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Pathological Interaction between DNA Repair and Mitochondrial Dysfunction in ALS

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of cortical and spinal cord motor neurons. Several mechanisms have been implicated in the pathogenesis of the disease, including mitochondrial dysfunction, oxidative stress, and genome instability. Recently, a combined role between impaired DNA repair and subsequent mitochondrial dysfunction has emerged as a novel pathological interaction in neurodegeneration. This is exemplified by mutations in the RNA-/DNA-binding proteins FUS and TDP-43 as well as superoxide dismutase 1 (SOD1) gene, all related to familial ALS. In this regard, evidence supports either downregulation or impaired recruitment of DNA repair enzymes in both nuclear and mitochondrial genomes. In addition, evidence also suggests a complex metabolic dysregulation as a critical component in the promotion of the disease. This chapter aims to integrate the molecular mechanisms of this pathological interplay and the possible role in cytosolic protein aggregation and cell death in motor neurons.

Keywords: DNA repair, neurodegeneration, mitochondria, motor neuron

1. Genome instability in the context of ALS pathogenesis

ALS has been traditionally classified as sporadic or familial (fALS). Specifically, four genes account for up to 70% of all cases of fALS: *C9orf72*, *TARDBP* (encoding TDP-43), *SOD1*, and *FUS*. Despite the Mendelian inheritance pattern, familial forms of ALS are usually characterized by incomplete penetrance, whereas genetic pleiotropy or oligogenic inheritance is suggested in individuals with sporadic disease [1]. Several hallmarks of neurodegeneration are shared in both familial and sporadic ALS, such as protein aggregation, defective autophagy, impaired DNA damage response (DDR), and mitochondrial dysfunction [1–3]. As ALS is a complex disease, it is plausible to think that regardless of the etiology, there is an interplay between these hallmarks in the pathogenesis and pathological progression.

Considering the late age of onset and the neurological tropism, which is the exclusive neurological affectation, it is possible to highlight some aspects of the nervous system that are useful to understand the molecular pathology of the disease. First, due to its high rate of oxygen consumption and metabolic activity, the nervous system is more susceptible to DNA damage [4]. Single-strand breaks (SSBs) are considered the most common damage to DNA in cells [5], mainly derived

from reactive oxygen species [6]. Even physiological brain activity can also cause DNA double-strand breaks (DSBs) in neurons [7]. However, as neurons do not divide, homologous recombination (HR) is not available for DNA repair. In addition, to maintain normal functioning, neurons must ensure to keep mitochondrial homeostasis. Thus, there are different areas with high demands for ATP like synaptic terminals, active growth cones, or axonal branches that contain more mitochondria than other cellular domains [8, 9]. This dependency on mitochondrial homeostasis makes neurons more susceptible and more likely to be affected by mutations in genes regulating mitochondrial dynamics. For example, mutations in MFN2 and GDAP1 (which regulate mitochondrial fusion and fission, respectively) are related to Charcot-Marie-Tooth [10, 11], a peripheral neuropathy that resembles some of the clinical manifestations of ALS, especially in motor neurons. Thus, a disruption in normal nuclear and mitochondrial DNA (mtDNA) repair would affect motor neurons in a progressive way. Supporting this idea, several works have reported mtDNA mutations in presymptomatic animal models of ALS [12]. In fact, similar to CMT, mitochondrial axonal transportation has also been implicated in ALS. The SOD1-G93A mice showed alterations in the axonal traffic of mitochondria at a presymptomatic stage, specifically in motor neurons [13].

Interestingly, recent studies demonstrated that loss-of-function mutations in *KIF5A* are also a cause of ALS [14, 15]. *KIF5A* gene encodes for a specific motor protein implicated in the axonal transport of mitochondria. Although it was previously related with CMT and spastic paraplegia [16, 17], the new variants associated with ALS are primarily located at the C-terminal cargo-binding tail domain. Notably, patients harboring loss-of-function mutations displayed an extended survival relative to typical ALS cases.

A second aspect behind neurons' susceptibilities is their high rate of transcription. As they depend on the available DNA repair machinery, genomic stability is crucial for the maintenance of homeostasis. Transcription-driven DNA damage can arise from several sources, like the collapse of transcription machinery and subsequent DSBs, damage to genomic segments that have been opened up for transcription, and the formation of unnatural R-loop structures [18–21]. In the case of ALS cells, deficient DNA repair was reported more than three decades ago [22]. It seems that the DDR system in ALS loses adaptive capacity in dependency on the underlying genetic mutation [23]. The next chapter will address the role of the main genes involved in fALS in the generation of genomic instability as a hallmark of neurodegeneration.

