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Review

Biomolecular Modifications Linked to Oxidative Stress in Amyotrophic Lateral Sclerosis: Determining Promising Biomarkers Related to Oxidative Stress

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Abstract: Reduction–oxidation reactions are essential to cellular homeostasis. Oxidative stress transcends physiological antioxidative system damage to biomolecules, including nucleic acids and proteins, and modifies their structures. Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease. The cells present in the central nervous system, including motor neurons, are vulnerable to oxidative stress. Neurodegeneration has been demonstrated to be caused by oxidative biomolecular modifications. Oxidative stress has been suggested to be involved in the pathogenesis of ALS. Recent progress in research on the underlying mechanisms of oxidative stress in ALS has led to the development of disease-modifying therapies, including edaravone. However, the clinical effects of edaravone remain limited, and ALS is a heretofore incurable disease. The reason for the lack of reliable biomarkers and the precise underlying mechanisms between oxidative stress and ALS remain unclear. As extracellular proteins and RNAs present in body fluids and represent intracellular pathological neurodegenerative processes, extracellular proteins and/or RNAs are predicted to promise diagnosis, prediction of disease course, and therapeutic biomarkers for ALS. Therefore, we aimed to elucidate the underlying mechanisms between oxidative stress and ALS, and promising biomarkers indicating the mechanism to determine whether therapy targeting oxidative stress can be fundamental for ALS.

Keywords: oxidative stress; amyotrophic lateral sclerosis (ALS); oxidative protein modification; oxidative DNA damage; oxidative RNA damage; biomarker

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1. Introduction

Among the various biochemical responses supporting our life, reduction–oxidation (redox) reactions play important roles in energy production by mitochondria, intracellular protein quality control, and intracellular signal transduction cascade. Several types of reactive species, including reactive oxygen species (ROS), reactive nitrogen species, and reactive sulfur species, are essential factors in redox signaling in biology [1,2]. These reactive species are produced by cellular homeostatic metabolism and exogenous pro-oxidant factors, including environmental and atmospheric pollution, heavy metals, or tobacco [3]. Among these reactive species, two ROS species, hydrogen peroxide (H_2O_2) and superoxide anion radical ($O_2^{\bullet -}$), are key redox signaling agents generated under the tight control of growth factors and cytokines by over 40 enzymes [4]. The physiological concentrations of ROS regulate numerous cellular functions, including cellular signaling pathways, phosphorylation of proteins, signaling transduction via cell membrane receptors, and activation of ionic channels and transcription factors; the physiological intracellular concentration of H_2O_2 is maintained at approximately 1–100 nM and that of $O_2^{\bullet -}$ is 10^{-11} M, much lower

than that of H_2O_2 [5]. Supraphysiological concentrations of H_2O_2 and $O_2^{\bullet -}$ lead to nonspecific oxidation and irreversible damage to biomolecules, resulting in growth arrest and cell death, as demonstrated in various diseases, including neurodegenerative diseases [1,2,6]. Conversely, to prevent biomolecules from nonspecific and irreversible damage, the cells have evolved several antioxidant defenses, including activation of various antioxidant molecules to counteract the injurious effects of ROS. As such, a number of antioxidant enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX), and glutathione reductase (GSHRd), exist in cells [7].

The cellular redox state maintains an equilibrium between oxidation and reduction reactions. Oxidative stress, which is the consequence of oxidative damage to cells and organs by increased generation of ROS and/or decreased effects of antioxidant defenses, is responsible for damage to various biomolecules, including nucleic acids and proteins, and contributes to stress-induced aging [8]. Neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), are incurable and characterized by progressive neuronal cell loss in the central nervous system (CNS). Since the ability of cells to maintain their normal redox state is reduced during the normal aging process, aging is the most important risk factor for neurodegenerative diseases [9]. Furthermore, the CNS is enriched in polyunsaturated fatty acids that consume a large amount of oxygen and redox-active metals that actively participate in ROS generation, whereas the CNS has low levels of antioxidants. The brain is more vulnerable to oxidative stress than other parts of the body [10,11]. Therefore, the evidence of a significant connection between oxidative stress and neurodegenerative disease is increasing, and therapies aimed at reducing cellular ROS levels are expected to be neuroprotective therapies for multiple neurodegenerative diseases [11].

ALS is the most common adult-onset lethal motor neuron disease and is characterized by the selective degeneration of both upper and lower motor neurons. These degenerations cause progressive muscle weakness and atrophy, leading to respiratory failure and death within a few years following disease onset [12,13]. The ALS-associated gene, *superoxide dismutase 1* (*SOD-1*), an enzyme that converts superoxide radicals into hydrogen peroxide, was identified in 1993 [14]. Since then, although a large number of pathogenic hypotheses have been proposed, oxidative stress has been considered one of the pathogenic hypotheses in ALS [15]. In addition, the evidence of perturbed cellular redox regulatory mechanisms and associated proteins in both sporadic and familial ALS is increasing [16]. Edaravone, a free radical scavenger that eliminates lipid peroxides and hydroxyl radicals, was recently approved for ALS patients, suggesting that modifying the redox regulation could be a therapeutic strategy for ALS [17]. However, as the precise understanding of the association between disturbed redox regulation and motor neuron death is unclear, the administration of edaravone is not particularly effective and is not a fundamental therapy. To develop more successful therapies, the establishment of diagnostic biomarkers for early phase ALS and predictive and pharmacodynamic biomarkers for initiation of therapy is important. However, the vast majority of ALS cases are sporadic; thus, the diagnosis of ALS is not determined by genetic screening [12]. A diagnosis of ALS is currently based on a combination of clinical assessment and electrophysiological examination using El Escorial criteria and Awaji criteria, and no reliable diagnostic biomarkers have been established [18,19].

