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REVIEW

Retinal Damage in Amyotrophic Lateral Sclerosis: Underlying Mechanisms

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease resulting in a gradual loss of motor neuron function. Although ophthalmic complaints are not presently considered a classic symptom of ALS, retinal changes such as thinning, axonal degeneration and inclusion bodies have been found in many patients. Retinal abnormalities observed in postmortem human tissues and animal models are similar to spinal cord changes in ALS. These findings are not dramatically unexpected because retina shares an ontogenetic relationship with the brain, and many genes are associated both with neurodegeneration and retinal diseases. Experimental studies have demonstrated that ALS affects many "vulnerable points" of the retina. Aggregate deposition, impaired nuclear protein import, endoplasmic reticulum stress, glutamate excitotoxicity, vascular regression, and mitochondrial dysfunction are factors suspected as being the main cause of motor neuron damage in ALS. Herein, we show that all of these pathways can affect retinal cells in the same way as motor neurons. Furthermore, we suppose that understanding the patterns of neuro-ophthalmic interaction in ALS can help in the diagnosis and treatment of this disease.

Keywords: ALS, retina, retinal involvement, neuro-ophthalmology, mitochondrial dysfunction, excitotoxicity

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the development of progressive paralysis and muscle atrophy, leading to disability and death on average 3–5 years after the first clinical manifestations. ALS has a hereditary origin with a traceable contribution of familial predisposition in 5–10% of cases.[1,2] In the remaining 90–95% of cases, the disease develops sporadically without a strong connection with genetic links.[3,4] According to twin-based data, the concordance of ALS is about 65%.[5] Currently, 8 genes (*SOD1, TARDPB, FUS, OPTN, VCP, UBQLN2, C9ORF72* and *PFN1*) are known to be most commonly mutated in ALS, and more than 100 genes have been identified as candidates for the association with sporadic ALS.[6–9] There also exist evidences, confirming role of environmental factors such as heavy metals exposition, pesticides poisoning, soccer playing and others, in the development of sporadic ALS.[10]

Paralysis and other ALS symptoms are caused by damage to the upper motor neurons in the primary motor cortex and lower motor neurons in the brainstem and spinal cord. Degeneration of motor neurons results in the decline of the ability to control skeletal muscles and finally in death by respiratory failure. About half of patients, along with impaired motor function, have cognitive and behavioral deficits, which often are signs of the development of frontotemporal dementia (FTD), a condition that is a part of the same disease continuum as ALS.[11,12]

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The pathways of the development and progression of ALS still has many unclarified details and are subject to active study. The formation of pathological aggregates, mitochondrial dysfunction, oxidative stress, glutamate-induced excitotoxicity and impaired protein utilization processes are now considered among the most significant factors in the pathogenesis of ALS. There are still a number of uncleared points in our knowledge about the molecular pathogenesis of ALS. For instance, there is inexplicable contrast between the duration of the asymptomatic and clinical stages of ALS. The pathological process can occur in motor neurons for decades and not manifest itself clinically but, in just 1–2 years, can lead to a dramatic loss of neuromuscular transmission.[13] Moreover, it remains unclear why many individuals with ALS-associated mutations do not develop any clinical or pathological signs of the disease throughout their entire life.[4]

Are Motor Neurons the Only Target of ALS?

The progressive paralysis is the basic and pathognomonic symptom of ALS. However, the conception describing ALS as an only neuromuscular disease is outdated.[12] Motor symptoms are often complicated by cognitive deficits[14] and olfactory nerve damage.[15]

Furthermore, in some syndromic forms ALS might be complicated by extrapyramidal functions and hearing impairment[16,17] as well as the presence of schizophrenia.[18] There are also well documented skin[19] and sensory[20] abnormalities in ALS patients that may precede/accompany ALS.

Currently, the diagnosis of ALS is based on the El Escorial (or its revised version) criteria, which assess the signs of damage to the upper and lower motor neurons in various areas of the body, defined as bulbar, cervical, thoracic and lumbar areas. Due to the heterogeneity and ambiguity of clinical manifestations in the early stages of ALS, misdiagnosis remains a very common problem.

In this review, we summarize the available information on another non-classical ALS target and present data about possible mechanisms of retinal damage in this disease.

Premises for Retinal Damage in ALS

Although the visual impairment is not a routine complaint in ALS patients, a range of oculomotor disorders have been reported in ALS, including ophthalmoplegia, defective pursuit eye movements, saccadic impairments, nystagmus, and the abnormal Bell's phenomenon.[21,22] Furthermore, a growing body of evidence have revealed that visual dysfunction in ALS can also be caused by impaired retinal function.[23] Several studies have indicated the presence of direct morphological and functional signs of retinal degeneration in patients and model animals with ALS.

