C. elegans* has established itself as a favoured model organism in the field of neurodegenerative disease research. Through analysis of gene mutations pertinent to these disease, it provides a unique opportunity to identify pathogenic molecular pathways and explore promising therapeutic options.

Keywords: C. elegans ; gain-of-toxicity ; SOD1 ; TDP-43 ; FUS ; C9ORF72

1. Amyotrophic Lateral Sclerosis (ALS)

ALS is a lethal motor neuron disease characterised by the selective and gradual loss of motor neurons in the spinal, bulbar and cortical regions [1]. The vast majority of ALS cases are sporadic, while 5–10% of patients exhibit apparent autosomal dominant inheritance [1][2]. Several causative genes have been linked to familial ALS, including Cu/Zn-binding superoxide dismutase (*SOD1*), TAR DNA-binding protein (*TDP-43*), fused in sarcoma (*FUS*) and the chromosome 9 opening reading frame 72 (*C9ORF72*) [3].

2. Cu/Zn-Binding Superoxide Dismutase (SOD1) Models

SOD1 was first identified as a causative gene of ALS in 1993 [4]. It functions as an antioxidant catalyst for the conversion of superoxide radicals into dioxygen and hydrogen peroxide, essentially preventing superoxide from damaging the cell [5]. To date, over 170 missense point mutations in *SOD1* have been discovered, accounting for 10–20% of familial ALS cases [5][6]. Although the exact molecular mechanism of SOD1 protein-related toxicity has not yet been delineated, increasing evidence supports that mutated SOD1 exerts its cytotoxic effects in a gain-of-function manner, causing aggregation, mitochondrial dysfunction, oxidative stress elevation and proteostasis disruption [7][8].

The gain-of-toxicity effects have been observed in transgenic *C. elegans* by introducing human SOD1 mutants. The overexpression of human SOD1 (G93A) in *C. elegans* motor neurons led to prominent SOD1 aggregates, axon guidance failure and motor defects [9][10]. Similarly, worms with the pan-neuronal expression of human SOD1 (G85R) displayed insoluble SOD1 aggregates, a reduced axonal size and number and significant locomotory impairment [11][12]. When overexpressing disease-associated SOD1 mutations (A4V, G73R and G93A) in *C. elegans* body wall muscles, it yielded similar gain-of-toxicity phenotypes, manifesting as the presence of SOD1 aggregates and severe appearance and locomotion anomalies upon exposure to paraquat-induced oxidative stress compared to a control strain [13]. In general, these studies have managed to recapitulate some of the characteristic clinical phenotypes of ALS, such as the progressive loss of motor capabilities, presence of toxic protein aggregates and axonal abnormalities [14].

The above models in different tissues have greatly facilitated genetic and drug screenings related to SOD1 toxicity. In the mammalian system, SOD1 neurotoxicity has been linked to the proteostasis network. The upregulation of the ubiquitin-proteosome pathway or autophagy activities effectively mitigates SOD1 toxicity [15]. A genome-wide RNA interference (RNAi) screen using the SOD1 (G93A) model in *C. elegans* corroborated the protective role of the proteostasis network in suppressing SOD1 toxicity and identified 63 genetic modifiers that were efficient in alleviating SOD1 aggregation. These modifiers incorporated different aspects of the proteostasis network from the chaperone system and ubiquitin-proteosome pathway to autophagy [16]. In another model, TorsinA, an ER protein acting in a chaperone-like fashion, attenuated SOD1 (G85R)-induced ER stress, promoted the proteasomal degradation of mutant SOD1 protein and rescued behavioural defects [17]. Interestingly, genes regulating ageing have also been identified to modulate SOD1 toxicity. The overexpression of *daf-16* alleviated aggregates formation and reversed the paralytic phenotype elicited by SOD1 mutations. Consistently, metformin, a lifespan extension drug, showed protective effects against SOD1-induced cytotoxicity. It significantly increased the lifespan and mitigated SOD1-induced locomotor dysfunctions, partially relying on

a *daf-16*-dependent pathway [18]. Subsequently, metformin has recently entered a phase 2 clinical trial to examine its safety and efficacy in ALS patients [19].