2. Role of ALS-related genes in DDR

The hexanucleotide GGGGCC repeat expansion in *C9ORF72* is one of the most common genetic causes of both ALS and frontotemporal dementia (FTD). It was recently demonstrated that these expansions could cause defective DNA repair, manifested by higher levels of DSBs and impaired DDR [24]. Defective ATM-mediated DNA repair was found as a consequence of p62 accumulation, which impairs H2A ubiquitylation and perturbs ATM signaling. Another study reported that c-H2AX, p-ATM, 53BP1, and PARP1 were upregulated in C9orf72 patient spinal cords [25]. However, the mechanism behind the damage to the genome was not addressed. Authors suggest that R-loops, as well as the expression of dipeptide repeat proteins, are more likely to be the cause. Consistent with this notion, elevated levels of DNA damage markers γH2AX, ATR, GADD45, and p53 were present in motor neurons differentiated from iPSC lines from C9orf72-mutant ALS patients in response to oxidative stress [26].

In a model of C9orf72-induced ALS, the overexpression of SETX or depletion of p62 was capable of reducing γH2AX foci in MRC5 cells. In fact, the combined over-expression of SETX and depletion of p62 further reduced DSB levels compared to levels observed by SETX overexpression or p62 depletion alone [24]. Interestingly, mutations in SETX cause both ataxia with oculomotor apraxia type 2 (AOA2) (auto-somal recessive) and amyotrophic lateral sclerosis 4 (ALS4) (autosomal dominant). The N-terminal protein interaction and C-terminal RNA/DNA helicase domains are conserved in the *Saccharomyces cerevisiae* SETX homolog Sen1p. In a mutant model of Sen1p in *S. cerevisiae,* alterations in redox state, unfolded protein response, TOR, and severe loss of mitochondrial DNA were demonstrated [27].

Other ALS-related genes can cause DNA damage. The cytoplasmic inclusions of TDP-43 and FUS seen in ALS can be derived from a toxic gain of function, which, in turn, triggers motor neuron cell death [18]. As the majority of ALS-causing mutations are located within the C-terminus of FUS, it has been suggested that these mutations impair the DNA pairing function of FUS, compromising genome stability [28]. Moreover, depletion of either FUS or TDP-43 in cells treated with α-amanitin (an RNA Pol II inhibitor) led to higher DNA strand breaks [18]. It also was demonstrated that after UV damage-induced transcription arrest, FUS local-izes at genomic sites where active transcription has been arrested by DNA damage, and it does so together with BRCA1 [18]. TDP-43 is also able to localize at sites of transcription-associated DNA damage, given its colocalization with γH2AX and phosphorylated RPA. Interestingly, TDP-43 also colocalized with γH2AX and phosphorylated RPA in undamaged cells, consistent with its role in preventing or repairing spontaneously arising DNA damage [18].

FUS and TDP-43 are also required to maintain R-loop homeostasis since their depletion leads to R-loop-mediated genomic instability [29]. It is speculated that RNA processing factors prevent R-loop by binding to the nascent RNA transcript and blocking R-loop formation. In this regard, it has been shown that FUS and TDP-43 colocalize with active RNA polymerase II at sites of DNA damage along with BRCA1, either to prevent or repair R-loop-associated DNA damage, normally considered an indicator of defective transcription and/or RNA processing [18].

3. Mitochondrial dysfunction in ALS

The space-time location of mitochondria is vital for the metabolic requirements of the nervous system, especially in the case of motor neurons. As neurons can-not rely on glycolysis, mitochondria are crucial to meet the high energy demands mainly by oxidative phosphorylation (OXPHOS). Several aspects of mitochondrial dynamics have been involved in the pathogenesis of ALS. For example, ATP genera-tion was markedly decreased in neuronal cells of mutant SOD1-G93A mice [30, 31]. Moreover, cytosolic ATP levels were significantly reduced in neuroblastoma cells expressing mutant SOD1-G37R and in rotenone-treated SOD1-G93A neuronal cells [32]. Impairment of intracellular Ca^{2+} homeostasis is also considered as a hallmark of mitochondrial dysfunction in neurodegeneration. In this regard, an imbalance in Ca^{2+} dynamics has been reported in cells expressing both mutant SOD1-G93A and SOD1-G37R [33, 34] and in motor neurons from mutant SOD1-G93A transgenic mice [35].

Mitochondrial fusion and fission are also key processes to preserve organelle functioning and cellular homeostasis. Dynamin-related protein 1 (Drp1) influ-ences cell survival and apoptosis by mediating the mitochondrial fission process in mammals [36]. An excessive mitochondrial fragmentation and dysfunction were reported in patient-derived fibroblasts and cultured motor neurons of several

familial forms of ALS expressing SOD1 mutant [37]. In the same article, authors demonstrated that inhibition of Drp1/Fis1 interaction led to a significant reduction in ROS levels and improved mitochondrial function and structure. Mutations in SOD1, TARDBP, or FUS are related to protein aggregation. In this regard, aggregated proteins can also contribute to mitochondrial dysfunction. Moreover, ATP decrease and ROS increase are the main features of mitochondrial damage. While ROS can increase Drp1 leading to sustained mitochondrial fission and fragmentation, a decrease in ATP levels can impair autophagy and proteasomal degradation. This can worsen protein aggregates and trigger ER stress [37, 38].