As a definite diagnosis of neurodegenerative diseases comes from histological observation of the spinal cords and brains, accurate antemortem diagnosis of these diseases is currently impossible. A biomarker is characterized as an indicator of normal biological processes or pathogenic processes that must be objectively measured and evaluated [20]. Therefore, noninvasive or minimally invasive biomarkers, including easily accessible body fluids or tissues that reflect disease-specific pathological events in the CNS, are needed. Liquid biopsy targeting the patient's body fluids, including serum and cerebrospinal fluid (CSF), is less invasive than conventional tissue biopsy and can be an alternative diagnostic tool [21]. Extracellular proteins and RNAs representing homeostatic intracellular environments are secreted from several cell types in the CNS tissue, and neuronal interactions via extracellular proteins and RNAs exert key functions in neurite growth, synaptic func-

tion, and neuronal regeneration [22,23]. Therefore, extracellular proteins and RNAs have been considered promising biomarker candidates for various types of neurodegenerative diseases [24].

In this review, we summarize the oxidative biomolecular alterations involved in the pathogenesis of ALS and promising treatments related to oxidative stress in these diseases. Moreover, we discuss promising biomarker candidates linked to oxidative stress in ALS.

2. Oxidative Biomolecular Modification Leading to Neurodegeneration

As described in the introduction section, aging leads to increased oxidative stress and the brain is highly susceptible to ROS damage, whereas the function of antioxidant systems declines with age [25,26]. Therefore, oxidative biomolecular modifications, including proteins and/or nucleic acids, increase with age, especially in the brain, leading to neurodegeneration induced by oxidative stress [26]. Abnormal protein aggregation, including amyloid in Alzheimer's disease (AD), tau in Parkinson's disease (PD), and transactive response DNA/RNA binding protein of 43 kDa (TDP-43) in ALS, are pathological hallmarks of neurodegenerative diseases [27–29]. Therefore, elimination of these abnormal protein aggregates is a therapeutic strategy for fundamental therapy of neurodegenerative diseases, and changes in the expression levels of protein and RNA in body fluids related to these abnormal protein aggregates must be a biomarker. In addition, accumulation of DNA and RNA damage and impairment of DNA repair pathways have been found primarily in neuronal tissues, and changes in expression levels of noncoding RNA due to oxidative stress have also been recognized in neuronal tissues, suggesting that oxidative damage to DNA and RNA causes neurodegenerative diseases. In this section, we review oxidative biomolecular modifications due to redox dysregulation (Figure 1).

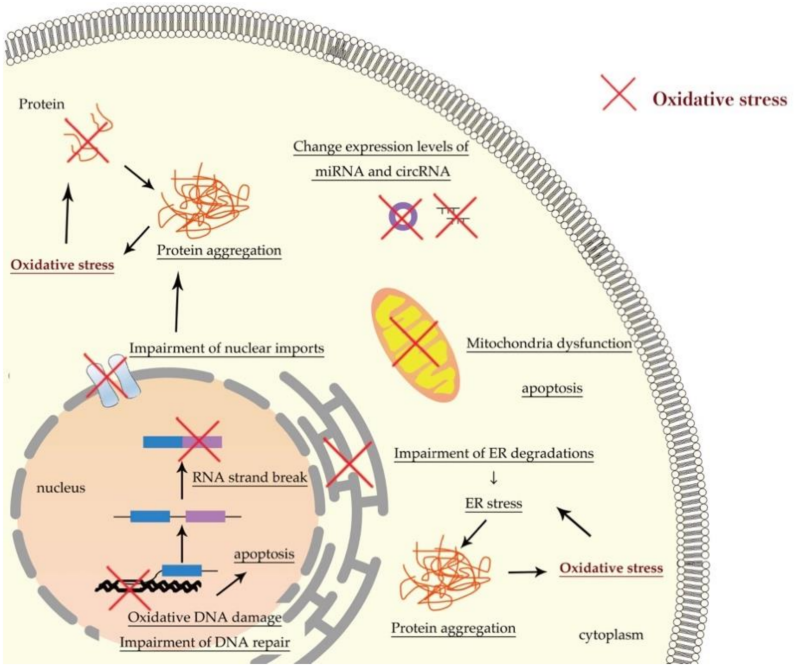

Figure 1. Oxidative molecular modifications causing protein aggregation. Oxidative biomolecular modifications including proteins or nucleic acids occurred in both the nucleus and cytoplasm. Oxidative modifications of proteins can lead to conformational changes and protein misfolding, resulting in protein aggregation. Moreover, endoplasmic reticulum (ER) stress due to impairment of ER degradation and impairment of nuclear import results in protein aggregation. Oxidative damage of DNA and RNA, impairment of DNA repair pathways, and mitochondria dysfunction lead to apoptosis.