3. TAR DNA-Binding Protein (TDP-43) Models

Mutations in *TDP-43* account for approximately 3% of familial ALS cases [20]. TDP-43 is a ubiquitously expressed DNA- and RNA-binding protein of 43 kDa that regulates transcription and alternative mRNA splicing and RNA stability [21]. In ALS patients, the sequestration and redistribution of phosphorylated TDP-43 proteins into intracytoplasmic ubiquitinated inclusions, accompanied by a significant depletion in natural nuclear TDP-43, were discovered in their brain samples [21][22][23]. A gain-of-toxicity from nuclear TDP-43 mislocalisation to cytosolic inclusions has been reported to contribute to TDP43 proteinopathy [21][24].

The pan-neuronal expression of ALS-linked human TDP-43 mutants (G290A, A315T, Q331K, M337V) elicited neurotoxicity in *C. elegans*. Worms exhibited distinct neurotoxic features including motor dysfunction, compromised longevity and solid inclusions with phosphorylated protein aggregates, analogous to the hallmarks of TDP-43 proteinopathy in humans [24][25]. When expressed in motor neurons alone, TDP-43 (A315T) caused the progressive deterioration of locomotor function, cytoplasmic insoluble aggregates and motor neuron degeneration, which resembled the cellular phenotypes of human ALS [26].

Phosphorylation has been identified to play an important role in TDP-43 toxicity in *C. elegans*. Using a *C. elegans* model, Liachko et al. [25] located the phosphorylation site at serine residues 409/410 (s409/410), as a main driving factor for the higher toxicity of mutant TDP-43 (G29A, M337V). In addition, a potent phosphatase, calcineurin, was recognised for its precise dephosphorylation at the s409/410 sites. The genetic inhibition of this phosphatase in *C. elegans* profoundly promotes phosphorylated accumulation and aggravates motor deficits [27]. Another drug screen has revealed an alternative potent drug candidate for its neuroprotective effects in treating TPD-43 mutant-caused neurotoxicity that resembles familial ALS characteristics in *C. elegans*. α-Methyl-α-phenylsuccinimide (MPS), an active metabolite of a widely used anti-epileptic drug, ethosuximide, rescued the locomotor deficits and extended the lifespan in the TDP-43 (A315T) model [28]. This effect was mainly mediated through the DAF-16-dependent insulin-like pathway, indicating the importance of the ageing pathway in relation to treating TDP-43 neurotoxicity [28]. These studies exemplify the practicability and robustness of the *C. elegans* model system for the high-throughput drug discovery of new drug candidates.

4. Fused in Sarcoma (FUS) Models

About 4% of familial ALS cases are attributed to mutations in *FUS*, a gene encoding DNA- and RNA-binding proteins that regulate DNA damage, RNA transcription, splicing and transport [29][30]. Similar to TDP-43, the proteinopathy of mutant FUS proteins is characterised by the cytosolic accumulation of toxic FUS aggregates alongside a loss of wild-type [31] proteins, dysfunctional mRNA metabolism and motor neuron degeneration [32][33].

The overexpression of human FUS mutations (R514G, R521G, R522G, R524S and P525L) pan-neuronally in *C. elegans* showed characteristic neuropathological changes, such as cytosolic aggregates, a gradual decline in locomotor activities and a reduced lifespan. The severity of each mutant corresponded to the level of clinical severity of each one in humans and failed to be restored by the WT FUS protein, indicating gain-of-function toxicity [31]. A consistent phenotype was observed in another study conducted by Vaccaro et al. [26], where they introduced full-length FUS variant S57Δ in *C. elegans* motor neurons. Labarre A [34] engineered a single-copy human FUS mutant model in motor neurons, which provoked a similar gain-of-toxicity phenotype, manifesting as progressive locomotory defects and destructive neuromuscular junctions. Prior studies have suggested a link between FUS toxicity and autophagy. For further investigation, Baskoylu et al. [35] introduced disease-causing mutations (R524S, P525L) into *C. elegans* FUS orthologue *fust-1*. The study revealed that the neurotoxicity of *fust-1* was partially due to the disturbance in autophagy following the loss of *fust-1*, highlighting possible cellular mechanisms of FUS proteinopathy [35]. Taken together, these models closely mimic the clinical features of mutant FUS-related ALS cases and provide valuable insights into the cellular mechanisms and pathogenesis of the disease.

