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The Molecular Mechanisms and Therapeutic Approaches of Amyotrophic Lateral Sclerosis (ALS)

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Abstract. Amyotrophic Lateral Sclerosis (ALS) is a chronic, progressive neurodegenerative disease that primarily damages upper and lower motor neurons. This leads to muscle weakness, atrophy, and ultimately impairs motor function. Currently, there is no cure. Its pathogenesis is closely linked to genetic and environmental factors, as well as their interactions. Approximately 10% of cases are caused by gene mutations. The main pathogenic genes include C9orf72, SOD1, FUS, and TARDBP, which damage neurons through mechanisms such as RNA metabolism disorders and toxic protein aggregation. Among environmental factors, toxin exposure, pesticide contact, and unhealthy lifestyle habits can accelerate neurodegeneration via oxidative stress and mitochondrial damage. In terms of treatment, current strategies mainly focus on targeted interventions. Drugs like tofersen, which target SOD1 mutations, are already in clinical use. However, treatments for genetic abnormalities such as C9orf72, FUS, and TARDBP remain in the research phase. Additionally, chelating agents can be used to remove heavy metals, and anti-inflammatory drugs to block the damage process in response to environment-related pathogenic factors. This article systematically reviews the genetic and environmental risk factors, core molecular mechanisms, and targeted therapeutic strategies for ALS, aiming to provide a theoretical reference for early intervention and the development of novel treatment options for this disease.

Keywords: Amyotrophic lateral sclerosis, Gene, Targeted therapeutic strategies

1. Introduction

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is a chronic and progressive neurodegenerative disorder. It primarily damages upper motor neurons, lower motor neurons, as well as the trunk, limb, and craniofacial muscles innervated by these neurons. Specifically, the nerve fibers of upper motor neurons originate from the brain, extend downward to connect with the spinal cord, and are responsible for transmitting motor commands from the brain to the spinal cord level. In contrast, the fibers of lower motor neurons directly emerge from the spinal cord and ultimately distribute to muscles throughout the body, tasked with further relaying the commands received by the spinal cord to the muscles and triggering muscle contraction [1].ALS exerts a devastating impact on both sets of motor neurons — as the disease progresses, upper and lower motor neurons gradually degenerate and die. When motor neurons are damaged, their ability

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to transmit signals is completely lost, leaving them unable to send instructions for muscle contraction or relaxation to the muscles. Deprived of regulation by nerve signals, the muscles lose normal functional support, leading to symptoms such as weakness and atrophy, which ultimately impair the body's motor capacity [2].

Worldwide, the annual incidence is about 1-2 cases per 100 000 people, and the average life expectancy after diagnosis is only 3-5 years. The cause of most ALS is still unclear, so it cannot be completely cured at present. Current therapeutic drugs such as riluzole can only play a weak role, if it can prolong the life of patients by 2-3 years, it is not a radical cure. Therefore, the pathogenic factors and treatment of this disease are still of great concern. At present, about 10% of ALS patients can be clearly traced to genetic factors, that is, specific gene mutations leading to the occurrence of the disease. In the remaining 90% of patients, the cause of the disease is unknown. Most current theories believe that its occurrence is closely related to the complex interaction between genetic factors and external environmental factors, which may induce the degeneration of motor neurons under the joint influence of both factors. Therefore, this article intends to explore the risk factors, molecular mechanisms and corresponding treatment methods of ALS, in order to provide more theoretical reference for future diagnosis and treatment [3].

2. Genetic factors

More than 40 disease-treating genes have been identified, of which C9orf72, SOD1, FUS and TARDBP are the most common and well-studied.