2.1. Oxidative Modifications of Proteins Linked to Protein Aggregation

Since the rate of the oxidant reaction depends on the concentration of the target and proteins are major components of most biological systems, proteins are major targets for oxidative stress; therefore, protein oxidative modifications occur easily [30,31].

Although physiological oxidative stress is useful for physiological homeostasis, excessive oxidative stress can lead to conformational changes, protein misfolding, and accumulation of insoluble aggregates, resulting in neurodegeneration [32]. ROS can generate various post-translational modifications, such as the alteration of amino acids [30,33,34]. Among the amino acids, cysteine residues, which are critical for protein folding, function, and stability, are crucial for the maintenance of cellular redox homeostasis, and internal disulfide bond formation between Cys32 and Cys41 by oxidation have been shown to cause protein aggregation [35,36]. Additionally, oxidative stress promotes protein aggregation by modulating chaperone protein activity, such as preventing the interaction between chaperone proteins and heat shock proteins and perturbing the translational process [37]. The endoplasmic reticulum (ER), which has a higher ratio of oxidation similar to extracellular space, is the main component of protein folding in eukaryotic cells, and ER-associated degradation plays a crucial role in preventing protein accumulation and aggregation [38]. Oxidative stress and dysregulation of the ER redox balance can inhibit ER-associated degradation in response to unfolded proteins. These changes lead to protein misfolding, ER stress, and protein aggregation, resulting in neurodegeneration [1]. Moreover, oxidative stress also inhibits classical nuclear import via induction of relocation of Nup153 and importin-β and impairs autophagy, leading to protein aggregation [39,40]. Furthermore, protein aggregations tend to accumulate in foci, and oxidative stress acts as a sensor that triggers protein recruitment into foci [41].

2.2. Oxidative DNA Damage Linked to Apoptosis

A number of exogenous and endogenous agents, including oxidative stress and even normal cellular processes, can induce DNA damage, suggesting that oxidative DNA damage is an inevitable consequence of cellular metabolism. Several DNA repair pathways, including DNA base excision repair (BER) and the nucleotide excision repair pathway, function as correction mechanisms for the daily amounts of DNA damage [42,43]. This said, ROS levels are increased with age, in contrast to the decrease in antioxidant system ability, and neurons are highly susceptible to DNA damage [44,45]. Moreover, higher levels of oxidative DNA damage and impairment of DNA repair pathways have been shown to lead to increased p53 activity, ultimately resulting in apoptosis. As such, the accumulation of oxidative DNA damage is thought to contribute to neurodegeneration [46].

Mitochondria, which are the heart of redox reactions and generate ROS species, play essential roles in the survival of various cells, including motor neurons [47]. Mitochondrial DNA is more exposed to ROS than nuclear DNA because mitochondrial DNA exists in the proximity of the inner mitochondrial membrane in which ROS is formed, lacks protective histones, and has less efficient repair [48]. Age-associated increase in oxidative mitochondrial DNA damage reduces mitochondrial axonal transport. Moreover, oxidative damage of mitochondrial DNA genes encoding subunits of the mitochondrial respiratory chain due to ROS impairs adenosine triphosphate production [49,50]. These alterations lead to mitochondrial dysfunction and, ultimately, apoptosis. Furthermore, oxidative mitochondrial DNA damage accelerates oxidative stress [51]. Additionally, the accumulation of mutations in both nuclear and mitochondrial DNA due to oxidative damage also leads to the production of altered proteins, resulting in alteration of protein constructs and abnormal aggregation [52,53].

2.3. Oxidative RNA Damage

RNA is essential for maintaining cellular homeostasis and plays an important role in protein synthesis. As RNA accounts for approximately 80% of the total cellular nucleic acids, RNA can also be a major target of oxidative stress [54]. In addition, RNA may

be more vulnerable to oxidative damage than DNA because of its characteristic single-stranded structure and lack of protection by hydrogen bonding and specific proteins [55,56]. Direct RNA strand breaks, translation errors, and protein synthesis disorders are induced by oxidative damage [57–59]. Moreover, since the spatial positioning of messenger RNA (mRNA) exists close to the mitochondria and temporal dynamics of RNA oxidation is shorter than that of RNA translation, a large amount of mRNA oxidation occurs [60]. RNA oxidation is not random, but instead highly selective, and abnormal processing of proteins and a decrease in protein expression leading to protein misfolding are caused by oxidative modification of mRNA [61,62]. Therefore, oxidative RNA modification, which occurs not only in protein-coding RNAs but also in noncoding RNAs, also contributes to aging and the underlying mechanisms of neurodegeneration. Noncoding RNAs, including microRNAs (miRNAs) and circular RNAs (circRNAs), are regulators of gene expression, crucial neuronal differentiation, survival, and activity. Several miRNAs can be oxidized themselves and regulate the expression levels of many genes involved in antioxidant defense pathways [63]; for example, oxidative modification of miR-184 reduced expression levels of Bcl-xL and Bcl-w due to misrecognitions, leading to apoptosis [64], and miR-27a influences redox homeostasis due to reduced expression levels of nuclear factor E2-related factor 2 (NRF2), which is a major regulator of antioxidant elements [65]. In addition, several circRNAs can be related to neurodegeneration via modulation of oxidative stress; for example, circHIPK3 can regulate oxidative stress due to work through a signaling network that consists of circHIPK3 and miR-29a [66].