5. Chromosome 9 Open Reading Frame 72 (C9ORF72) Models

Hexaneulotide (GGGGCC) repeat expansions within a non-coding region of the *C9ORF72* gene have been implicated to be responsible for 10–40% of familial cases, making this the unprecedently most frequent ALS-causing gene [36][37][38]. C9ORF72 proteins play a role in the regulation of intracellular endolysosome trafficking in the autophagy-lysosome

pathway [39]. Typically, more than 30 hexanucleotide repeats is considered etiopathogenetic, although, in some ALS cases, the repeat counts can reach hundreds to thousands [38][40].

The overexpression of human C9ORF72 in *C. elegans*, consisting of 29 hexanucleotide repeats, either globally or pan-neuronally, causes a severe age-dependent decline in motility in parallel to a shortened lifespan [41]. This finding was further corroborated by a separate study, where worms expressing 75 GGGGCC repeats pan-neuronally developed a shortened lifespan, locomotor defects and distinct dipeptide repeat (DPRs) protein aggregates [42].

Although how exactly C9ORF72 confers toxicity remains enigmatic, a combination of loss-of-function and gain-of-function has been speculated [37][43]. Loss-of-function toxicity is a result of the perturbed regulation of normal gene expression, which ultimately leads to C9ORF72 haploinsufficiency [43]. In terms of gain-of-function toxicity, the leading theory is based on repeat-associated non-AUG (RAN) translation, translating sense and antisense transcripts containing GGGGCC repeats and producing five toxic dipeptide repeat (DPRs) proteins with the propensity to aggregate intracellularly [44]. The five DPRs translated from GGGGCC repeats include poly-glycine-alanine (GA), poly-glycine-proline (GP), poly-glycine-arginine (GR) in the sense direction and poly-proline-arginine (PR) and poly-proline-alanine (PA) in the antisense direction [43]. Several studies have reported that arginine-containing dipeptides PR and GR possess the highest toxicity. Worms expressing 50 repeats of PR or GR in either muscle or motor neurons developed an age-dependent paralytic pattern and stunted growth [45]. It is noted that the nuclear localisation of the peptide is required to exert toxic effects [45]. On this basis, Snoznik, et al. [46] performed a forward genetic screen and identified *spop-1*, an orthologue for human SPOP (a conserved nuclear E3 ubiquitin ligase adaptor protein), responsible for the neurotoxicity of PR50 and GR50. The inhibition of *spop-1* significantly improved the abnormal behavioural phenotypes in worms, presenting a potential druggable target for the alleviation the neurotoxicity of arginine-related dipeptides [46].