The phenomenon of retinal damage in ALS may be considered as a consequence of the embryonic commonality of nervous and retinal tissues. Several proteins prone to the formation of aggregates in motor neurons are highly expressed in the retina. One more premise for the retinal involvement is the presence of genetic associations common to glaucoma and ALS, including polymorphic variants of *OPTN, TBK1, PFN1*, and *ATXN2* genes. Finally, sufficient evidence exists that most neurodegenerative processes in the central nervous system (CNS) tend to involve the retina in the pathogenetic process.[24]

Clinical Evidence for Retinal Damage in ALS

In 2014, Fawzi et al revealed the in vivo and postmortem signs of retinal damage using ophthalmologic examination, contrast and color vision testing, immunohistochemistry and morphometry in two patients with the *C9orf72* mutation and the clinical picture of ALS.[25] In 2015, the same research group published another study confirming the association between retinopathy and ALS. The authors found axonal degeneration of ganglion cells by autopsy, as well as significant thinning of the retinal nerve fiber layer (RNFL) and reduced total macular thickness by optical coherence tomography (OCT). The researchers also presented the results of the eye fundus study in transgenic *UBQLN2*^{P497H} mice. They reported large ubiquilin-2-positive aggregates, mainly in the inner plexiform layer (IPL) and less often in the outer plexiform layer.[26]

Ringelstein et al reported significant thinning of the RNFL and inner nuclear layer (INL) according to the OCT data in ALS patients.[27] Similar results, expanding views about the retinal involvement, were then obtained by other research teams. Rohani et al examined 20 ALS patients and 25 healthy subjects. The average thickness of the RNFL was significantly reduced in ALS patients compared with controls. Notably, it was found in this study that retinal thinning positively correlated with the patients' motor functions, as determined by the revised ALS functional rating scale (ALSFRS-R). An important finding of this study was the revealed asymmetry of the contralateral

retinal lesions. The unequal degree of the left and right eye damage indicates that asymmetric CNS damage in ALS is not limited to the motor system.[28]

Hübers et al, using OCT and ophthalmic tests, performed an intravital morphological and functional study of the eye fundus in 71 ALS patients and 20 control subjects. The research was supplemented by an assessment of the motor neuron degeneration degree using fractional anisotropy, making it possible to analyze the correlation between motor and ophthalmic disorders. The study also revealed a significant thinning of the INL and RNFL in patients compared with controls, as well as a significant correlation between retinal thickness and the values of corticospinal tract fractional anisotropy.[29] These results were then confirmed, by another clinical exam, where Simonett et al observed a positive correlation between macular RNFL thickness and some spirometric parameters in ALS patients.[30]

Boven et al found that 64% of 25 examined ALS patients had color vision deficiency. Additionally, 72% of the ALS patients had color vision below the 50th percentile (of normal), 52% below the 25th percentile, 24% below the 10th percentile, and 8% below the 2nd percentile comparing with distribution in normal subjects. Thus, a diffuse color discrimination deficit was found in ALS subjects at a younger age than in control subjects. The method used in this work may have high diagnostic value because color vision assessment is a simple and quick test that can be easily performed in a neurological clinic, where most ALS patients are treated.[31]

In another recent study ophthalmologic examination was conducted for 5 ALS patients (10 eyes) and 10 healthy volunteers (20 eyes) revealed several changes comprising the following: 1) a significant increase in the inner ring macular thickness of the temporal and lower regions of the eye fundus; 2) significant macula lutea thinning in the lower regions of the inner and outer macular rings; and 3) significant thinning of the peripapillary RNFL in the upper and lower quadrants. Additionally, some pathological changes in the retina were correlated with motor functions according to the ALSFRS-R exam.[32]

However, the notion about correlation between ALS and structural changes in the retina remains controversial as some studies did not find retinal changes in ALS patients significantly different compared to healthy volunteers. Roth et al analyzed the retinas of 76 ALS patients (144 eyes) and 54 healthy controls (108 eyes) using OCT. The study did not obtain data confirming a difference in the retinal thickness of patients and healthy subjects, and no correlations were found between retinal and neurological state.[33] Moss et al also found no associations between visual acuity and an ALS diagnosis (generalized estimating equation models accounting for age).[34]

Notably, neurodegenerative changes in ALS were also found in other parts of the visual system in addition to the eye fundus. In 1991, Kushner et al examined the postmortem brain tissue slices of ALS patients and observed generalized reactive gliosis of cortical areas. The glial response in "cerebral infarction-like" cytological manner was particularly expressed in the occipital zone, containing the primary and extrastriate visual cortex regions.[35] Later, these findings were confirmed by electrophysiological data. Münte et al recorded the evoked potentials in three different visual experiments. The evoked potentials in all 14 healthy subjects contained the P1 component, which was absent in ALS patients. The P1 component is another indicator of visual cortex function because it emanates from the lower temporal-occipital regions.[36]

Results of studies discussed above are summarized in Table 1.