More than two decades ago, Kong and Xu reported that in mice expressing SOD1-G93A, the onset of the disease involved a decline of muscle strength and a transient explosive increase in vacuoles derived from degenerating mitochondria. Interestingly, this damage did not involve motor neuron death at the time of onset. Based on their results, the authors suggested that SOD1-mutant toxicity was mediated by damage to mitochondria in motor neurons [39]. The early findings of mitochondrial dysfunction were also confirmed by Magrané and colleagues, who studied the mitochondrial transport within the sciatic nerve in SOD1-G93A and TDP-43-A315T mice. Defects of retrograde mitochondrial transport were detected at 45 days of age in both mice, before the onset of symptoms [40]. In the SOD1-G93A mice, mitochondrial morphological abnormalities were apparent at day 15 of age, thus preceding transport abnormalities. Conversely, in TDP-43-A315T mice, morphological abnormalities appeared after the onset of transport defects. Interestingly, the authors reported neither morphological nor mitochondrial distribution changes in sensory neurons [40].

Another study evaluated the role of SOD1 mutations in mitochondrial homeostasis, in spinal cord sections from early symptomatic 10-month mice. Authors showed that mutant SOD1 binding to mitochondria disrupts normal distribution and morphology as an early pathogenic feature. In their work, mitochondria from SOD G85R/G37R mice became progressively smaller and rounder and are unevenly distributed along axons [41]. As in SOD1 mutant experiments, oxidative stress and DNA damage were increased in iPSC-derived C9ORF72 motor neurons in an age-dependent manner [26]. Poly (GR) preferentially binds to mitochondrial ribosomal proteins and compromised mitochondrial function, which could lead to increased oxidative stress. Reducing oxidative stress partially rescued DNA damage in C9ORF72 motor neurons cells [26].

The role of mutant FUS and TDP-43 has also been evaluated in mitochondrial dysfunction. In cultured neurons expressing FUS-R495X, it was revealed that mutant FUS controlled the translation of genes that were associated with mitochondria function, which resulted in a significant reduction of mitochondrial size [42]. Specifically, protein levels of KIF5B, DNM1L, and CSDE1 were significantly reduced in R495X-expressing neurons. FUS is also able to translocate and accumulate inside mitochondria. Following this approach, it was revealed that FUS could interact with mitochondrial chaperonin HSP60 and this interaction mediates FUS localization to the organelle, leading to damage [43]. This damage derives from reduced mitochondrial membrane potential and increased production of ROS. Authors also reported elevated HSP60 expression in two of three cases of FTLD-FUS patients' brain samples. Curiously, mutations in the *HSPD1* gene which encodes for HSP60 protein have also been found in patients with spastic paraplegia type 13 [44]. Another work revealed that mitochondrial impairment is a critical early event in FUS proteinopathy. When mutant FUS-P525L accumulated inside mitochondria, it interacted with the mitochondrial ATP synthase catalytic subunit ATP5B and reduced mitochondrial ATP synthesis. Importantly, FUS accumulation also induced the mitochondrial unfolded protein response (UPTmt), making the damage even worse [45].

Similarly, mutant TDP-43 accumulates in the mitochondria of neurons in subjects with ALS or frontotemporal dementia (FTD). Wild-type and mutant TDP-43 preferentially bind to mitochondria-transcribed mRNAs encoding respiratory complex I subunits ND3/ND6, causing complex I disassembly [46]. The suppression of TDP-43 mitochondrial localization abolished mitochondrial dysfunction and neuronal loss and improved the phenotypes of transgenic mutant TDP-43 mice. Mutant FUS can also alter mitochondrial-endoplasmic reticulum (ER) communication. Stoica and colleagues showed that FUS disrupts the VAPB-PTPIP51 complex, impairing ER-mitochondria association. As a consequence, there was a perturbation of Ca^{2+} uptake by mitochondria and impaired ATP production [47]. Remarkably, inhibition of glycogen synthase kinase-3b (GSK-3b) corrected FUS-induced defects in ER-mitochondria associations and mitochondrial Ca^{2+} levels.

