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Review article

Oxidative stress and mitochondrial damage in the pathogenesis of ALS: New perspectives

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ABSTRACT

This review attempts to reconcile the present dual view of the mechanisms operating in Amyotrophic Lateral Sclerosis (ALS). On one side, oxidative stress, mitochondrial damage and protein aggregation are considered as causative of the disease, as strongly supported by evidence obtained in models based on the expression of ALS-typical mutant SOD1. On the other hand, evidence from models expressing ALS-typical mutations in RNA-binding proteins such as FUS and TDP43 indicate that mRNA (dys)metabolism is a major pathway in this disease. A critical analysis of existing literature suggests that there may be more than one point of intersection.

Contents

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a fatal motor neuron disease characterized by degeneration of upper and lower motor neurons. Despite patients show a large variability in age and site of onset, as well as severity and involvement of cognitive deficits, they almost invariably die for respiratory failure within few years after diagnosis [1]. ALS cases are classically subdivided in sporadic forms (sALS) and familial forms (fALS) due to inheritable, mostly autosomal dominant, genetic mutations. This definition is not univocal: the classification of affected individuals may depend on the knowledge of the family history, the technique used to detect the mutation and on how penetrant the disease gene is. Thus, it is not surprising that gene mutations causing fALS are also found in a significant proportion of apparently sporadic cases [2]. This is the case for mutations in the gene encoding the ubiquitous enzyme Cu, Zn superoxide dismutase (SOD1).

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; FTLD, Frontotemporal Lobar Degeneration; mPOS, mitochondrial precursor over-accumulation stress; ROS, Reactive Oxygen Species; UPRam, Unfolded Protein Response Activated by Mistargeting of proteins; UPRmt, mitochondrial unfolded protein response.

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SOD1 is a mainly cytosolic antioxidant enzyme, converting superoxide to molecular oxygen and hydrogen peroxide. Its pivotal function in the complex defense against Reactive Oxygen Species (ROS) that are produced by the cell during normal cellular metabolism has obviously suggested a role for oxidative stress in the pathogenesis of ALS. Evidence for a role of oxidative stress in ALS comes from analysis of post-mortem tissues from fALS and sALS patients showing a widespread accumulation of oxidative damage to proteins, lipids and DNA [3]. Transgenic mice expressing mutant human SOD1 forms, that experience age-dependent motor neuron degeneration with cellular and biochemical damage to nerve fibers and spinal cord tissues, also show clear signs of increased protein and lipid oxidation [3]. As well demonstrated for SOD1 and TDP43 (see below), oxidative stress may also lead the formation of unfolded protein aggregates that are invariably found in ALS motor neurons [4,5] and that may be hardly removed by impaired protein degradation system and autophagy [6,7].

Since oxidative phosphorylation in mitochondria is the major source of ROS, oxidative stress may be linked to abnormalities in these organelles. Mitochondria-related pathogenic mechanisms have been the subject of intense research over the past 20 years (reviewed in Ref. [8]) and it is now clear that they are a hallmark of ALS that manifests in term of altered morphology and dynamism resulting in energy deficit, calcium mishandling and induction of death pathways.

However, oxidative stress and mitochondrial damage cannot represent the only mechanisms operating in the pathogenesis of ALS; thanks to recent advances in genetics, we now know that ALS is associated to mutations in at least 20 genes, coding for proteins related to cell functions as diverse as RNA metabolism (TARDBP, FUS/TLS, Senataxin, Ataxin2, HNRNPA2/B1, ELP3, HNRNPA1), vesicle trafficking (Alsin, FIG4, OPTN, VABP, CHMP2B) and proteasomal function (UBQLN2, VCP) [9]. Interestingly, almost half of the familial cases are linked to an expanded GGGGCC (G_4C_2) hexanucleotide repeat in an untranslated region of the C9orf72 gene [2]. Because of the particular nature of this mutation, different possibilities are still open for C9orf72 toxicity. This may stem from reduced expression of the C9orf72 protein, whose functions are still unclear; otherwise, repeat-containing RNAs might either undergo RAN translation (repeat-associated non-ATG translation) resulting in the accumulation of toxic poly-dipeptides repeat proteins (DRPs) in particular poly(Gly-Pro), poly(Gly-Ala), and poly(Gly-Arg), that are indeed present in tissues of affected patients [10], or trap specific RNA-binding proteins, thus causing deficits in RNA processing including regulation of splicing and mRNA transport [11,12].