Interestingly, retinal abnormalities were regularly observed in patients with Western Pacific ALS and parkinsonism-dementia complex (ALS/PDC) which is clinically indistinguishable from classical ALS elsewhere. ALS/PDC is purely environmental disease, most plausibly caused by exposure to certain plant-derived neurotoxins in local food or medicine, or both.[37] These neurotoxins cause ALS-specific neuromuscular phenotype and ophthalmological sign described as linear retinal pigmentary epitheliopathy. Despite there is no understanding of the etiology and nature of Western Pacific ALS, neuro-ophthalmologic correlations in this pathology may indicate retinal involvement in classical ALS. Data, revealing the link of this rare sporadic form of ALS and the retinal pathology detailed in the review.[38]

Possible Mechanisms of Retinal Damage in ALS

Protein Aggregation and Dysfunction

The presence of proteinaceous inclusions in spinal cord is an obligatory sign of ALS. These inclusions may include diverse components such as neurofilaments, ubiquitin, RNA-binding proteins, and the antioxidant enzyme superoxide dismutase 1 (SOD1) and others. In most cases, such inclusions are immunopositive to ubiquitin/p62, ubiquilin-2 and p-TDP43.[39,40]

Table 1 Retinal Pathology in ALS Patients, Clinical Observations

Subjects	Method(s)	Symptoms/Pathomorphology	Reference
2 patients with ALS caused by mutation in *C9ORF72* gene	• Neuro-ophthalmologic exam; • OCT; • Postmortem histological exam of retina and optic nerve (morphometry, immunohistochemistry)	• Axonal degeneration of ganglion cells; • Significant thinning of the RNFL; • Reduced total macular thickness; • p62-positive inclusions at all levels of the INL	Fawzi et al, 2014[25]
20 patients with clinically definite and 4 patients with probable ALS	• SD-OCT	• Subtle reduction in the macular thickness and the RNFL; • Thinning of the INL	Ringelstein et al, 2014[27]
20 ALS patients	• SD-OCT	• Significant thinning of the RNFL; • Positive correlation between ALSFRS-R score and RNFL thickness; • Asymmetry of the contralateral retinal lesions	Rohani et al, 2018[28]
71 ALS patients	• SD-OCT; • Diffusion tensor imaging	• Significant thinning of the INL and RNFL; • Correlation between retinal thickness and the values of corticospinal tract fractional anisotropy	Hübers et al, 2016[29]
21 ALS patients	• SD-OCT	• Significant thinning of the RNFL; • Positive correlation between RNLF thickness and pulmonary function tests	Simonett et al, 2016[30]
25 patients with a diagnosis of definite or probable ALS	• L'Anthony D15 color test (desaturated)	• 64% subjects had impaired colour vision (more prominent in younger ALS patients)	Boven et al, 2017[31]
76 ALS patients	• SD-OCT	• No differences	Roth et al, 2013[33]
25 individuals with sporadic possible, probable or definite ALS	• Assessment of binocular or monocular high contrast visual acuity or low contrast visual acuity	• No differences	Moss et al, 2016[34]
5 ALS patients	• SD-OCT	• Increased thickness of the inner macular ring temporal and inferior areas; • Progressive macular thinning in the inner and outer macular ring inferior areas; • Progressive pRNFL thinning in the superior and inferior quadrants; • Moderate correlation between some OCT pRNFL parameters and ALSFRS-R score	Rojas et al, 2019[32]

Abbreviations: ALS, amyotrophic lateral sclerosis; OCT, optical coherence tomography; SD-OCT, spectral domain OCT; RNFL, retinal nerve fiber layer; INL, inner nuclear layer; ALSFRS-R, revised ALS functional rating scale.

SOD1

SOD1 is a Cu/Zn-dependent enzyme whose function is to remove excess superoxide anion from the cell by converting it to oxygen. The gene encoding this protein was the first found to be associated with ALS. The gene encoding this protein was the first gene showed to be linked to ALS. Mutant SOD1 have instable structure with loss of enzyme function and prone to formation of insoluble aggregates resulting in oxidative stress and neurotoxicity.[41] To date, more than 180 different mutations have been identified in the *SOD1* gene, causing about 12% of familial and approximately 2% of sporadic cases of ALS.[11]

Retinal involvement of SOD1 was confirmed in murine model with ALS-causative *hSOD1G93A* transgene.

Studying these mice, Ringer et al found a pronounced vacuolization of neurons both in olfactory bulb and retina on the 60th day after birth. The study of retinal tissue dynamics at different periods revealed an increase in the vacuole size to the disease's final stage. hSOD1-immunoreactive vacuoles were localized mainly in the dendrites of excitatory neurons in the retina IPL.[42]

Mutant SOD1 may be involved in retinal pathology not only because of its proteotoxic effect but also because of the antioxidant function loss. A study conducted by Hashizume et al identified several retinal abnormalities in SOD1-deficient mice. For instance, aged *Sod1*$^{-/-}$ mice exhibited decreased amplitudes of a- and b-waves of the electroretinogram, evoked by stimuli of different intensities. Histological examination showed progressive retinal degeneration and abnormalities in the inner and outer layer of nuclear cells. Additionally, electron microscopy revealed swollen cells and degenerated mitochondria in the inner nuclear layer and outer layer of nuclear cells in transgenic animals, indicating cell death by necrosis.[43] Further, the same research group complemented these results by clinical data reporting significant decrease in the serum level of SOD1 in normal tension glaucoma patients.[44]