Mitochondrial DNA damage is also important in the context of neurodegenerative diseases [48, 49]. Maintaining mitochondrial DNA stability is critical for cellular function, especially in the context of the nervous system. Several pathways have been implicated in mtDNA repair, but base excision repair (BER) is the predominant one [50]. Oxoguanine glycosylase 1 (OGG1) is an enzyme that plays a major role in the mitochondrial BER pathway, removing 8-hydroxy-2-deoxyguanosine (8-OHdG). In the spinal cord of SOD1 mutant transgenic mice, the presence of 8-OHdG was progressively accumulated in the ventral horn neurons from early and presymptomatic stage (25 weeks) [51]. This was a suggestion that an oxidative damage to mitochondrial DNA was affecting spinal motor neurons at a very early stage of the disease. Early and selective impairment of DNA repair enzymes in mitochondria was also reported in presymptomatic transgenic mice carrying a mutant SOD1 gene [51]. Notably, the selective expression of these enzymes in spinal neurons is closely related to the selective involvement of motor neurons in ALS.

In the ALS but not control brains, levels of a common mitochondrial DNA deletion mutation (mt DNA4977) were an average of more than 30-fold in Brodmann area 4 [52]. In addition, the oxidative damage derived from 8-oxoG was accumulated in the mitochondria of motor neurons in ALS, and according to previous findings, OGG1 did not repair the damage efficiently, driving the loss of motor neurons in ALS [53]. Likewise, motor neurons in G93A-mSOD1 transgenic mice undergo slow degeneration characterized by mitochondrial swelling and formation of DNA single-strand breaks prior to double-strand breaks occurring in both nuclear and mitochondrial DNA [54]. These cells accumulated mitochondria from the axon terminals and generated higher levels of ROS/RNS. Despite experimental evidence demonstrating mtDNA damage, more research is required to elucidate the mechanisms that lead to mitochondrial damage in ALS. The mechanisms that can link the DNA repair deficiency induced by errors in ALS-associated proteins and the subsequent mitochondrial dysfunction in terms of genetic integrity are not yet understood. We believe that this is an issue that should be taken into account for future studies.

4. Nuclear-mitochondrial interplay and genomic integrity in ALS

4.1 The role of SIRT1-PARP1 axis

Poly (ADP-ribose) polymerase 1 (PARP1) is a NAD+-dependent protein. It is able to posttranslationally modify itself and other proteins involved in multiple DDR. PARP1 is also crucial for the stabilization of DNA replication forks and chromatin remodeling [55]. Deletion of *Parp1* gene in *Xrcc1* knockout mice is able to prevent neurodegeneration, indicating that the overactivation of PARP1 is a neurotoxic

consequence of defective DNA repair [56]. Recently, it was demonstrated that FUS can bind directly to PAR, the polymer made by PARP1 [57]. Authors revealed that FUS is recruited to chromosomal sites of oxidative DNA damage and that this recruitment is reduced by the FUS-R521G mutation. Additionally, when cells lack PARP1, FUS failed to accumulate at sites of UVA laser-induced damage. Moreover, under oxidative stress, PARP1 activity increases, leading to an accumulation of ADP-ribose polymers and NAD+ depletion. This condition induces a metabolic and energetic crisis driving cell death [58]. As PARP1 hyperactivation and toxicity have been implicated in diseases like Alzheimer's, Parkinson's, and Huntington's, a predominant role in ALS is also plausible [59].

Sirtuins are also NAD-dependent proteins. SIRT1 is known as a nuclear and cytoplasmic deacetylase, which is predominantly expressed in neurons in the context of the nervous system [60]. Notably, PARP1 consumes NAD+, reducing SIRT1 activity by increasing PARylation of DNA and proteins involved in DDR. Thus, SIRT1 activity appears to be impeded by PARP1 hyperactivation [61]. Interestingly, NAD+ replenishment shows a reactivation of SIRT1 and prevented neurodegeneration [62]. Thus, compromised DNA repair leads to PARP1 hyperactivation, resulting in the depletion of NAD+ levels, inhibiting SIRTs (**Figure 1**). Notably, the Km of SIRT1 for NAD+ is higher than that of PARP1, so when NAD+ levels become so low following cell stress or senescence, SIRT1 no longer has the chance to regulate the activity of PARP1 [61]. Cantó and colleagues demonstrated that deletion of *Parp1* gene increased NAD+ levels and SIRT1 activity in brown adipose tissue and muscle. *Parp1* −/− mice presented a higher mitochondrial content, resulting in increased energy expenditure and protection against metabolic disease. As previously reported, authors showed that pharmacologic inhibition of PARP in vitro and in vivo increased NAD+, leading to SIRT1 expression and enhanced oxidative metabolism [63].