That altered RNA metabolism plays a major role in the pathogenesis of ALS is indicated also by the association of the disease with mutations in several RNA binding proteins [13–15] including TDP43 and FUS, that participate in key RNA metabolism steps such as RNA transcription, splicing, transport, degradation and translation. Furthermore, these proteins share a subset of RNA targets, which may be part of disease-relevant pathway [16–20]. Giving the critical role of RNA processing in maintaining the health of metabolically active cells, mutation or cytoplasmic accumulation of RNA-binding proteins (as in the case of FUS and TDP43) or trapping of RNA-binding proteins (as in the case of C9orf72) might cause genome-wide disruptions in nearly all steps of RNA processing. Considering that mutations in C9orf72, TDP43 and FUS, account for about half of familial ALS cases and might also contribute to the development of sporadic ALS, the impact of misregulated RNA processing on ALS development seems to be unquestionable. Thus, when looking for a common triggering event causing sporadic and familial cases of the disease linked to different mutations, we are in front of two apparently distinct theories; the first considering oxidative stress, mitochondrial abnormalities and protein aggregation as leading aspects of ALS pathogenesis, the second pointing to RNA dysmetabolism as a central pathway in the mechanisms underlying the disease. Yet, there is now evidence of a close relationship between these two aspects of disease pathogenesis.

2. Oxidative stress and mitochondrial damage cause RNA dysmetabolism

A first indication of a link between oxidative stress and RNA-dysmetabolism came from the observation that neuroblastoma cells treated with paraquat (a well-known inducer of oxidative stress and mitochondrial damage) show changes in the splicing pattern of some pre-mRNA that are crucial for motor neuron viability [21]. These alterations seem to be relevant in ALS, since those data were extended to neuronal cells and brain and spinal cord of transgenic mice expressing G93A-SOD1 ($SOD1^{G93A}$ mice), where mitochondrial damage is linked to changes in the relative abundance of selected alternatively spliced mRNAs, including a set of mRNAs coding for proteins involved in axon sprouting and other neuron-related pathways [22].

More recently, the susceptibility of TDP43 to oxidative stress has been demonstrated in different cellular models treated with inducers such as arsenite, paraquat and hydrogen peroxide. Oxidative stress causes TDP43 delocalization from the nucleus to the cytoplasm and increases its tendency to aggregate ([23] and reference therein) and it is likely that in these conditions an alteration of one or more steps of RNA processing takes place. Similar evidence exists for a direct susceptibility of FUS to oxidative stress, in terms of aggregation and delocalization [24]. Beside its RNA binding properties, this protein shares with TDP43 the ability to form inclusions in spinal cords of sALS and fALS patients. Investigations on the nature of some of these inclusions revealed that TDP43 [25] and FUS [24,26,27], co-localize with Stress Granules (SG) in patients and in cellular models [28]. SGs are formed when eukaryotic cells undergo oxidative stress (or other cellular stress such as heat shock, glucose deprivation, viral infection) as a mechanism to rapidly modulate gene expression. These protective structures allow the prioritized translation of stress response genes by storing house-keeping mRNAs until the stress conditions persist [28]. Since ALS motor neurons endure oxidative stress, partially due to mitochondrial dysfunction, it is not surprising that SGs play a role in this pathology as in other neurodegenerative diseases [29]. However, under prolonged oxidative stress the permanence of SGs might become detrimental, representing the first step leading to the entrapping of active endogenous form of FUS and TDP43 in stable aggregates [24,30] and this may lead to a loss of function of these two nuclear proteins. For instance, aggregation of FUS causes skipping of exon 7 in pSMN2 minigene [26] and TDP43 sequestration in SGs causes the alteration of the splicing pattern of its target POLDIP3/SKAR [31].

On the other hand, it is well known that expression of G_4C_2 repeat-containing C9orf72 RNA leads to the formation of RNA *foci* and SGs, as well as inclusions of poly(Gly-Pro), poly(Gly-Ala), and poly(Gly-Arg) dipeptide repeat proteins (DRPs) in cellular models [10] and in mice [32]. The presence of C9orf72 mutation could induce the persistence of SGs in cells, possibly contributing to the formation of stable aggregates that might sequester proteins regulating RNA metabolism, converging in the pathological mechanism hypothesized above. As a proof of concept, it has been shown that poly(GA)-inclusions are able to sequester RNA binding proteins as well as proteins involved in nucleocytoplasmic transport in a murine model exhibiting poly(GA) pathology and ALS-like neurodegeneration [33]. These initial observations suggest that C9orf72 itself may be involved in RNA dysmetabolism through an indirect pathway.