TDP-43

The TDP-43 (encoded by the *TARDBP* gene) protein is the most often detected component of pathological inclusions in various forms of ALS. In healthy neurons, this protein is located mainly in the nucleus,[45,46] where its functions are associated with the regulation of RNA metabolism and transcription as well as with the formation of intranuclear structures – paraspeckles.[47] However, a certain amount of TDP-43 is also found in the cytoplasm. Generally, TDP-43 is a DNA- and RNA-binding protein involved in biological processes such as DNA repair,[48] transcription suppression, alternative splicing regulation, microRNA synthesis and RNA transport.[45,49,50] More than 20 different mutations in *TARDBP* have been identified, together accounting for about 1–5% of all ALS familial cases.[51]

At the moment, there are no studies revealing the involvement of TDP-43 in ALS-associated retinal injury. However, Ward et al have found the linkage between the depletion of the TDP-43 nuclear pool and retinal thinning in the murine model of FTD on the background of a *Grn* gene mutation.[52] This finding indicates the possible involvement of TDP-43 in retinal damage for genetically and pathologically overlapped ALS and FTD.

Recently, histological evaluation of postmortem enucleation specimens collected from subjects with chronic traumatic encephalopathy (CTE) showed accumulation of phosphorylated TDP-43 (pTDP-43) in retinal inner nuclear layer interneurons on the background of normal morphological state and retinal thickness. TDP-43 staining was commonly found in CTE eyes (7/8 cases), but rarely seen in control eyes (1/8) suggesting that TDP-43 is an important player in the visual impairment reported in patients with CTE.[53]

FUS

About 5% of familial cases of ALS are associated with mutations in the gene encoding the FUS protein (fused in sarcoma).[54–56] FUS is closely similar to TDP-43 in its structural and functional features: both proteins have a glycine-rich, prion-like domain, which determines their tendency to aggregation, contain RNA-recognizing RRM motifs.[57–60]

TDP-43 and FUS are involved in the net of interconnected nuclear and cytoplasmic processes, including DNA damage repair, mRNA processing and transport, translation, cellular stress response.[60–63] That emphasizes the importance of impaired DNA/RNA metabolism and protein homeostasis as a factor determining the sensitivity of motor neurons to damage and, consequently, to the development of neurodegeneration.[64]

At the moment, there are no direct evidence showing the association between pathogenic FUS and retinal damage. Nevertheless, FUS contributes in N-methyl-D-aspartate receptors (NMDARs) subunits transport in RGN,[64–66] suggesting its dysfunction can affect glutamate transmission.

OPTN

Defective optineurin (*OPTN* gene) is another causal protein for the ALS development. An association between *OPTN* polymorphism and ALS was first discovered in a small group of patients in the Japanese population.[67] Further research confirmed the strong linkage between *OPTN* mutations and ALS development.[68–70] Normally, optineurin is responsible for the inhibition of the nuclear factor kappa-B (NF-kB).[71] It acts as an autophagy receptor[72] as well as participates in the regulation of vesicular transport and maintenance of the Golgi apparatus functions.[73] In pathological conditions, mutant optineurin forms thread-like neuronal TDP-43- and ubiquitin-positive inclusions. Inclusions of a similar composition are also

formed during mutations in *UBQLN2* gene, coding another ALS-causative protein ubiquilin-2.[74]

As already mentioned, *OPTN* is a gene associated with both ALS and glaucoma. In a 2002 study of families with normal tension glaucoma, Rezaie et al found that *OPTN* mutations are associated with 16.7% of disease cases.[75] Glaucoma-related *OPTN* mutations are mostly missense mutations, while ALS-related mutations include deletions, missense mutations, and nonsense mutations. In general, glaucoma-associated mutations are not associated with ALS, with one exception, a two-base pair insertion in exon 6, which is very rare.[76] Nevertheless, optineurin was shown to be involved in retinal damage and it can be important link in our understanding of ophthalmic side of ALS.

C9ORF72

The most common mutation in ALS is hexanucleotide repeat expansion at the *C9ORF72* locus, that was found in more than 30% of familial and about 7–9% of sporadic cases of ALS in the European population.[11,77] Patients with this mutation have up to hundreds or thousands GGGGCC repeats in *C9ORF72* locus whereas no more than 25 repeats are presented normally.[78] Patients with this type of mutation can develop both ALS and FTD. The functions of the protein encoded by *C9ORF72* have not been finally determined, but its interaction with the family of small Rab-GTPases, in which it acts as a regulator of autophagy[79] and endosomal transport[80] has been shown. This protein interacts with various components of the nuclear pore complex, participating in nuclear-cytoplasmic transport.[81] It was shown that mutations in *C9ORF72* lead to increased nuclear permeability.[82] Protein product of *C9ORF72* is also involved in the regulation of lysosome function[83] and formation of stress granules.[84] GGGGCCs translated into dipeptides (DPR, dipeptide repeat proteins) through ATG-independent translation (repeat-associated non-ATG (RAN) translation) can form intranuclear and cytoplasmic aggregates.[85–88] Another mechanism of C9ORF72 expansion toxicity is forming of GGGGCC-contained RNA foci that can interact with some proteins, important for RNA metabolism, for example ADARB2, thereby disrupting their function.[89–91]