SIRT1 is vital in the maintenance of metabolic homeostasis [64]. SIRT1 can activate the peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) through deacetylation [65]. PGC-1a can regulate genes of the ROS defense system. It has been shown that PGC-1a can protect WT neural cells from oxidative stress by increasing the expression of ROS-detoxifying genes including SOD1/SOD2 and UCP2 [66]. SIRT1 may also deacetylate PGC-1α to induce mitochondrial biogenesis by increasing mitochondrial gene expression via nuclear respiratory factor 1 (NRF-1) and nuclear-encoded mitochondrial transcription factor A (TFAM) [67]. Interestingly, it was revealed that PGC-1 and SIRT1 are also present inside the mitochondria and are in close proximity to mtDNA [68]. In addition, an unexpected role for serotonin (5-HT) was also recently demonstrated. Fanibunda and colleagues showed that in rodent cortical neurons, serotonin is a regulator of mitochondrial biogenesis, via 5-HT2A receptor-mediated recruitment of the SIRT1-PGC-1α axis [69].

SIRT1 can form a protein complex with the Forkhead transcription factor FOXO3 and promote its deacetylation. SIRT1 induces several effects mediated by FOXO3 like cell cycle arrest and transcription of DNA repair target genes [70]. Cantó and colleagues demonstrated that AMPK enhances SIRT1 activity by increasing cellular NAD+ levels [71]. This resulted in the deacetylation and modulation of the activity of downstream SIRT1 targets including PGC-11α and FOXO1/FOXO3a transcription factors. Thus, SIRT1 could promote both mitochondrial biogenesis in conditions of energy deficiency in disease or induce the clearance of damaged mitochondria [72].

In XPA-deficient cells, a model of xeroderma pigmentosum, the DNA repair deficiency leads to PARP1 activation, and the attenuated NAD+/SIRT1/PGC-1α axis resulted in defective mitophagy. The condition could be rescued either by
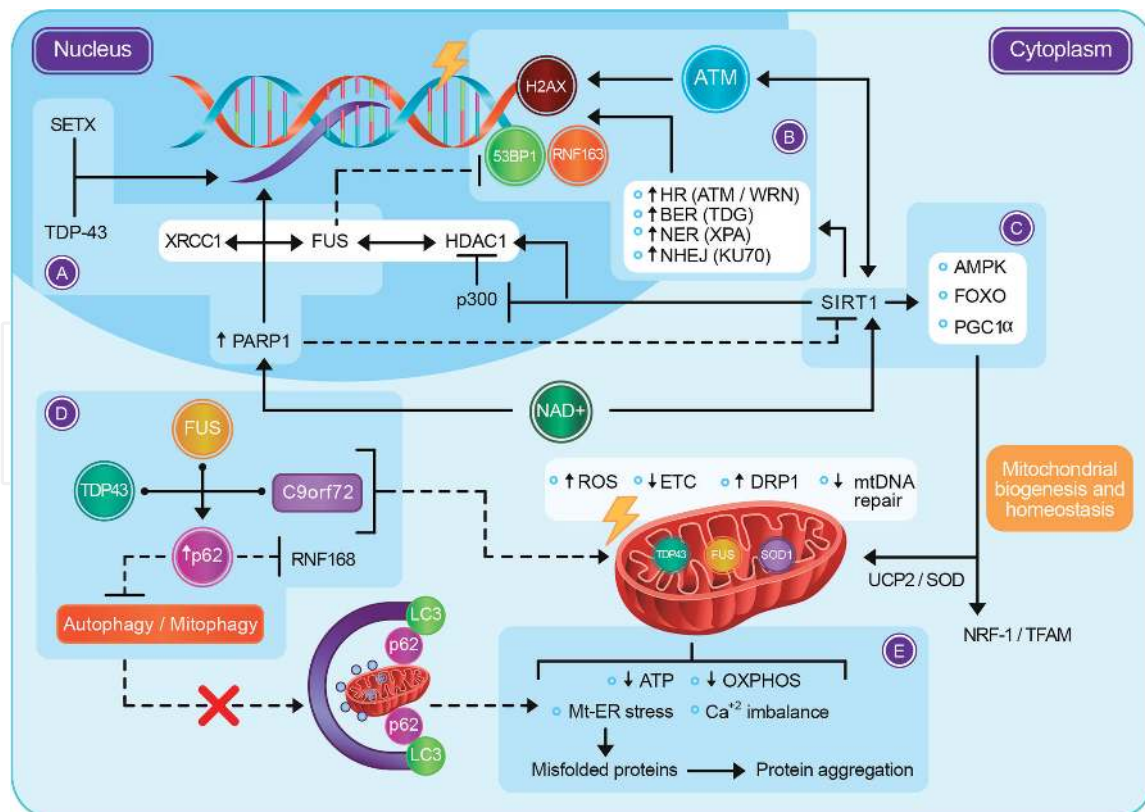
Figure 1.
Nuclear-mitochondrial interplay in the context of ALS. (A) Activation of PARP1 upon DNA damage facilitates DNA repair but inhibits SIRT1 due to NAD+ depletion. FUS binds directly to PAR, the polymer made by PARP1 in chromosomal sites of oxidative DNA damage. Both TDP-43 and FUS localize at genomic sites where active transcription has been arrested by DNA damage and also maintain R-loop homeostasis. SETX is also necessary for R-loop repair. In addition, FUS interacts with HDAC1 and enhances its activity in both physiological conditions and DNA damage. (B) SIRT1 positively regulates DDR. SIRT is able to deacetylase HDAC1, ATM, WRN, TDG, XPA, and KU70. (C) SIRT1 also regulates mitochondrial homeostasis through AMPK, FOXOs, and PGC1α. These enzymes regulate mitochondrial biogenesis and oxidative stress, transcribing proteins such as UCP2 and SODs. (D) Accumulation of misfolded proteins leads to the aberrant p62 expression, disrupting normal mitophagy. Likewise, defective ATM-mediated DNA repair is a consequence of p62 accumulation and RNF168 inhibition. C9orf72 can also cause defective DNA repair and p62 accumulation with the subsequent impaired mitophagy. (E) ALS-related mitochondrial dysfunction leads to mitochondrial fragmentation through DRP1 overexpression, decreased ATP production, higher ROS levels, mtDNA damage, decrease in OXPHOS, and Ca+2 imbalance. FUS can accumulate inside the mitochondria, leading to impaired ATP production and increased ROS levels. C9ORF72 can also generate oxidative stress and mtDNA damage in motor neurons. TDP-43 preferentially bind to mitochondria-transcribed mRNAs, causing complex I disassembly. SOD1 mutations can decrease cytosolic ATP levels, impair intracellular Ca2+ homeostasis, generate excessive mitochondrial fragmentation, and deregulate DDR. The final effect of this cascade is derived from mitochondria-ER stress, consequent misfolded proteins, and further protein aggregation. Dotted lines illustrate pathological interactions.