2.1. C9orf72 gene

C9orf72 is the most important pathogenic gene in familial ALS. It is located in the short arm of human chromosome 9, and its mutation form is "G4C2 hexanucleotide repeat expansion", that is, the abnormal duplication of a specific G4C2 segment within the gene (the normal number of repeats is usually less than 30, and the mutation increases to hundreds to thousands of times). This mutation accounts for about 40% of familial ALS cases and also exists in a small number of sporadic ALS (sALS) cases (about 5%-7%). It is the most important known ALS pathogenic gene. The pathogenic mechanism of G4C2 is mainly through two ways to damage motor neurons. First, the abnormally repeated G4C2 segment will transcribe a large number of Rnas containing repetitive sequences, which will form "RNA aggregates" in the cell and interfere with the normal RNA metabolism (such as obstructing the transport and translation of other Rnas), leading to cell dysfunction. Secondly, these abnormal Rnas will also produce a variety of toxic proteins containing repetitive amino acids (such as polyglycine-alanine, polyglycine-arginine, etc.) through "repeat-associated non-ATG translation", which will accumulate in the nucleus and cytoplasm of motor neurons. The destruction of cytoskeleton structure and inhibition of mitochondrial function eventually leads to neuronal death.

2.2. SOD1 gene

SOD1 is the first identified pathogenic gene for ALS. The SOD1 gene (superoxide dismutase 1 gene) is located on chromosome 21, and its encoded SOD1 protein is an important intracellular antioxidant enzyme. Its normal function is to remove superoxide anion free radicals in the body and protect cells from oxidative stress damage. Its mutations currently account for about 10% to 20% of familial ALS cases and are also present in 1% to 2% of sporadic cases. The core problem of ALS

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caused by SOD1 gene mutations is "abnormal protein function". On the one hand, some mutations will cause SOD1 protein to lose its original antioxidant ability, leading to a large amount of intracellular free radicals accumulation and oxidative stress damage. On the other hand, and more critically, the mutated SOD1 protein "misfolds" and forms insoluble protein aggregates. These aggregates not only fail to perform normal functions but also deposit in the cytoplasm and mitochondrial membrane of motor neurons, destroying mitochondrial energy metabolism function, interfering with neurotransmitter transport, and activating the "apoptotic pathway" in the cells, which eventually leads to neuronal apoptosis.

2.3. FUS and TARDBP genes

They are key pathogenic genes affecting RNA metabolism. Mutations in FUS (the fusion protein gene) and TARDBP (the TAR DNA-binding protein gene), both "RNA-binding protein genes," account for 4%-5% and 2%-3% of familial ALS cases, respectively, and are detected in a small amount (about 1%) of sporadic cases. The pathogenic mechanism of these two genes is similar, and they are closely related to "RNA metabolism disorder". Generally, FUS and TARDBP proteins are responsible for the regulation of RNA transcription, splicing, transport and degradation, and are key molecules to maintain the normal function of nerve cells. When these two genes are mutated, the encoded proteins will have abnormal nuclear localization, showing that they should originally play a role in the nucleus, but after the mutation, a large number of proteins are retained in the cytoplasm and toxic protein aggregates are formed. These aggregates can hinder the normal processing and transport of RNA, leading to the failure of nerve cells to synthesize essential proteins. They can also damage the function of "stress granules" (RNA-protein complexes formed by cells in response to stress) in the cytoplasm, interfere with the cell's stress defense mechanism, or directly damage mitochondria and endoplasmic reticulum, leading to intracellular environment disorder. This eventually leads to motor neuron degeneration [4].

3. Environmental factors

3.1. Toxicant exposure

Long-term intake of water and aluminum cooking utensils with excessive aluminum content can lead to the accumulation of neurotoxic proteins, interfere with calcium signals, destroy mitochondria, and promote the aggregation of toxic proteins. The incidence of ALS in people in contaminated areas is 2-3 times higher. Lead (mainly from industrial waste gas) may inhibit enzyme activity and block neurotransmitter transmission; Mercury (mainly from seafood), on the other hand, may cross the blood-brain barrier and damage cell membranes, and workers associated with mercury are at increased risk. Cadmium and arsenic can accelerate neurodegeneration through oxidative damage and mitochondrial destruction.