The connection between hexanucleotide expansion and ophthalmologic disorders demonstrated by Fawzi et al has already been mentioned previously.[25] In this study, dipeptide aggregates were identified as a probable cause of decreased visual function in a patient with familial ALS and expansion of the GGGGCC hexanucleotide repeats in the *C9ORF72* gene (C9-ALS). After the death of this patient, a morphological and immunohistochemical examination of the retina, optic nerve and CNS was performed, revealing p62-positive, pTDP43-negative perinuclear inclusions in the inner nuclear layer of the retina and brain. In-depth analysis showed that most of the p62-positive retinal inclusions were found in bipolar cells of the cones, as well as in some amacrine and horizontal cells.

Endoplasmic Reticulum Stress

Endoplasmic reticulum (ER) stress represents the state when ER is unable to maintain a balance between the synthesis and utilization of produced proteins. As a result of this imbalance, misfolded proteins accumulate in the cytoplasm that leads to cell damage.[92–94] Chronic or severe ER stress triggers apoptotic cell death.[95,96] ER stress is considered as a mechanism of vulnerability of motor neurons to pathology in ALS.[97–99] Signs of ER stress were found in tissues from patients with familial and sporadic forms of ALS, as well as in cellular and animal models of the disease.[100–103] Moreover, ER stress is one of the earliest pathological event in the familial forms of ALS. Additionally, mutations in *PDIA1* and *PDIA3* genes, which are directly involved in the maintenance of protein homeostasis, were associated with ALS.[104,105]

Nerve cells, including photoreceptors, have a high basic level of metabolism and protein synthesis, making them more sensitive to ER stress. Inability of retinal cells to cope with ER stress caused by abnormal protein aggregation or dysfunction of key proteins involved in this process can be considered as a mechanism for the development of ophthalmic diseases.[106] Malfunction of key ER stress signaling proteins was shown to be associated with retinal pathology. For instance, mutations in ER stress sensor gene *ATF6* lead to age-dependent degradation of photoreceptors in both humans[107] and mice.[108] Dysfunction of another ER stress mediator XBP-1 also leads to retinal degeneration.[109] Induction of ER stress by the chemical substance tunicamycin causes the death of photoreceptor cells.[110,111] Additionally, activation of ER stress is observed in light-induced retinal degeneration[112] and death of retinal ganglion cells (RGC) caused by damage to the optic nerve.[113]

Disruption of Nuclear Import

As already noted, dysregulation of nuclear-cytoplasmic transfer is one of the important factors in the pathogenesis of ALS. A disruption in the structure of the nuclear localization domain promotes the release of several proteins into the cytoplasm, where they form aggregates.[82] Such events occur, for instance, with the mutant FUS or TDP-43. Another reason for the loss of nuclear localization is mutations in proteins that provide nuclear-cytoplasmic transfer.[114]

Disruption of nuclear import has also been shown in the retinas of mice with FTD symptoms.[52] Cho et al demonstrated that retinal RGN and motor neurons share common mechanisms of dysregulation of nuclear-cytoplasmic transport due to the loss of *Ranbp2*. Moreover, similar to motor neurons, RGN respond by hypertrophy and a decrease in the axonal caliber of axons. Functionally, these effects are accompanied by a delay in visual cortical responses to light stimuli.[115]

Vascular Regression

The retinal vasculature is one of the most vulnerable tissue to various pathological processes.[116] In this regard, the data concerning changes in retinal vessels in ALS have particular interest. Clinical and experimental data accumulated in recent years has indicated that vascular abnormalities can precede neurodegeneration and aggravate it. For example, changes in the microvessels of the skin, muscles, and CNS were found in ALS patients.[117,118]

Transgenic mice expressing mutant forms of *SOD1* and *FUS* are predisposed to vascular disorder development whereas vasotropic drugs can delay disease onset in them. Thus, Crivello et al found that the systemic administration of recombinant human angiopoietin increased survivability, retarded motor dysfunction, and protected against the loss of motor neurons and vascular regression in *SOD1G93A* mice.[119] Later, the same research group found a significant decrease in the vascular density of the lumbar spinal cord in FUS (1–359) mice.[120]

An endothelium pathology,[121,122] accompanied by decreased *Ang1* and *Vegf* expression,[123] develops in mutant SOD1 G93A mice even before disease onset. Some studies show a decrease in CNS vascular perfusion in mice and ALS patients.[121,124,125]