PARP1 inhibition or by supplementation with NAD+ [73]. In a different work, Scheibye-Knudsen and colleagues showed that hyperactivation of PARP1 drives SIRT1 depression in Cockayne syndrome (CS). Similar to previous findings, NAD+ replenishment rescued the phenotype in CS, but in this case, they also demonstrated that diet can also increase SIRT1 activity [62]. Following the same line, it was revealed that NAD+ levels are reduced in aged mice and *Caenorhabditis elegans* [74]. Genetic or pharmacological restoration of NAD+ prevented age-associated metabolic decline and promoted longevity in worms. These effects were associated with deacetylase sir-2.1 levels, the homolog of SIRT1. Indeed, hyperacetylation of the SIRT1 substrate PGC-1α resulted from low levels of NAD+ in aged mice [74]. Supporting this approach, it was demonstrated that the intracellular nicotinamide phosphoribosyltransferase (iNAMPT) is essential to projection neuron function and viability. The iNAMPT is the rate-limiting enzyme of the mammalian NAD+ biosynthesis. When eliminating *Nampt* in adult mice, the resulting phenotype

resembled ALS: motor neuron degeneration, hypothermia, motor dysfunction and paralysis, reduced general motor activity, and anxiety-like behaviors. Remarkably, nicotinamide mononucleotide (NMN), a NAD+ precursor, improved health span, restored motor function, and extended lifespan [75]. Since the authors also found that iNAMPT protein levels were significantly reduced in the spinal cord of ALS patients, the NAD+/SIRT1 axis represents an outstanding therapeutic opportunity.

For a long time, the beneficial effect of resveratrol has been controversial due to inconsistent results and tissue-dependent effects. Price and colleagues showed that a moderate dose of resveratrol is able to stimulate the AMPK activity, increase NAD+ levels, enhance mitochondrial biogenesis, and improve mitochondrial function. All of these functions were entirely dependent upon SIRT1 in skeletal muscle [76]. Interestingly, a tenfold higher dose of resveratrol activated AMPK in a SIRT1-independent manner, although improvements in mitochondrial function were SIRT1 dependent [76]. Finally, it was demonstrated that resveratrol-mediated SIRT1 activation protects against p25 and mutant SOD1-G93A neurotoxicity both in vitro and in vivo [77].

4.2 The role of SIRT in DDR

Beyond its role in metabolism, SIRT1 is also important in DNA repair. In post-mitotic neurons, SIRT1 was rapidly recruited to DSBs where it showed a synergistic relationship with ATM, stimulating its autophosphorylation and stabilizing ATM at DSBs' sites [78]. Additionally, authors reported that after DSBs' induction, SIRT1 also bound HDAC1, a neuroprotective histone deacetylase, stimulating its enzymatic activity. This activity is necessary for the nonhomologous end joining (NHEJ) pathway [78]. Likewise, upon exposure to radiation, SIRT1 can enhance DNA repair capacity and deacetylation of repair protein Ku70, involved in NHEJ as well [79].