3. Biomolecular Modifications Associated with Oxidative Stress in ALS

Aging and cellular senescence are risk factors for various neurodegenerative diseases. Aberrant protein aggregation is considered a pathological hallmark of neurodegenerative diseases such as β-amyloid in AD, α-synuclein in PD, and TDP-43 in ALS. Age-associated increase in oxidative stress contributes to protein misfolding and aggregation, and these protein aggregations cause upregulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) activity, oxidant generation, and overactivated microglia, resulting in altered fluidity, permeability, transport, and metabolic processes [10,67]. Moreover, postmortem brain tissues from patients with neurodegenerative diseases have been reported to increase the expression of markers of ROS damage and nucleic acid damage, including glutathione (GSH) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) [26,68–70]. Therefore, oxidative stress has been studied in various neurodegenerative diseases in relation to the degeneration of neurons, microglia, astrocytes, and the blood–brain barrier [71].

ALS is the most common adult-onset lethal motor neuron disease, characterized by progressive muscle weakness and atrophy, leading to respiratory failure and death within a few years following disease onset [12,13]. The analysis of postmortem neuronal tissue, CSF, serum, and urine from patients with sporadic or familial ALS harboring SOD-1 mutations showed redox system upregulation, suggesting that oxidative stress contributes to the pathogenesis of both sporadic and familial ALS [72–75]. In addition, several previously published studies have demonstrated that markers of oxidative damage to proteins, DNA, and RNA are increased in both sporadic and familial ALS patients [68–70]. Nonetheless, because the expression levels of various antioxidant enzymes and parameters of mitochondrial function differ between sporadic ALS and familial ALS, it is suggested that distinct mechanisms of oxidative stress are likely to act between sporadic ALS and familial ALS [76]. As the disease progresses, oxidative stress might be increased by nutritional deficiency, cachexia, psychological stress, and impending respiratory failure [10]. In addition, a correlation between oxidative stress measured by positron emission tomography of the brain with ^{62}Cu diacetyl-bis (N4-methylthiosemicarbazone) and clinical severity in ALS was recently reported [77]. Oxidative stress might be both a cause and consequence of the disease, and is associated with pathogenesis as well as disease progression.

3.1. Abnormal Protein Aggregations and Oxidative Stress in ALS

Aberrant protein aggregation, including SOD-1 and TDP-43, is the main pathological hallmark of familial and sporadic ALS. Aberrant protein aggregation is induced by oxidative stress, and conversely, oxidative stress is induced by aberrant protein aggregation. Oxidative modifications to proteins have been considered as one of the mechanisms of motor neuron death in both sporadic and familial ALS.

SOD-1 is localized in the cytosol, nucleus, peroxisomes, and mitochondria. As SOD-1 plays an important role in the antioxidant defense of the cell by switching from $O_2^{\bullet -}$ to O_2 and H_2O_2 [78], the absence of SOD-1 causes an increase in oxidative stress. In ALS patients, more than 170 mutations have been identified, and aberrant aggregation of SOD-1 exists in spinal motor neurons from patients with sporadic and familial ALS [79,80]. Moreover, the misfolded form of SOD-1 exists in the CSF of patients with sporadic ALS [81]. The deleterious effects of a toxic gain of function due to mutant SOD-1 and aberrant aggregation of SOD-1 have been considered as one of the pathogeneses of motor neuron death in ALS [82]. SOD-1 could become a target for oxidative stress, leading to aberrant aggregation [83], and an aberrant aggregation of SOD-1 contributes to ubiquitin/proteasome system dysfunction and interferes with mitophagy processes, which are the clearance of damaged mitochondria, through optineurin sequestration [84,85]. In addition, mutated SOD-1 could lead to oxidative damage by promoting reverse $O_2^{\bullet -}$ production through the dissociation of zinc from SOD-1, hyperactivation of NOX-dependent $O_2^{\bullet -}$ production, and decrease in the expression levels of NRF2 [86–89]. In addition, the presence of mutated SOD-1 could lead to impairment of the respiratory chain and mitochondrial redox homeostasis [90]. Studies of the antioxidant enzyme activity of SOD-1 have reported inconsistent results; one study showed that the activities in pyramidal cells of the cerebral cortex and in spinal motor neurons from sporadic ALS patients were reduced [91], whereas another study showed that the activity in spinal motor neurons from ALS patients did not change [92].