References

1. Sabatelli, M.; Conte, A.; Zollino, M. Clinical and Genetic Heterogeneity of Amyotrophic Lateral Sclerosis. Clin. Genet. 2013, 83, 408–416.
2. Funalot, B.; Desport, J.-C.; Sturtz, F.; Camu, W.; Couratier, P. High Metabolic Level in Patients with Familial Amyotrophic Lateral Sclerosis. Amyotroph. Lateral Scler. 2009, 10, 113–117.
3. Caldwell, K.A.; Willicott, C.W.; Caldwell, G.A. Modeling Neurodegeneration in Caenorhabditiselegans. Dis. Model. Mech. 2020, 13, dmm046110.
4. Rosen, D.R.; Siddique, T.; Patterson, D.; Figlewicz, D.A.; Sapp, P.; Hentati, A.; Donaldson, D.; Goto, J.; O'Regan, J.P.; Deng, H.-X.; et al. Mutations in Cu/Zn Superoxide Dismutase Gene Are Associated with Familial Amyotrophic Lateral Sclerosis. Nature 1993, 362, 59–62.
5. Banci, L.; Bertini, I.; Boca, M.; Girotto, S.; Martinelli, M.; Valentine, J.S.; Vieru, M. SOD1 and Amyotrophic Lateral Sclerosis: Mutations and Oligomerization. PLoS ONE 2008, 3, e1677.
6. Kaur, S.J.; McKeown, S.R.; Rashid, S. Mutant SOD1 Mediated Pathogenesis of Amyotrophic Lateral Sclerosis. Gene 2016, 577, 109–118.
7. Kitamura, A.; Inada, N.; Kubota, H.; Matsumoto, G.; Kinjo, M.; Morimoto, R.I.; Nagata, K. Dysregulation of the Proteasome Increases the Toxicity of ALS-Linked Mutant SOD1. Genes Cells 2014, 19, 209–224.
8. Tokuda, E.; Furukawa, Y. Copper Homeostasis as a Therapeutic Target in Amyotrophic Lateral Sclerosis with SOD1 Mutations. Int. J. Mol. Sci. 2016, 17, 636.
9. Li, J.; Huang, K.X.; Le, W.D. Establishing a Novel C. elegans Model to Investigate the Role of Autophagy in Amyotrophic Lateral Sclerosis. Acta Pharmacol. Sin. 2013, 34, 644–650.
10. Li, J.; Li, T.; Zhang, X.; Tang, Y.; Yang, J.; Le, W. Human Superoxide Dismutase 1 Overexpression in Motor Neurons of Caenorhabditis elegans Causes Axon Guidance Defect and Neurodegeneration. Neurobiol. Aging 2014, 35, 837–846.
11. Boccitto, M.; Lamitina, T.; Kalb, R.G. Daf-2 Signaling Modifies Mutant SOD1 Toxicity in C. elegans. PLoS ONE 2012, 7, e33494.
12. Wang, J.; Farr, G.W.; Hall, D.H.; Li, F.; Furtak, K.; Dreier, L.; Horwich, A.L. An Als-Linked Mutant SOD1 Produces a Locomotor Defect Associated with Aggregation and Synaptic Dysfunction When Expressed in Neurons of Caenorhabditis elegans. PLoS Genet. 2009, 5, e1000350.
13. Oeda, T.; Shimohama, S.; Kitagawa, N.; Kohno, R.; Imura, T.; Shibasaki, H.; Ishii, N. Oxidative Stress Causes Abnormal Accumulation of Familial Amyotrophic Lateral Sclerosis-Related Mutant SOD1 in Transgenic Caenorhabditis

elegans. Hum. Mol. Genet. 2001, 10, 2013–2023.