Moreover, pathological changes in the macro- and microvasculature of the eye fundus have been directly described in ALS patients. In particular, an increase in the thickness of the outer wall of the superior or inferior temporal retinal artery was found compared with that in healthy controls. At the same time, the character of visible changes indicates a possible deposition of b-amyloid in the vascular wall.[126]

Excitotoxicity

Another obvious pathway for retinal damage during ALS may be an increase in glutamatergic transmission.[127,128] The involvement of glutamate, its receptors and transporters in neuronal death has been found in many neurodegenerative processes, including ALS,[129] Parkinson's disease,[130,131] Alzheimer's disease,[132–134] dementia with Lewy bodies[132] and Huntington's disease.[135] Interestingly, the only drug that prolongs survival of ALS patients is riluzole, the glutamate neurotransmission blocker.[136,137] At the same time, the toxic effects of glutamate on the retina are well-known.[138,139] Actually, retina is the first tissue in which glutamate-induced injury was discovered.[140]

Acting as a classic excitatory neurotransmitter,[141] glutamate is involved in various processes: synaptogenesis, synaptic plasticity, long-term potentiation, and energy metabolism.[142,143] This amino acid realizes its effects through ionotropic and metabotropic receptors. NMDA-, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA-) and kainate belong to ionotropic glutamate receptors.[144] Metabotropic glutamate receptors are presented by 8 types (mGluR1-8) and divided into three groups depending on the structure and function. Their stimulation is associated with the activation of G-proteins and has a broad effect on neuronal functioning, including the glutamate release level and ion influx degree.[143]

An increase in glutamatergic transmission due to several pathological processes leads to the damage and death of neurons – so called "glutamate excitotoxicity". Excessive glutamatergic stimulation results in the increased intake of calcium, zinc, sodium and potassium. The main important role in glutamate excitotoxicity is shown for the calcium overload. Influx of Ca^{2+}-ions activates the caspase-dependent and caspase-independent pathways of apoptosis[145,186-188] as well as stimulates oxidative and nitrosative stress.[146,147] The key cellular transductors of glutamate excitotoxicity are ionotropic NMDA receptors (NMDAR's). The stimulation of glial NMDARs leads to an increase in the production of proinflammatory cytokines, whereas mice with type 1 NMDAR deficiency are significantly protected from glutamate excitotoxicity.[148] Similarly, administration of

NMDAR's-blockers such as ketamine or memantine, ameliorates retinal injury in rodents.[149,150]

Another intracellular factor mediating the retinotoxic effects of glutamate is GTPase RhoA.[151,152] Activated RhoA triggers nerve cell damage cascades[153] that upregulate inflammatory pathways.[154] Pharmacological inhibition of this factor significantly reduces damage to the ganglion cell layer and IPL of the rat retina with NMDA-induced retinopathy.[151,152] A more than twofold increase in brain RhoA kinase is found in mice with the *SODG93A* mutation and an ALS clinical and morphological picture.[155] Thus, brain cells become much more sensitive to the toxic effects of glutamate. If the same increase in the expression of this enzyme occurs in the retina (which is very likely), it is logical to assume that the eye fundus becomes much more sensitive to the glutamatergic effects during ALS.

According to its wide range of functions mGluRs may also be involved in retinal damage during ALS. Accumulated data show that stimulation of glial mGluRs may contribute to glial proliferation and astrogliosis in ALS.[156] Important role of mGluRs was especially shown for group I. Bonifacino et al showed a significant increase in the expression of group I mGluRs (types 1 and 5) in *SOD1G93A* mice. The authors suggest that exactly group I mGluRs can cause an increase in glutamate release, triggering glutamate-induced neurodegenerative processes.[157] mGluR5 levels were also increased in human ALS brains in vitro. Simultaneously, group I mGluRs play an important role in physiology and pathology of retina. For instance, in Müller cells, mGluR5 receptors are known to modulate the transcription and translation of an inward-rectifying potassium ion channel, $K_{ir}4.1$.[158] Furthermore, mGluR5 is activated in a rat model of chronic ocular hypertension, leading to suppression of Kir currents and reduced expression of $K_{ir}4.1$.[159] Interestingly, suppression of mGluR5 activity can ameliorate both neurodegenerative and retinal pathology. Inhibition of mGluR5 ameliorated retinitis pigmentosa in rats[160] whereas pharmacological allosteric mGluR5 inhibitor CTEP reversed the course of neurodegeneration in transgenic murine models of AD.[161]

Mitochondrial Dysfunction

Mitochondria, known as "energy plants of the cell", are responsible for the production of the cell's most "energy currency" in the form of ATP.[162] In addition to ATP production, mitochondria are involved in various other cellular processes, including amino acid and nucleotide metabolism, protein synthesis, fatty acid metabolism, ion homeostasis, and apoptosis.[163,164] Impaired mitochondrial function or mitochondrial dysfunction (MD) is a key link in cell damage during many hereditary and acquired disorders. MD arises from an inadequate number of mitochondria or an inability to provide necessary substrates to mitochondria, as well as a dysfunction in their electron transport and ATP-synthesis machinery.[165]