The aberrant aggregation of TDP-43, DNA- and RNA-binding protein encoded by *TARDBP* is the main pathological hallmark of many forms of familial and sporadic ALS and is used to determine the severity and stage of disease progression [93,94]. The intrinsic aggregation prone to TDP-43 has been attributed to the C-terminal glycine-rich domain, and activated caspases cleave TDP-43 to generate C-terminal fragments, which are particularly prone to aggregate formation [95,96]. Oxidative stress resulting in mitochondrial dysfunction due to activated caspases has been shown to induce TDP-43 aggregation [97]. In addition, oxidative stress causes TDP-43 mislocalization and increases its tendency to aggregate by promoting the acetylation of TDP-43 [98]. TDP-43 aggregation sequesters some miRNAs and proteins, resulting in changes in gene expression, which causes a global mitochondrial imbalance that increases oxidative stress [99]. Stress granules (SGs), which represent membrane-less organelles composed of RNAs and proteins, are transiently formed under stress conditions, including oxidative stress, to reprogram RNA translation [100]. Oxidized TDP-43 recruited into SGs has been observed in ALS [101,102], and ALS-linked mutant TDP-43 is incorporated into SGs earlier than wild-type TDP-43, and these mutants form significantly larger stress granules [103]. Moreover, the ALS-linked mutant TDP-43 influenced the NRF2 antioxidative pathway, which is a major regulator of antioxidant elements, through interactions with the family of heterogeneous nuclear ribonucleoproteins (hnRNPs) [104].

3.2. Oxidative DNA Damage and Impairment of DNA Repair in ALS

Oxidative DNA damage accumulates in the nuclear DNA and mitochondrial DNA of aging neurons and has been suspected to play an important role in the pathogenesis of both sporadic ALS and familial ALS [69]. Since guanine has a lower electron reduction potential than the other DNA bases, 8-OHdG is the most abundant oxidative alteration in DNA among more than 20 oxidation products. Additionally, 8-OHdG has been employed as a marker of oxidative damage to DNA [105,106]. The levels of 8-OHdG in both nuclear DNA and mitochondrial DNA of brain tissue increased with aging [107], and increased levels

of 8-OHdG have been identified in the nuclear DNA of the motor cortex derived from sporadic ALS patients and the spinal cord derived from both sporadic ALS and familial ALS harboring SOD-1 mutations [68,108,109]. In addition, increased levels of 8-OHdG have been observed in nuclear DNA from the frontal cortex and spinal motor neurons and in mitochondrial DNA from spinal motor neurons of transgenic mice harboring SOD-1 mutations, but not from the cerebellum [110,111]. In addition, in spinal motor neurons of sporadic ALS patients, colocalization of 8-OHdG and activated p53 is recognized [109], and in motor neurons of the SOD-1 mutant mouse, which has been proposed as a model mouse of familial ALS harboring SOD-1 mutation, somal and mitochondrial swelling, formation of DNA strand breaks, and activation of p53, which triggers apoptosis as a result of the accumulation of DNA damage, was observed [112]. Similarly, higher levels of oxidative DNA damage and increased levels of apoptosis and p53 activity were observed in SH-SY5Y cells overexpressing the mutant SOD-1 protein, fused in sarcoma (FUS) knockdown SH-SY5Y cells, induced pluripotent stem cells (iPSCs) derived from C9ORF72-ALS patients [113–115]. Therefore, oxidative DNA damage is thought to be involved in motor neuron death in both sporadic and familial ALS.

The accumulation of abnormal DNA due to impairment of DNA damage repair was hypothesized approximately 40 years ago [116]. Apurinic/apyrimidinic endonuclease 1 (APE1) is a transcription factor involved in redox regulation and an enzyme involved in DNA repair, especially in BER [117], and negatively regulates NRF2 [118]. The levels of APE1 in the motor cortex and spinal cords derived from sporadic ALS were increased and APE1 localization was altered compared with those in control patients [119]. Furthermore, cytosolic mislocalization of APE1 is suggested to trigger oxidative DNA damage in spinal motor neurons of SOD-1 mutant mice [120]. Moreover, epigenetic mechanisms involved in gene expression are impaired by mislocalization of TDP-43, and the hypomethylation of the promoter of APE1 has been recognized in C9ORF72-ALS patients [109,121]. In contrast, other studies demonstrated that the activity of APE1 was lower in patients with sporadic ALS, and the loss of immunoreactivity for APE1 was seen in spinal motor neurons of SOD-1 mutant mice [122,123]. The expression levels and activities of another DNA repair element, 8-oxoguanine glycosylase (OGG1), which removes oxidized guanine from DNA and poly (ADP-robose) polymerase-1 (PARP-1), which is activated by oxidative DNA damage, have been investigated. The impairment of mitochondrial OGG1 activity in spinal motor neurons of sporadic ALS [124], increased expression levels of nuclear Ogg1 in the spinal motor neurons of mutant SOD-1 mice [123], and increased expression levels of PARP-1 in astrocytes and the motor cortex—but not in spinal motor neurons of sporadic ALS—have been recognized [125]. Moreover, impairment of DNA damage repair is recognized in spinal motor neurons of C9ORF72-ALS patients and is suspected to be associated with impairment of interaction between FUS and histone deacetylase 1 (HDAC1) and the loss of nuclear TDP-43 and SOD-1 [53,126,127].

These lines of evidence suggest that oxidative DNA damage and impairment of DNA repair are involved in the pathogenesis of sporadic ALS and familial ALS.

3.3. RNA Modifications Associated with Oxidative Stress in ALS

Oxidative stress and RNA metabolism are considered to be the pathogenesis of ALS, and there is increasing evidence of the relationship between these two aspects. Oxidative stress causes abnormalities in RNA metabolism, and conversely, abnormalities in RNA metabolism cause oxidative stress [128]. Indeed, increased oxidative RNA modification and alteration of splicing and expression of mRNA are recognized in the spinal motor neurons of SOD-1 mutant mice [129,130]. Moreover, oxidative RNA modification is an early event in the course of the disease and precedes the death of motor neurons [62,129].