14. Yang, X.; Ji, Y.; Wang, W.; Zhang, L.; Chen, Z.; Yu, M.; Shen, Y.; Ding, F.; Gu, X.; Sun, H. Amyotrophic Lateral Sclerosis: Molecular Mechanisms, Biomarkers, and Therapeutic Strategies. Antioxidants 2021, 10, 1012.
15. Shahheydari, H.; Ragagnin, A.; Walker, A.K.; Toth, R.P.; Vidal, M.; Jagaraj, C.J.; Perri, E.R.; Konopka, A.; Sultana, J.M.; Atkin, J.D. Protein Quality Control and the Amyotrophic Lateral Sclerosis/Frontotemporal Dementia Continuum. Front. Mol. Neurosci. 2017, 10, 119.
16. Silva, M.C.; Fox, S.; Beam, M.; Thakkar, H.; Amaral, M.D.; Morimoto, R.I. A Genetic Screening Strategy Identifies Novel Regulators of the Proteostasis Network. PLoS Genet. 2011, 7, e1002438.
17. Thompson, M.L.; Chen, P.; Yan, X.; Kim, H.; Borom, A.R.; Roberts, N.B.; Caldwell, K.A.; Caldwell, G.A. Torsina Rescues Er-Associated Stress and Locomotive Defects in C. elegans Models of ALS. Dis. Model. Mech. 2014, 7, 233–243.
18. Xu, H.; Jia, C.; Cheng, C.; Wu, H.; Cai, H.; Le, W. Activation of Autophagy Attenuates Motor Deficits and Extends Lifespan in a C. elegans Model of ALS. Free. Radic. Biol. Med. 2022, 181, 52–61.
19. Safety and Therapeutic Potential of the FDA-Approved Drug Metformin for C9orf72 ALS/FTD. Identifier NCT04220021. U.S. National Library of Medicine. 2023. Available online: https://clinicaltrials.gov/study/NCT04220021 (accessed on 22 December 2023).
20. Lagier-Tourenne, C.; Cleveland, D.W. Rethinking Als: The Fus About Tdp-43. Cell 2009, 136, 1001–1004.
21. Sreedharan, J.; Blair, I.P.; Tripathi, V.B.; Hu, X.; Vance, C.; Rogelj, B.; Ackerley, S.; Durnall, J.C.; Williams, K.L.; Buratti, E.; et al. Tdp-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis. Science 2008, 319, 1668–1672.
22. Nakashima-Yasuda, H.; Uryu, K.; Robinson, J.; Xie, S.X.; Hurtig, H.; Duda, J.E.; Arnold, S.E.; Siderowf, A.; Grossman, M.; Leverenz, J.B.; et al. Co-Morbidity of Tdp-43 Proteinopathy in Lewy Body Related Diseases. Acta Neuropathol. 2007, 114, 221–229.
23. Hasegawa, M.; Arai, T.; Akiyama, H.; Nonaka, T.; Mori, H.; Hashimoto, T.; Yamazaki, M.; Oyanagi, K. Tdp-43 Is Deposited in the Guam Parkinsonism-Dementia Complex Brains. Brain 2007, 130 Pt 5, 1386–1394.
24. Zhang, T.; Mullane, P.C.; Periz, G.; Wang, J. Tdp-43 Neurotoxicity and Protein Aggregation Modulated by Heat Shock Factor and Insulin/Igf-1 Signaling. Hum. Mol. Genet. 2011, 20, 1952–1965.
25. Liachko, N.F.; Guthrie, C.R.; Kraemer, B.C. Phosphorylation Promotes Neurotoxicity in a Caenorhabditis elegans Model of Tdp-43 Proteinopathy. J. Neurosci. 2010, 30, 16208–16219.
26. Vaccaro, A.; Tauffenberger, A.; Aggad, D.; Rouleau, G.; Drapeau, P.; Parker, J.A. Mutant Tdp-43 and Fus Cause Age-Dependent Paralysis and Neurodegeneration in C. elegans. PLoS ONE 2012, 7, e31321.
27. Liachko, N.F.; Saxton, A.D.; McMillan, P.J.; Strovas, T.J.; Currey, H.N.; Taylor, L.M.; Wheeler, J.M.; Oblak, A.L.; Ghetti, B.; Montine, T.J.; et al. The Phosphatase Calcineurin Regulates Pathological Tdp-43 Phosphorylation. Acta Neuropathol. 2016, 132, 545–561.
28. Wong, S.Q.; Pontifex, M.G.; Phelan, M.M.; Pidathala, C.; Kraemer, B.C.; Barclay, J.W.; Berry, N.G.; O'Neill, P.M.; Burgoyne, R.D.; Morgan, A. α-Methyl-α-phenylsuccinimide ameliorates neurodegeneration in a C. elegans model of TDP-43 proteinopathy. Neurobiol. Dis. 2018, 118, 40–54.
29. Vance, C.; Rogelj, B.; Hortobágyi, T.; De Vos, K.J.; Nishimura, A.L.; Sreedharan, J.; Hu, X.; Smith, B.; Ruddy, D.; Wright, P.; et al. Mutations in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6. Science 2009, 323, 1208–1211.
30. Dormann, D.; Rodde, R.; Edbauer, D.; Bentmann, E.; Fischer, I.; Hruscha, A.; Than, M.E.; Mackenzie, I.R.A.; Capell, A.; Schmid, B.; et al. ALS-Associated Fused in Sarcoma (FUS) Mutations Disrupt Transportin-Mediated Nuclear Import. EMBO J. 2010, 29, 2841–2857.
31. Murakami, T.; Yang, S.-P.; Xie, L.; Kawano, T.; Fu, D.; Mukai, A.; Bohm, C.; Chen, F.; Robertson, J.; Suzuki, H.; et al. ALS mutations in FUS cause neuronal dysfunction and death in Caenorhabditis elegans by a dominant gain-of-function mechanism. Hum. Mol. Genet. 2012, 21, 1–9.
32. Kwiatkowski, T.J., Jr.; Bosco, D.A.; Leclerc, A.L.; Tamrazian, E.; Vanderburg, C.R.; Russ, C.; Davis, A.; Gilchrist, J.; Kasarskis, E.J.; Munsat, T.; et al. Mutations in the FUS/TLS Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis. Science 2009, 323, 1205–1208.
33. Dormann, D.; Haass, C. Tdp-43 and Fus: A Nuclear Affair. Trends Neurosci. 2011, 34, 339–348.
34. Labarre, A.; Tossing, G.; Maios, C.; Doyle, J.J.; Parker, J.A. A Single Copy Transgenic Mutant Fus Strain Reproduces Age-Dependent ALS Phenotypes in C. elegans. MicroPubl. Biol. 2021.