MD has been implicated to play a role in motor neuron death in ALS. The fragmentation of mitochondria as well as changes in mitochondrial morphology and expression of fusion/fission proteins are well described in ALS and have pronounced effects on normal mitochondrial function.[166] Defective mitochondrial transport may be responsible for the accumulation of abnormal mitochondria in motor neuron axons seen in the animal models of ALS and also in human patients.[167]

It has been shown that many genes and proteins associated with both familial and sporadic ALS and FTD, including FUS,[168,169] TDP-43,[170,171] SOD1[172,173] and C9ORF72,[174] are involved in mitochondrial function, causing mitochondrial damage associated with neurodegeneration.[175,176]

Like motor neurons, retinal cells, have a very high mitochondrial density and dependence on aerobic metabolism.[177,178] Approaches to treat mitochondria are seen as an effective way of therapy for retinal diseases such as glaucoma.[179] Mitochondrial genes are among the most highly expressed in the retina, accounting for about 10% of the transcriptome.[180] Mutations in genes associated with mitochondrial function are very often manifested in the form of ophthalmic diseases, such as Leber's hereditary optic neuropathy,[181,182] dominant optic atrophy,[183] Wolfram's syndrome,[184] and age-related macular degeneration.[185] All of these findings indicate that mitochondrial dysfunction arising in ALS influences the retina state and MD in ALS is one of the likely pathways for retinal degeneration.

Possible mechanisms of retinal damage in ALS that have been discussed above are represented in outline in Figure 1.

Perspectives

Significant point in the field of ALS studies is the understanding that the disease can extend far beyond motor neurons. Detected morphological and functional retinal disorders in patients indicate the retina is also one of

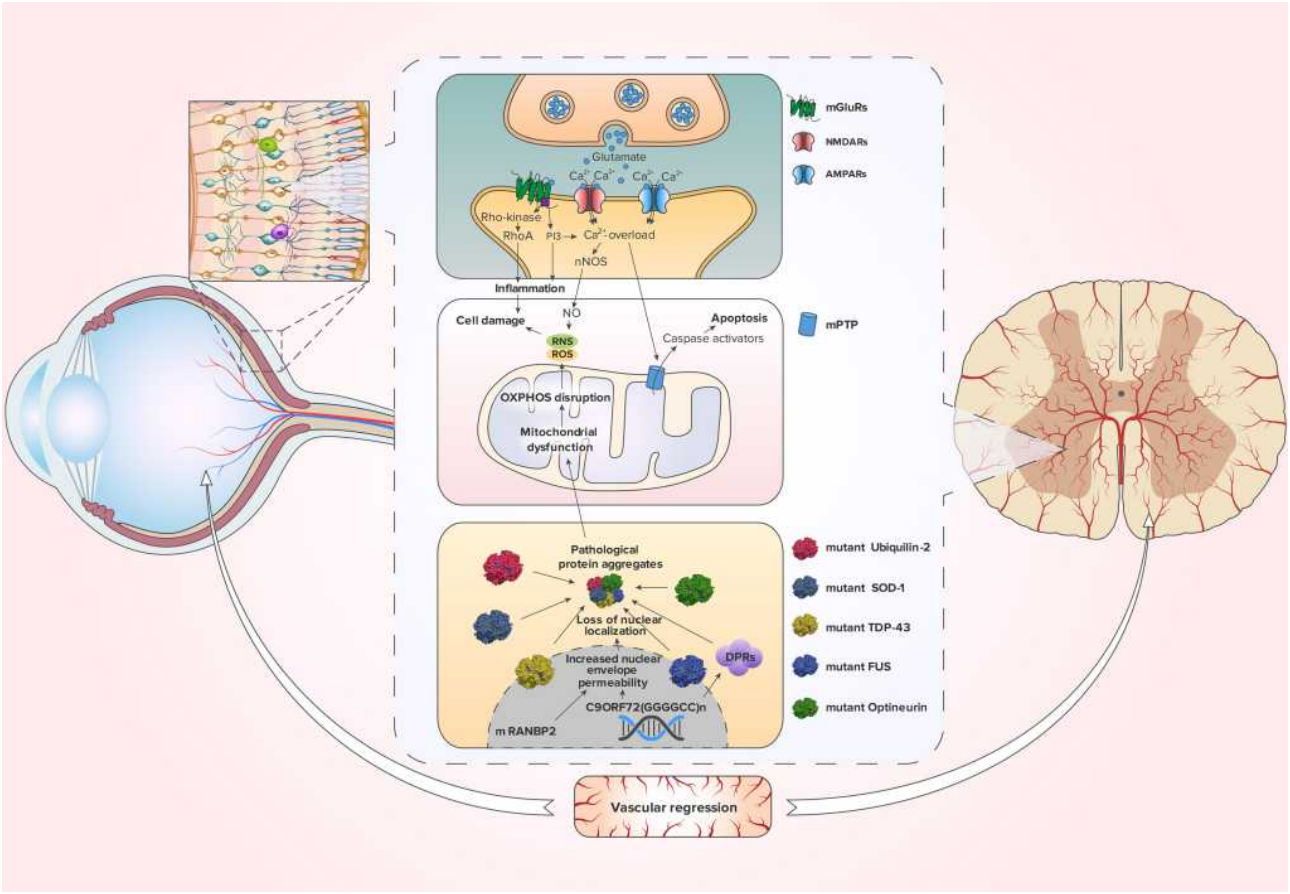

Figure 1 Pathological pathways that retina cells can share with motor neurons in ALS.