On the whole, these data indicate a link between chronic exposure to oxidative stress and RNA-dysmetabolism through SGs formation and trapping of RNA-binding proteins. This concepts is supported by the recent report that increasing the level of Oxidative Stress Resistance Protein 1 (Oxr1), which is up-regulated in spinal cords of ALS patients and binds FUS and TDP43, induces a decrease in their cytoplasmic localization and aggregation, in splicing changes of a mitochondrial gene and in mitochondrial defects in neuron-like cells. Conversely, silencing Oxr1 increases FUS and TDP43 inclusions under conditions of oxidative stress [34]. Interestingly, when formation of FUS and TDP43 inclusions is induced, mitochondrial damage is increased, thus establishing a detrimental feed-forward loop. This loop might be linked to the mitochondrial localization of a fraction of these mutant proteins [35,36] and sustained through the mitochondrial precursor over-accumulation stress (mPOS) recently described in yeast [37]. In fact, mPOS can suppress a large network of genes modulating mRNA decapping, transcript-specific translation, protein chaperoning and turnover, and upregulates several ribosome-associated proteins. Whether TDP43, FUS or other ALS-linked proteins are involved in mPOS is currently not known.

3. RNA dysmetabolism causes oxidative stress and mitochondrial damage

A number of reports describe mitochondrial alterations in SOD1-related ALS but, unpredictably, this is true also for FUS and TDP43-related cases and cellular models (reviewed in Refs. [8,14]). As mentioned above, these two proteins colocalize with mitochondrial markers in cellular and animal models of ALS and thus might alter the functions of these organelles [35,36,38], although the timing of mitochondrial damage may be different. In fact, mitochondrial morphological abnormalities appear in $SOD1^{G93A}$ mice at 15 days of age, well before abnormalities of mitochondrial axonal transport, while they appear after the onset of transport defects in TDP43(A315T) mice [38].

But how can two (mostly nucleo-cytosolic) DNA/RNA binding proteins such as TDP43 and FUS cause mitochondrial damage? A possibility is that damage of mitochondria is induced directly (through sequestration or other unknown mechanisms) by the small fraction of these proteins that localizes into these organelles. A similar situation may occur also in neurons expressing expanded C9orf72 GGGGCC repeats, as we have demonstrated by immunoprecipitation and mass spectrometry analysis that several mitochondrial proteins are direct interactors of the repeat in mouse brain and spinal cord [11]. Alternatively, damage may be induced through the interaction, or loss of it, of those proteins with other, *non*-mitochondrial proteins. On this line, one appealing hypothesis on the mechanism that involves TDP43 comes from studies on cancer cells. It is well known that activation of FOXO3a causes the downregulation of many nuclear-encoded genes with mitochondrial function, with a consequent reduced expression of mitochondrial proteins and decreased activity of respiratory complexes [39]. Since nuclear TDP43 exerts a negative control over FOXO transcription factors (including FOXO3a) [40], when TDP43 leaves the nucleus (i.e. when carrying ALS mutations, or in a condition of oxidative stress) and relaxes its negative control of these transcription factors, mitochondrial damage may be induced. Along the same line, it is known that FUS interacts with PGC-1α, a well-known transcriptional co-activator that regulates genes involved in energy metabolism. This interaction mediates transcription of several genes coding for proteins involved in the protection from oxidative stress, such as MnSOD and catalase [41]. We can speculate that when FUS is mutated and/or aggregated in the cytosol, its interaction with PGC-1α is affected, causing reduced expression of oxidative stress protection genes, increase of basal levels of ROS and mitochondrial damage.

A last possibility is that mutations in TDP43 and FUS (and maybe in other ALS proteins involved in RNA metabolism) have a direct effect on the regulation of specific mRNAs coding for proteins involved in mitochondrial physiology. This hypothesis is supported by the recent observation that ALS-related TDP43 mutations are responsible for the alteration of the splicing pattern of nuclear-transcribed mRNAs coding for Mtfr-1 (Mitochondrial fission regulator-1), an inner mitochondrial membrane protein involved in mitochondrial fission [34].

Obviously, further studies are required to investigate how FUS, TDP43 and C9orf72 repeats might regulate oxidative stress response and mitochondrial physiology and how this might impact on ALS disease.

4. Protein folding and ALS-linked RNA binding proteins

As mentioned in the Introduction, accumulation of misfolded proteins is an hallmark of ALS pathogenesis and it can lead to the imbalance of the protein degradation pathway. As a proof that this pathway is pivotal for ALS, mutations in genes encoding several key components of protein quality control are found in some familial cases, including mutations in dynein and dynactin, which are involved in the retrograde transport of autophagosomes from axons to the cell body, in proteins containing the ubiquitin association domain (Ubqln2 and Optineurin) and in the autophagic adaptor SQSTM1/p62 ([42] and refs. therein). FUS itself, beside its different roles in RNA metabolism, is endowed with a SUMO (small ubiquitin-like modifier) E3 ligase activity and sumoylation of SOD1, TDP43 and other proteins may participate in the pathogenesis of ALS [43].