Among the ALS-related genes, RNA-binding proteins encoded by *TARDBP*, *FUS*, and *SOD-1* are implicated in miRNA processing [131], and some miRNAs regulate the expression levels of genes related to oxidative stress [65]. In ALS patients, miRNAs are involved in oxidative stress, which is involved in the pathogenesis of ALS.

MiR-27a, which plays a role in muscle proliferation, and miR-142-5p, which functions in inflammation and cell apoptosis, regulates oxidative stress via inhibition of NRF2 expression directly [132,133], and the expression levels of miR-27a were increased in the skeletal muscle of sporadic ALS [134]. MiR-338-3p, a brain-specific miRNA, is involved in mitochondrial function by regulating the expression of multiple nuclear-encoded mitochondrial mRNAs [135]. Indeed, the expression levels of miR-338-5p were increased in neuromuscular junctions of sporadic ALS and in the spinal cord and motor cortex of SOD-1 mutant mice [136,137]. Moreover, miR-338-3p modulates apoptosis-associated tyrosine kinase mRNA levels in neurons, resulting in the apoptosis of mature neurons and neurodegeneration of oligodendrocytes. In addition, miR-338-3p suppresses the expression levels of SLC1A2 mRNA, suggesting a role in glutamate clearance, which is suspected to be one of the pathogenesis of ALS [24,138]. MiR-34a, which is involved in cell cycle regulation, also regulates oxidative stress via direct inhibition of NRF2 expression [139]. Moreover, miR-34a is involved in oxidative stress-induced apoptosis due to the regulation of tumor protein 53 (TP53) and sirtuin 1 (SIRT1) expression, and the expression levels of miR-34a are decreased in iPSCs derived from sporadic ALS patients and in the spinal cord and brain stem of SOD1 mutant mice [140,141]. MiR-155 is involved in inflammatory response and mitochondrial function. The expression levels of miR-155 were increased in skeletal muscles of ALS patients and in the spinal cord of SOD-1 mutant mice and both sporadic and familial ALS patients [142–144]. These changes were recognized during disease progression and in early-stage and end-stage in SOD-1 mutant mice and ALS patients [142,145,146].

Intriguingly, enoxacin, a fluoroquinolone antibiotic, rescued the expression of miR-34a, and inhibition of miR-155 in SOD-1 mutant mice has been shown to prolong survival [141,143,144]. Therefore, a treatment strategy for miRNA dysregulation may be useful for ALS.

Although circRNAs have been demonstrated to modulate redox homeostasis, circRNAs related to both oxidative stress and the pathogenesis of ALS have not been identified.

3.4. Treatment Linked to Oxidative Stress in ALS

The evidence that oxidative biomolecular modification is involved in the pathogenesis of ALS is increasing; therefore, it is necessary to recognize redox dysregulation as a therapeutic target.

Edaravone, a free radical scavenger that eliminates lipid peroxides and hydroxyl radicals, is the only approved antioxidant drug for ALS patients [17]. Oxidative stress has been implicated in the pathogenesis of ALS, and edaravone has been shown to inhibit motor neuron death and abnormal SOD1 aggregation in G93A mutant SOD1 transgenic mice, suggesting that edaravone might ameliorate disease progression [147]. Moreover, edaravone, but not other antioxidants, has been demonstrated to have other neuroprotective functions, including inhibition of Bcl-2 apoptotic pathways, augmentation of nitric oxide release from vascular cells and platelets, and suppression of ER stress, leading edaravone to be the most promising therapeutic agent for targeting redox dysregulation in patients with [148–150]. In a phase three clinical study and meta-analysis, edaravone showed a significantly smaller decline in the revised ALS functional rating scale (ALSFRS-R) score compared with a placebo, without significant adverse effects in the early stage of ALS patients [17,151]. Furthermore, long-term (18 months) administration of edaravone improved the ALSFRS-R score and survival rate, and therapeutic effects in patients outside Japan have been reported [152,153]. Additionally, reduced concentrations of the oxidative damage marker, 3-nitrotyrosine (3-NT), and improved antioxidative activity after intravenous administration of edaravone have been demonstrated [154,155]. Therefore, although some controversial studies on the therapeutic effects of edaravone in ALS patients have been reported [156,157], edaravone hardly has harmful adverse effects and may inhibit disease progression in the early stages of ALS.

In addition, other multiple antioxidants and combinations of apoptotic inhibitors, anticancer agents, and antioxidants have been identified as potential therapeutic agents.

Vitamins, including vitamin E, vitamin C, and coenzyme Q10 (CoQ10) have been suspected to be therapeutic agents because of their ability to regulate antioxidant systems, and clinical trials using these compounds have been conducted [158–160]. Additionally, to gain further effects by adding apoptotic inhibitors or anticancer agents, clinical studies using a combination of vitamins, CoQ10, anti-inflammatory agents, antiapoptotic agents, or anticancer agents have been conducted [161–163]. EH301, a combination of two antioxidants, pterostilbene and nicotinamide riboside, has been shown to suppress disease progression and improve ALSFRS-R and forced vital capacity in a small number of ALS patients [163]. However, other clinical trials have failed to show improvement in symptoms and/or suppression of disease progression, suggesting that these therapeutic strategies using monotherapy and/or combination therapy of antioxidants are not effective for ALS patients.