35. Baskoylu, S.N.; Chapkis, N.; Unsal, B.; Lins, J.; Schuch, K.; Simon, J.; Hart, A.C. Disrupted Autophagy and Neuronal Dysfunction in C. elegans Knockin Models of FUS Amyotrophic Lateral Sclerosis. Cell Rep. 2022, 38, 110195.
36. Renton, A.E.; Majounie, E.; Waite, A.; Simon-Saánchez, J.; Rollinson, S.; Gibbs, J.R.; Schymick, J.C.; Laaksovirta, H.; van Swieten, J.C.; Myllykangas, L.; et al. A Hexanucleotide Repeat Expansion in C9orf72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. Neuron 2011, 72, 257–268.
37. DeJesus-Hernandez, M.; Mackenzie, I.R.; Boeve, B.F.; Boxer, A.L.; Baker, M.; Rutherford, N.J.; Nicholson, A.M.; Finch, N.A.; Flynn, H.; Adamson, J.; et al. Expanded Ggggcc Hexanucleotide Repeat in Noncoding Region of C9orf72 Causes Chromosome 9p-Linked FTD and ALS. Neuron 2011, 72, 245–256.
38. Woollacott, I.O.C.; Mead, S. The C9ORF72 Expansion Mutation: Gene Structure, Phenotypic and Diagnostic Issues. Acta Neuropathol. 2014, 127, 319–332.
39. Farg, M.A.; Sundaramoorthy, V.; Sultana, J.M.; Yang, S.; Atkinson, R.A.; Levina, V.; Halloran, M.A.; Gleeson, P.A.; Blair, I.P.; Soo, K.Y.; et al. C9ORF72, Implicated in Amytrophic Lateral Sclerosis and Frontotemporal Dementia, Regulates Endosomal Trafficking. Hum. Mol. Genet. 2014, 23, 3579–3595.
40. Smeyers, J.; Banchi, E.-G.; Latouche, M. C9ORF72: What It Is, What It Does, and Why It Matters. Front. Cell. Neurosci. 2021, 15, 661447.
41. Wang, X.; Hao, L.; Saur, T.; Joyal, K.; Zhao, Y.; Zhai, D.; Li, J.; Pribadi, M.; Coppola, G.; Cohen, B.M.; et al. Forward Genetic Screen in Caenorhabditis elegans Suggests F57A10.2 and acp-4 As Suppressors of C9ORF72 Related Phenotypes. Front. Mol. Neurosci. 2016, 9, 113.
42. Sonobe, Y.; Aburas, J.; Krishnan, G.; Fleming, A.C.; Ghadge, G.; Islam, P.; Warren, E.C.; Gu, Y.; Kankel, M.W.; Brown, A.E.X.; et al. A C. elegans Model of C9orf72-Associated ALS/FTD Uncovers a Conserved Role for eIF2D in RAN Translation. Nat. Commun. 2021, 12, 6025.
43. Pang, W.; Hu, F. Cellular and Physiological Functions of C9ORF72 and Implications for ALS/FTD. J. Neurochem. 2021, 157, 334–350.
44. Cleary, J.D.; Ranum, L.P. New Developments in RAN Translation: Insights from Multiple Diseases. Curr. Opin. Genet. Dev. 2017, 44, 125–134.
45. Rudich, P.; Snoznik, C.; Watkins, S.C.; Monaghan, J.; Pandey, U.B.; Lamitina, S.T. Nuclear Localized C9orf72-Associated Arginine-Containing Dipeptides Exhibit Age-Dependent Toxicity in C. elegans. Hum. Mol. Genet. 2017, 26, 4916–4928.
46. Snoznik, C.; Medvedeva, V.; Mojsilovic-Petrovic, J.; Rudich, P.; Oosten, J.; Kalb, R.G.; Lamitina, T. The Nuclear Ubiquitin Ligase Adaptor SPOP is a Conserved Regulator of C9orf72 Dipeptide Toxicity. Proc. Natl. Acad. Sci. USA 2021, 118, e2104664118.