Mitochondria have their own dedicated machinery that promotes accurate control of protein folding, including specific chaperones that mediate protein import and folding, and proteases that degrade unfolded and/or misfolded proteins [44]. The mitochondria-localized chaperones include mtHsp70, a member of the Hsp70 family, as well as Hsp60 and Hsp10, that are also found in the cytosol [45]. It has been demonstrated that FUS physically interacts with Hsp60, both in the cytosol and in mitochondria [36] and that TDP43 interacts with cytosolic Hsp70 [31,46,47]. Since mutations of FUS or TDP43 do not affect binding with the chaperones [36,48], we may hypothesize that in pathological conditions FUS and TDP43 aggregates may trap and sequester those chaperones, thus resulting in a general impairment of protein folding control. This may have a widespread influence on the cell physiology, including the ability to respond to oxidative stress. Indeed, misfolded SOD1 was detected in spinal cords of patients with both FUS-fALS and sALS with TDP43 pathology [49].

Another effect of an interference with protein folding control might be a dysfunction of mitochondrial protein sorting pathways. Cytosolic chaperones are able to bind newly synthesized proteins keeping them unfolded until the recognition of the mitochondrial import machinery takes place [50]. Trapping of cytosolic chaperones may result in lowering of mitochondrial proteins, including those of the electron transport chain which are nuclear DNA-encoded, and also in the activation of the recently discovered Unfolded Protein Response Activated by Mistargeting of proteins (UPR^{am}), a defensive strategy aimed at counteracting the stall in mitochondrial protein import by increasing proteasome activity [51]. Furthermore, giving that Hsp60 resides also in mitochondria, FUS-dependent Hsp60 sequestration may have a more direct pathological impact on mitochondrial functions, due to the unavailability of the chaperone. In response to the consequent accumulation of unfolded or misfolded proteins beyond