SIRT1 also interacts with WRN both in vitro and in vivo, and this interaction is enhanced after DNA damage [80]. WRN is a member of the RecQ DNA helicase family with functions in maintaining genome stability. Moreover, the MRE11-RAD50-NBS1 (MRN) is a conserved nuclease complex that exhibits properties of a DNA damage sensor in the context of DSBs. SIRT1 can associate with the MRN complex and maintains NBS1 in a hypoacetylated state following ionizing radiation [81]. SIRT1 is also important for the base excision repair (BER) pathway. It was shown that SIRT1 deacetylates APE1 in vitro and in vivo following genotoxic insults [82]. Knockdown of SIRT1 increases cellular abasic DNA content, sensitizing cells to death induced by genotoxic stress. Interestingly, the activation of SIRT1 with resveratrol promoted binding of APE1 to XRCC1 [82]. Thymine DNA glycosylase (TDG) is an essential multifunctional enzyme also involved in BER. SIRT1 was shown to interact with TDG and enhance its glycosylase activity due to deacetylation [83]. Nucleotide excision repair (NER) is another important pathway in DNA repair. NER removes DNA damage induced by ultraviolet light (UV). Xeroderma pigmentosum group A (XPA) is a critical protein for this process. SIRT1 interacts with XPA, and the interaction is enhanced after UV irradiation [84]. In fact, down-regulation of SIRT1 sensitized cells to UV irradiation.

4.3 The role of FUS in DDR

FUS is important for both NHEJ- and HR-mediated DSB repair in neurons. As SIRT1, FUS interacts with HDAC1 and enhances its activity in both physiological conditions and DNA damage in cortical neurons [85]. The same was demonstrated in human-induced pluripotent stem cells (hiPSCs) and hiPSC-derived motor neurons. The degree of FUS mislocalization correlated well with the clinical severity

of the underlying ALS, with a higher accumulation of DNA damage in postmitotic mutated FUS motor neurons than in dividing hiPSCs [86]. Although FUS has been associated with multiple DNA repair pathways including DSB repair, quantification of the level of DNA SSBs vs. DSBs in FUS knockdown (KD) and knockout (KO) cells by comet analysis revealed that most unrepaired DNA strand breaks that accumulated after the loss of FUS were SSBs [87].

FUS protects the genome by facilitating PARP1-dependent recruitment of XRCC1/DNA ligase IIIα (LigIII) to oxidized genome sites and activating LigIII via direct interaction [88]. Cells presenting mutant FUS showed a significantly reduced association between this DNA repair protein complex, SSBs' accumulation, and ROS levels in motor neurons. LigIII was demonstrated to be essential enzyme for mtDNA integrity but dispensable for nuclear DNA repair [89]. LigI was critical for nuclear DNA repair in a cooperative manner with LigIII, but inactivation of LigIII resulted in mtDNA loss, mitochondrial dysfunction, and incapacitating ataxia in the mouse nervous system. However, as neurons do not divide, it is possible that LigIII is equally important for nuclear DNA repair. Following the idea that mtDNA integrity is vital in postmitotic tissues, the authors also found that inactivation of LigIII in cardiac muscle resulted in mitochondrial dysfunction and defective heart-pump function leading to heart failure [89]. More research is needed to elucidate the interaction of ALS-associated proteins with both nuclear and mitochondrial DNA repair enzymes (**Figure 1**).

4.4 Cross talk between auto-/mitophagy and DNA repair in ALS

Autophagy is a crucial process to eliminate misfolded proteins and organelles. Mitophagy is a special subroutine of autophagy, involved in the maintenance of mitochondrial homeostasis. An important protein regulating this process is p62. The molecular mechanism of p62-mediated mitochondrial defective clearance was demonstrated by Geisler and colleagues [90]. Knockdown of p62 significantly diminished mitochondria recognition by the autophagy machinery and its subsequent elimination [91]. Notably, accumulation of misfolded proteins leads to the aberrant p62 expression, which influences the balance of mitophagy, worsens mitochondrial dysfunction, and induces more protein aggregates [92]. This can explain the vulnerability of non-cycling cells to proteinopathies in the context of mitochondrial dysfunction [93–96].

Autophagy is also important to maintain functional DNA repair by preventing p62 accumulation. In the context of ALS, where p62 accumulates, RNF168-mediated H2A ubiquitylation (U) is perturbed, leading to impaired DSBs' repair and genomic instability [29]. Wang and colleagues reported that p62/SQSTM1, which accumulates in autophagy-defective cells, directly binds to and inhibits nuclear RNF168, which is crucial for histone H2A ubiquitination and DNA damage responses. As a result, DNA repair proteins such as BRCA1, RAP80, and Rad51 cannot be recruited to the sites of DNA double-strand breaks (DSBs), which impairs DSBs' repair [97]. The interaction between mitochondrial dysfunction, defective mitophagy, and protein aggregation should be the subject of further investigation. This could generate new therapeutic avenues in the context of neurodegenerative diseases that occur with proteinopathies.