3.2. Pesticides and herbicides

Cholinesterase in organophosphorus pesticides (such as dichlorvos) can lead to the accumulation of neurotransmitters, causing neuronal "excitotoxicity" and promoting oxidative stress. Paraquat can damage mitochondria and promote neuroinflammation. Glyphosate can interfere with amino acid synthesis, disrupt intestinal flora, aggravate nerve damage, and directly affect the survival of motor neurons in the core of ALS.

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3.3. Industrial chemicals

Benzene, toluene, vinyl chloride and other chemicals (chemical industry) damage nerve DNA, demyelinate, disturb RNA metabolism. For example, vinyl chloride induces abnormal FUS protein, which synergistically with genetic mechanism to accelerate motor neuron degeneration, and become an important cause of sporadic ALS.

3.4. Chronic cumulative damage caused by unhealthy living habits

Inhaling nicotine from long-term smoking causes blood vessels to shrink and nerve ischemia, and its tar polycyclic aromatic hydrocarbons damage DNA and carbon monoxide reduces oxygen carrying capacity. Studies have shown that people who smoke for 20 years have a 1.8 times higher risk of developing the disease, and it takes more than 10 years to quit smoking to reduce the risk. Excessive drinking is also one of the factors. Alcohol can directly penetrate the blood-brain barrier to damage the nerve, and the metabolite acetaldehyde promotes oxidative stress and inflammation, resulting in vitamin B1 deficiency and affecting the nerve energy supply. Als-like symptoms are present in 10% of patients with alcoholic peripheral neuropathy. In addition, staying up late and sleep disturbance are possible therapeutic factors, and insufficient sleep (< 6 hours) or poor quality can lead to elevated stress hormones, accumulation of neurotoxic substances, immune disorders, and increased neurological mortality in experimental mice [5].

3.5. Physiological and external stimulus

In general, the incidence is 1.5-2-fold higher in men than in women (androgen increases oxidative sensitivity, estrogen is protective); In addition, the incidence is generally high between the ages of 40 and 60 years because of the decline in nerve repair and antioxidant capacity. In addition, some head trauma and repeated and severe trauma can lead to neuromechanical damage, inflammation, and abnormal accumulation of pro-protein, and the incidence of ALS is 4 to 5 times higher. The waste produced by muscle hypoxia can damage the nerves and increase the probability of exposure to toxic substances. The risk of ALS in people who work for more than 40 hours per week is 1.7 times higher than that in ordinary people.

4. Treatment

4.1. Targeting "genetic causative factors"

4.1.1. For SOD1 mutations

Mutations in the SOD1 gene cause the proteins it makes to "misfold," and the misfolded proteins pile up and become toxic to nerve cells. One of the approved drugs, tozasentan, acts like scissors, finding mRNA from the mutated SOD1 gene, binding it, and degradation, reducing production of the wrong protein. Therefore, there's less toxic protein in the nerve cells. Clinical studies have found that it can significantly reduce the amount of SOD1 protein in the cerebrospinal fluid of patients and also slow down the decline of respiratory function and exercise ability, especially in patients with early disease and severe mutation.

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4.1.2. For the C9orf72 mutation

There is a "G4C2 hexanucleotide" in the C9orf72 gene that repeats too much, which will produce two toxic substances, such as abnormal RNA, which will disrupt the normal work of RNA in cells and load the nucleus; Specific toxic peptides, such as GP, GA, and GR peptides, can damage cellular structures. Two approaches are under study, such as antisense oligonucleotides (such as BIIB078) that specifically bind to the abnormal Rnas, preventing them from forming toxic structures, and reducing the production of toxic peptides. Rna-targeting small-molecule drugs (such as quizatinib), which cross the blood-brain barrier, find and bind to the G4C2 repeat RNA, and inhibit its toxicity, are currently in phase 2 clinical trials.