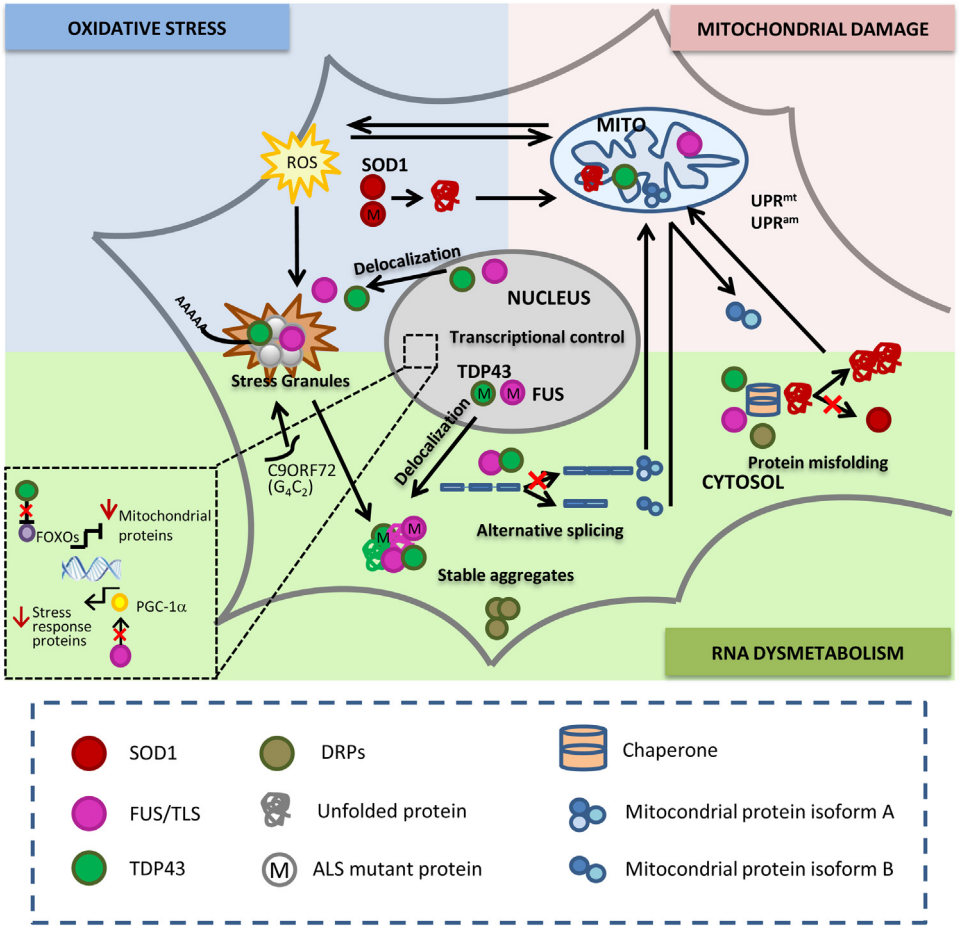

Fig. 1. Schematic representation of the pathogenic vicious cycle underling motor neuron degeneration in ALS. Oxidative stress and mitochondrial impairment are linked to protein unfolding and aggregation and to altered RNA metabolism. Details about these mechanisms can be found in the text.

the organelles chaperone capacity, cells could mount a mitochondrial unfolded protein response (UPR^{mt}). This is defined as a mitochondria-to-nucleus signal transduction pathway resulting in the induction of protective genes aimed to re-establish protein homeostasis within the mitochondrion. If these protective responses, UPR^{am} and UPR^{mt}, are not sufficient to restore mitochondrial function, or if the damage persists, defective organelles might enter the mitophagy pathway and cells could undergo apoptosis [52].

Interestingly, in the poly(GA)-murine model mentioned above, Zhang et al. have shown that poly(GA)-inclusions are able to sequester HR23A and HR23B, two proteins that are involved in proteasomal degradation, leading to an accumulation of ubiquitinated proteins that might contribute to the general protein degradation imbalance characterizing ALS pathology [33].

5. Iron homeostasis: another link?

Transition metals (copper and iron ions) can catalize the formation of ROS through the Fenton reaction and altered homeostasis of these metals has long been proposed as a factor contributing to the establishment of oxidative stress in ALS [53]. Signs of dysregulation of iron protein expression are found in SOD1^{G93A} mice [54] and in the skeletal muscle of ALS rats [55]. Similarly, ALS patients have altered iron metabolism, with high serum ferritin [56]. Copper chelation [57] and iron chelation [58] have positive effects in the SOD1^{G93A} mice, but definitive proof of the importance of copper and iron mishandling in ALS patients was never provided. Nonetheless, this line of research has found new input in the finding that the H63D polymorphism in the gene coding for human haemochromatosis protein (HFE), which is involved in iron metabolism, though not significatively linked to ALS cases [59] may act as disease-modifying gene in patients [60] and accelerates disease progression in SOD1^{G93A} mice [61].

What is more interesting in the context of this review, is that the H63D HFE genotype is also found in patients with Frontotemporal Lobar Degeneration (FTLD) [60], a disease that partly overlaps with ALS and that is often linked to mutations in FUS and TDP43 or to expanded C9orf72 repeat. Furthermore, iron accumulation has been found in post-mortem basal ganglia of FTLD patients [62]. How and whether this facet of oxidative stress is related to the presence of an altered RNA metabolism or to accumulation of protein aggregates is currently not known, but it certainly deserves further investigation, especially in the light of the observation that iron dyshomeostasis may be linked to dysregulation of autophagy [63].

6. Conclusion

For many years, pathways of oxidative stress and mitochondrial damage were considered clearly distinct from those of RNA metabolism, and therefore studies on the cause(s) of ALS faced a divergence of theories that was supported not only by the nature itself of the proteins involved (i.e. SOD1, an antioxidant enzyme, versus FUS and TDP43, two RNA binding proteins), but also by the evidence that SOD1 forms inclusions never overlapping with FUS and TDP43 aggregates in patients [5]. A number of recent

papers suggest a possible convergence of these two pathways, in a pathogenic vicious cycle where the first player may vary, for example depending on the mutation carried by the patient (Fig. 1). At the moment, it is difficult to distinguish which pathogenic aspects are the primary cause of disease and which are instead the reflection of a downstream damage, and it is still possible that we have underrated the importance of "secondary" activities of the proteins involved. This is well exemplified by a multitasking protein like FUS, which not only is involved in several different steps of mRNA metabolism [64] but also binds specific protein chaperones and has a SUMO E3 ligase activity.

Finally, oxidative stress is involved also in the interplay between motor neurons and non neuronal neighbor cells such as microglia and astrocytes, through mechanisms that are only partially understood ([65–67], and references therein) and in which a clear relevance of RNA dismetabolism has not been conclusively demonstrated.

Thus, ALS remains an extremely complex disease; hopefully the availability of more models and more complete information will help us understand its complexity and devise new therapeutic strategies.

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