Although redox dysregulation has been recognized as a pivotal therapeutic target, the clinical effects of edaravone in ALS patients are limited, and other antioxidant therapies have mostly been unsuccessful. Therefore, the development of more successful therapies is expected [70]. As preclinical studies of multiple therapeutic targets have used mutant SOD-1 mice, which do not exhibit TDP-43 pathology, which is a pathological hallmark of ALS, the results of the preclinical studies may not enhance survival and improve motor function in ALS patients [16]. Therefore, to develop more successful therapies, using cells and animals representing molecular abnormalities that occur in ALS patients in a preclinical study is important.

4. Promising Biomarker Candidates Associated with Oxidative Stress in ALS

Oxidative stress has been considered to be involved in the onset and disease progression of ALS, and the evidence of oxidative biomolecular modifications and changes in molecular expression levels in neuronal tissues of ALS patients have been increasing, suggesting that the detection of these alterations would be a promising biomarker. Therefore, oxidative stress markers derived from body fluids have been investigated in many studies [164]. In this section, we review promising biomarker candidates linked to oxidative stress in proteins and RNAs (Table 1).

4.1. Protein

Oxidative stress results from the increased generation of oxidants and/or decrease in antioxidants. Therefore, changes in the expression levels of oxidants and antioxidants have been investigated.

With regard to oxidants, the expression levels of oxidative stress products such as 8-OHdG and malone dialdehyde (MDA) and antioxidant system products such as SOD-1 and GPX have been reported to be altered in body fluids in ALS patients compared with those in controls; therefore, this change has been suspected to be a promising biomarker candidate for ALS. As the levels of 8-OHdG in plasma and CSF increased with aging, 8-OHdG has been well studied to determine whether it will come to be an oxidative stress biomarker [69]. Several studies have shown that 8-OHdG levels in CSF, plasma, and urine were elevated in both sporadic and familial ALS patients compared with disease-free control patients and patients with other neurological diseases [69,74,165,166]. Moreover, 8-OHdG levels in urine were negatively correlated with both the rate of change of the ALSFRS-R and forced vital capacity (FVC) [69]. Lipid peroxidation is one of several outcomes of oxidative stress. MDA is a potential oxidative stress biomarker that can be used to evaluate lipid peroxidation. The concentration of MDA in plasma was significantly increased in sporadic ALS patients compared with that in control patients [166–168]. In addition, 4-hydroxynonenal (HNE) is one of the most toxic products of lipid peroxidation, and its levels are significantly increased in plasma and CSF from sporadic ALS patients. Moreover, the levels of HNE in plasma positively correlate with the extent of disease [75]. 3-nitrotyrosine (3NT), formed by the nitration of protein-bound and free tyrosine residues, is also a promising biomarker of oxidative stress. Indeed, the levels of 3NT were increased in the spinal cord of familial and

sporadic ALS patients [72]. Moreover, the levels of 3NT have been shown to be increased in the CSF of patients with sporadic ALS [169]. However, it has been reported that the levels of 3NT in CSF did not change significantly between patients with sporadic ALS and controls [170].

Levels of antioxidants and antioxidant enzymes have also been considered as biomarker candidates for ALS. However, these results are inconsistent.

Regarding the antioxidant enzyme activity of SOD, several studies have shown that SOD activity is elevated in red blood cells (RBC) and plasma from sporadic ALS patients [167,171,172], whereas it has been shown that the activity is not changed significantly in RBC and plasma from sporadic ALS patients and reduced in RBC and CSF from sporadic and familial ALS patients [165,166,168,173–177]. Intriguingly, it has been reported that the antioxidant enzyme activity of SOD in bulbar onset sporadic ALS was significantly higher than in spinal onset sporadic ALS [167]. Deficiency of the antioxidant activity of GPX indicates cytotoxicity due to the increase in hydrogen peroxide and membrane lipid peroxidation [172]. This said, the antioxidant enzyme activity of GPX has also been shown to be inconsistent. Some studies have shown that the activity is reduced in whole blood, RBCs, and plasma from sporadic ALS patients [167,173,178], whereas other studies have shown that the activity is not changed in plasma from ALS patients [166,168,172]. Several studies have shown that the concentration of GSH in whole blood and plasma was further reduced in sporadic ALS patients than in controls [166,179], whereas some studies have shown that the concentration in plasma was not significantly changed in ALS patients [168,180]. Moreover, in patients with sporadic ALS, no significant temporal change during a 6-month period was observed [179]. In addition, the concentrations of glutathione disulfide (GSSG) in whole blood were significantly increased in patients with sporadic ALS compared with controls [166]. CoQ10 is an antioxidant and an enzyme cofactor in the mitochondrial electron transport chain. Levels of CoQ10 were not significantly increased in plasma and serum in sporadic ALS patients compared with those in control patients, and these levels were not influenced by clinical form, age at onset, or duration of disease [181–183]. However, the proportion of oxidized forms of CoQ10 was significantly higher in CSF and plasma derived from ALS patients compared with control patients and correlated with disease duration [184,185]. Uric acid (UA) is an important natural antioxidant that reduces oxidative damage to cellular components by scavenging free radicals [186]. The levels of UA and creatinine (Cr) in serum have been shown to be significantly decreased in patients with ALS than in controls [182,186–191]. Intriguingly, the levels of UA in bulbar-onset sporadic ALS patients were significantly decreased compared with those in spinal onset sporadic ALS patients, and those in female sporadic ALS patients were decreased compared with those in male sporadic ALS patients [189,191]. Moreover, the baseline levels of Cr and UA in serum were negatively correlated with the annual decline of ALSFRS-R, and the annual decline level of Cr in serum was positively correlated with the annual decline of ALSFRS-R [186–188,190]. However, some studies have reported that the levels of UA in plasma were not significantly changed, and no significant correlation between the levels of UA and ALSFRS-R was seen in sporadic ALS patients [185,189].