Notes: Excessive release of glutamate leads to the stimulation of NMDARs, AMPARs and mGluRs. Activated NMDARs and AMPARs open up and create Ca^{2+}-influx. Overload by Ca^{2+} causes mitochondrial permeability transition pore (mPTP) opening. As aresult, the mitochondrion swells, collapses, and releases caspase activators, which lead to caspase-dependent apoptosis.[175,176,186] Additionally, activation of NMDARs is closely coupled to the generation of nitric oxide (NO) through neuronal nitric oxide synthase (nNOS),[136] which promote reactive nitrogen species (RNS) and subsequent reactive oxygen species (ROS) production.[177] Moreover, through mGluRs, glutamate activates RhoA and IP3, which stimulate inflammation and cell damage.[187] ALS-associated mutations in SOD-1, Ubiquilin-2 and Optineurin, affecting their functions and causing protein aggregation, enhance mitochondrial dysfunction. Furthermore, mitochondrial dysfunction leads to the rupture of the oxidative phosphorylation (OXPHOS) process, resulting in the production of ROS. The same phenomenon occurs with the FUS proteins and TDP-43, which lose their nuclear localization with increasing nuclear permeability. The hexanucleotide expansion of the C9ORF72 gene and dysfunction of the RANBP2 protein contribute to the decrease in nuclear permeability. Dipeptide repeats (DPRs) that are encoded by disrupted C9ORF72 are also involved in aggregate formation. These processes can also be complicated by vascular regression.

possible ALS targets. Further study of retinal state in ALS is important because retinal changes can serve as one of the signs, contributing to early diagnostics or disease prediction. Indeed, the late diagnosis is one of the main problems in neurodegenerative diseases. While the process has already started at the molecular level, the patient does not feel any symptoms for a long time. Unfortunately, by the time the disease manifests itself, about 50% of neurons can be damaged.

At the moment, only one drug, riluzole, has been clinically proven to be effective in delaying death in ALS. A recent study has shown that riluzole acts by prolonging stage 4 ALS rather than by slowing the entire disease course or prolonging intermediate stages.[137] Edaravone, the second agent received FDA approval for ALS can slow the various stages progression but not influence lifespan.[189] Therefore, currently, the early detection of the disease for early initiation of therapy has not been confirmed to be strategically important for extending a patient's life. However, early detection or prediction of ALS remains important for studying drugs influencing early stages of ALS and for development approaches preventing or delaying the disease onset such as gene or cell therapy.

In addition to the practical aspect, the problem of retinal involvement in ALS is of fundamental importance. The retina is a very delicate tissue sensitive to any damaging influences. For instance, the retina is a prime target of

hypertension,[116] diabetes[190] and neurotoxic poisons[191]. Furthermore, the retina is predominantly consisted of nerve tissue and has a proteomic composition similar to the brain.[192] However, retinal damage is not a classic symptom of any neurodegenerative disease. As previously mentioned, some researchers have found no pathological changes or thinning of the retina in ALS patients. These findings can be explained by a simpler organization of the retina than that in the brain. Despite all the similarities in the organization of the retinal and nervous tissues, it is known that about 80–95% of all human genes are involved in the development and functioning of the brain, but for the retina, this number is about 65%.[180] However, there may be other undisclosed reasons for this phenomenon and elucidating the molecular nature of such paradox may shed light on the defense mechanisms that the retina, but not motor neurons, uses. Mimicking these mechanisms can help us in the development of new ways of neuroprotection.

Abbreviations

ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scale; AMPAR, α-amino -3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CNS, central nervous system; CTE, chronic traumatic encephalopathy; INL, inner nuclear layer; IPL, inner plexiform layer; FTD, frontotemporal dementia; mGluR, metabotropic glutamate receptor; MD, mitochondrial dysfunction; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NLS, nuclear localization signal; NMDAR, N-methyl-D-aspartate receptor; NR1, NMDAR subunit NR1; OCT, optical coherence tomography; OXPHOS, oxidative phosphorylation; PY-NLS, proline-tyrosine nuclear localization signal; Rab, Ras-related in brain; RGNs, retinal ganglion neurons; RhoA, Ras homolog family member A; RNFL, retinal nerve fiber layer; RNS, reactive nitrogen species; ROS, reactive oxygen species; SD-OCT, spectral domain OCT; SOD1, superoxide dismutase 1; TDP-43, transactive response DNA binding protein 43 kDa.

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