5. Therapeutic challenges and opportunities

Despite the clear role of mitochondria in neurodegeneration, the application of translational medicine in this field remains to be addressed. The lack of new

therapeutic options and the limitations of current genetic editing techniques make it difficult to have a clear path for future research. Due to the failure in targeting specific aspects of mitochondria, mitochondrial transplantation presents a new paradigm of therapeutic intervention that may benefit neuronal survival and regeneration in ALS and similar diseases. The clinical application of mitochondrial transplantation was extensively reviewed by Chang and colleagues already [98].

The importance of this approach has been demonstrated in different lines of research. For example, it was shown that astrocytes in mice release functional mitochondria that enter neurons and amplify cell survival signals after stroke [99]. Cardiomyocytes share several similitudes with neurons, including the postmitotic state, the high transcription rate, the similar metabolic profile, and the underlying dependence on mitochondrial homeostasis. Following myocardial ischemia and reperfusion (IR), several alterations have been demonstrated in mitochondrial structure and function. Mitochondrial transplantation has been proposed as a strong opportunity for the treatment of IR [100]. Masuzawa and colleagues showed in a model of ischemia-reperfusion injury that transplantation of autologously derived mitochondria immediately prior to reperfusion ameliorated the damage. By using New Zealand white rabbits, they demonstrated a complete recovery and showed that the transplanted mitochondria enhanced oxygen consumption, high-energy phosphate synthesis, and enhanced post-infarct cardiac function [101].

In a model of Parkinson's disease induced by the respiratory chain inhibitor MPTP, Shi and colleagues demonstrated in mice that intravenous injection of mitochondria prevented the progression of the disease. Specifically, the authors reported increased activity of the electron transport chain, decreased ROS levels, and prevention of cell apoptosis and necrosis [102]. Other approaches have been addressed following this so-called mitochondrial medicine approach in ALS, such as ketogenic diet, antioxidants, and metabolic targeting drugs [103]. Based on the evidence provided until this point, mitochondrial transplantation should be validated as a therapeutic option in ALS. The safety and efficacy, delivery strategies, the periodicity of the transplant, and the capture by the cells of interest should be rigorously analyzed experimentally. Thus, if its effectiveness is proven in animal models, hopefully, clinical trials can be performed soon.

6. Conclusions

The DNA repair deficiency is a hallmark that combines at the pathological level with mitochondrial dysfunction, which highlights the special dependence of neurons on genomic integrity and metabolic stability. This highlights what we called the pathological tropism of the nervous system. At this point, it is clear that whatever the etiology behind ALS and motor neuron degeneration, mitochondrial dysfunction is present in all fALS and sporadic ALS patients. The fact that mitochondrial damage appears in the presymptomatic stage of the disease raises an opportunity for targeting mitochondria and hopefully makes disease progression slower or even stops it. Mitochondrial transplantation represents a promising avenue for the following years, as well as NAD+ repletion therapy and mitophagy-inducing agents.

Acknowledgements

Conflict of interest

The authors declare no conflict of interests.

Nomenclature

ALS	amyotrophic lateral sclerosis
fALS	familial amyotrophic lateral sclerosis
DDR	DNA damage response
DSBs	double-strand breaks
NAD+	nicotinamide adenine dinucleotide
SETX	senataxin
ROS	reactive oxygen species
RNS	reactive nitrogen species
NHEJ	nonhomologous end joining
BER	base excision repair
SIRT	Sirtuin 1
FUS	fused in sarcoma
HDAC1	histone deacetylase 1
HiPSCs	human-induced pluripotent stem cells
PARP1	poly (ADP-ribose) polymerase 1
XRCC1	X-ray repair cross-complementing 1
TDP-43	TAR DNA-binding protein 43
SOD1	superoxide dismutase 1
C9orf72	chromosome 9 open reading frame 72
SSBs	single-strand breaks
HR	homologous recombination
MFN2	mitofusin 2
GDAP1	ganglioside-induced differentiation-associated protein 1
mtDNA	mitochondrial DNA
KIF5A	kinesin heavy chain isoform 5A
ATM	ataxia telangiectasia mutated
53BP1	p53-binding protein 1
UPRmt	mitochondrial unfolded protein response
FTD	frontotemporal dementia
ER	endoplasmic reticulum
GSK-3b	glycogen synthase kinase-3b
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator-1 alpha
iNAMPT	intracellular nicotinamide phosphoribosyltransferase
NMN	nicotinamide mononucleotide
RNF168	RING-type E3 ubiquitin transferase
BRCA1	breast cancer 1
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
AMPK	MP-activated protein kinase
FOXOs	forkhead box O proteins

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