4.2. RNA

RNAs, including noncoding RNA and miRNA, have been shown to be redox sensitive and contribute to redox signaling, indicating that RNAs could be biomarker candidates related to oxidative stress [70,192]. Some miRNAs involved in oxidative stress have been suspected to be promising biomarkers of ALS [193]. The expression levels of miR-27a, which regulates NRF2 expression, were decreased in serum and serum exosomes, and downregulation of miR-27a was correlated with the degree of muscle atrophy [194,195]. In addition, the expression levels of miR-142-5p, which regulate NRF2 expression, are decreased in the CSF of patients with sporadic ALS, and the expression levels of miR-155, which is implicated in mitochondrial dysfunction and neuroinflammation, are increased in peripheral monocytes from sporadic ALS [145,196]. Moreover, the expression levels of miR-

338-3p, which regulates expression of subunits of mitochondrial oxidative phosphorylation complexes, were increased in the serum, PBL, and CSF of patients with sporadic ALS patients [138,197].

Table 1. Promising biomarkers related to oxidative stress.

Proteins					
Related to Redox System	**Name**	**Kinds of Body Fluids**	**Changes**	**Related to Parameter of ALS**	**Reference**
Products of oxidative stress	8-OHdG	CSF Plasma Urine	Increase	8-OHdG levels in urine were negatively correlated with both the rate of change of the ALSFRS-R and the FVC	[69,74,165,166]
	MDA	Plasma	Increase	Not described	[166–168]
	HNE	Plasma CSF	Increase	HNE levels in serum were positively correlated with the extent of disease	[75]
	3-NT	CSF	Increase or no change (inconsistent result)	Not described	[169,170]
Antioxidant enzyme	Activity of SOD	RBC Plasma CSF	Increase or reduce or no change (inconsistent result)	The activity in bulbar onset sporadic ALS was significantly higher than in spinal onset sporadic ALS	[165–168,171–177]
	activity of GPX	Whole blood RBC Plasma	Reduce or no change (inconsistent result)	Not described	[166–168,172,173,178]
	GSH	Whole blood Plasma	Reduce or no change (inconsistent result)	No significant temporal change during 6 months was observed in sporadic ALS	[166,168,179,180]
	GSSG	Whole blood	Increase	Not described	[166]
	CoQ10	Plasma Serum	No change	CoQ10 levels were not influenced by clinical form, age at onset, and duration of disease	[181–183]
	Proportion of oxidized forms of CoQ10	Serum CSF	Increase	Proportion of oxidized forms of CoQ10 correlated with duration of disease	[184,185]
	UA	Serum Plasma	Reduce or no change (inconsistent result)	The levels of UA in bulbar onset sporadic ALS were significantly decreased compared with spinal onset sporadic ALS patients. The baseline levels of UA were negatively correlated with the annual decline of ALSFRS-R.	[182,186–191]
RNAs					
Related to Redox System	**Name**	**Kinds of Body Fluids**	**Changes**	**Related to the Parameter of ALS**	**Reference**
The NRF2-ARE pathway	miR-27a	Serum	Decrease	Downregulation of miR-27a was correlated with the degree of muscle atrophy	[194,195]
	miR-142-5p	CSF	Decrease	Not described	[145,196]
Mitochondrial dysfunction and neuroinflammation	miR-155	Peripheral monocyte	Increase	Not described	[145,196]
Mitochondrial dysfunction	miR-338-3p	Serum PBL CSF	Increase	Not described	[138,197]

5. Conclusions

In this review, we summarize currently established knowledge regarding oxidative biomolecular modifications and promising biomarker candidates linked to oxidative stress in ALS. Therapies targeting the elimination of oxidative stress, including edaravone administration, are developing and extensive evidence of an association between redox dysfunction and ALS is increasing, suggesting that oxidative stress is a pivotal therapeutic and biomarker target. However, the precise mechanisms underlying the relationship between oxidative stress and ALS has not been elucidated. If the present situation is to persist, it would be difficult to establish a therapy and biomarker linked to oxidative biomolecular modifications, and further investigations are required. If the underlying mechanisms between oxidative stress and ALS are clarified, oxidative biomolecular modifications would be not only be available as therapeutic targets, but also as diagnostic, predictive, and/or pharmacodynamic biomarkers.

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