4.1.3. Against FUS/TARDBP mutations

When FUS and TARDBP are mutated, they make RNA-binding proteins that should enter the nucleus, but instead remain in clumps in the cytoplasm, disrupting RNA transcription and splicing (key steps in cellular "information processing"). There are two main directions of research: using small molecule drugs to activate "nuclear import proteins" (such as KPNA2) to help these mutant proteins smoothly enter the nucleus and reduce the toxic accumulation in the cytoplasm; Using agonists for heat shock proteins, such as HSP70 and HSP90, helps the mutant proteins "fold back into the correct shape", reducing the risk of them clumps together [6].

4.2. Targeting "environmental causative factors"

For the toxicity caused by heavy metals (such as lead and mercury), chelating agents such as calcium sodium edeate can be used to combine with them to promote the excretion of toxins through urine, thereby reducing the damage to mitochondria and RNA. In the case of organophosphorus pesticide poisoning, atropine should be used to antagonize cholinergic toxicity, oxime compounds such as pralidoxime iodide should be used to restore acetylcholinesterase activity, and α1-antitrypsin should be added to prevent the degradation of motor neuron-related proteins [7]. In order to further block the subsequent process of injury, anti-inflammatory interventions are crucial. For example, etanercept can inhibit TNF-α or rilusole can be used to regulate glutamate toxicity and microglia function to delay neuronal death when the virus activates microglia to cause inflammatory response. It is also critical to correct nutritional abnormalities, including supplementation with B12, folic acid, and B6 in the presence of vitamin B12 deficiency to reduce homocysteine levels and protect neural axons, and supplementation with vitamin E in the presence of deficiency to enhance neuronal antioxidant defenses [8].

4.3. Targeting "gene-environment interaction factors"

The core of breaking toxic superposition is to simultaneously intervene the genetic susceptibility pathway and the environmental damage chain. Precise combination programs are needed for different combinations of genetic background and environmental exposure: In the case of APOE ε4 combined with long-term alcohol consumption, the toxic superposition can be inhibited by the combination of statins (regulating lipids and increasing APOE function), edaravone (anti-oxidation) and rapamycin derivatives (activating autophagy). In the scenario of SOD1 mutation combined with organophosphorus exposure, a combination of tozasentan (reduction of SOD1 synthesis), bortezomib (reproteasome function), and autophagy agonist (aggrecan clearance) can be used to break the vicious cycle of toxic effects [9,10].

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5. Conclusion

This article focuses on the systematic research of amyotrophic lateral sclerosis (ALS), focusing on its clinical characteristics, pathogenesis and treatment strategies. ALS is a progressive neurodegenerative disease characterized by the selective loss of upper and lower motor neurons. The clinical manifestations are progressive muscle weakness, atrophy and loss of motor function. At present, there is no radical cure for this disease, and the existing drugs can only limited delay the progression of the disease, and the prognosis is generally poor, so the clinical need is urgent. In terms of pathogenesis, both genetic and environmental factors participate in the occurrence of diseases. Among the genetic factors, a number of pathogenic genes have been found, including C9orf72, SOD1, FUS and TARDBP. The mechanism involves abnormal RNA metabolism and toxic protein aggregation. Environmental factors include chemical toxic exposure, unhealthy lifestyle, and epidemiological factors such as age and gender, which may aggravate neurodegeneration through oxidative stress and mitochondrial dysfunction. Current treatment research mainly focuses on targeted intervention strategies. For the genetic mechanism, antisense oligonucleotide therapy for SOD1 mutation has been developed, and small-molecule drugs and gene therapy have been explored on C9orf72, FUS/TARDBP and other related targets. For the injury related to environmental exposure, heavy metal chelation, antioxidant and anti-inflammatory treatments can be used to intervene. In addition, combination treatment strategies targeting the interaction between genetic and environmental factors are also being explored. In summary, the complexity of the multifactorial pathogenesis of ALS and the key direction of targeted therapy have been clarified. However, existing therapies still have limitations. In the future, it is necessary to further explore the gene-environment interaction mechanism and promote the development of new targeted drugs to achieve effective disease intervention and prognosis improvement.

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