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Different Typing Characteristics of Amyotrophic Lateral Sclerosis Model Mice and Their Significance in Research Progress

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease of unknown etiology, characterized by progressive muscle atrophy, weakness, and paralysis, ultimately leading to death due to respiratory failure. The pathogenesis of this disease remains unclear, and there are many clinical subtypes, such as SOD1, FUS, TDP-43, etc. This article will elaborate on the mechanisms and latest progress of the relevant subtypes of ALS, as well as analyze the differences among model mice

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS), commonly known as "ALS," is a heterogeneous neurodegenerative disease characterized by the degeneration of upper and lower motor neurons, and patients often die from respiratory failure Feldman et al. (2022). The annual incidence of ALS is about 1-2.6 cases /100,000 people, and the prevalence is about 6 cases / 100,000 people Goutman et al. (2022). The core pathological manifestation of ALS is the progressive death of motor neurons, and its pathological mechanism is complicated, and the treatment of ALS is very limited at present. Riluzole is the current standard drug for ALS treatment, but it can only extend the life of patients by 2 to 3 months, and it is expensive and has adverse effects such as nausea and fatigue Zhilong et al. (2022) , at present, there is no effective cure for ALS. In this article, the classification and latest progress of ALS are reviewed, and the characteristics and application prospects of different models of gene therapy in mice are described in detail based on preclinical studies and clinical conversion tests of animal models.

SOD1

Pathogenesis and recent progress of SOD1

SOD1 (superoxide dismutase 1) gene mutation is an important pathogenic factor of ALS. SOD1 mutations occur primarily through protein misfolding, forming fibra-like aggregates that accumulate inside cells and interfere with normal function Nishitoh et al. (2008). In addition, SOD1 mutants have prion protein-like properties that induce a similar structural transformation of normal SOD1 proteins, further intensifying protein aggregation. SOD1 mutant proteins can also enter the mitochondria, destroy the mitochondrial structure, cause mitochondrial swelling, ridge breakage, affect energy metabolism, reduce ATP production, and further aggravate cell damage Zhilong et al. (2022). Neuroinflammation and immune imbalances are thought to contribute to the development and progression of ALS. Studies in mouse models have shown that in the late stages of the disease in which mutant SOD1 is expressed, immune cells and factors shift toward toxic and damaging effects on neurons Qing et al. (2003) Microglia tend to M1 type, which is toxic to motor neurons. Astrocytes expressing mutant SOD1 are toxic to motor neurons and mediate neuroinflammation in ALS. Microglia were activated by the infiltration of ALS monocytes in the middle stage, which aggravated neuroinflammation. Mast cells are distributed in muscles and sciatic nerves, impairs axon integrity; Local activation of the complement system contributes to macrophage recruitment and accelerates disease progression.

On November 1, 2024, a research paper titled "Amyloid fibril structures and ferroptosis activation induced by ALS-causing SOD1 mutations" was published in Science Advances by the team of Liang Yi from Wuhan University and the team of Liu Cong from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. This study for the first time resolved the high-resolution cryo-EM structures of amyloid fibrils formed by the ALS-causing SOD1 mutants H46R and G85R, and revealed a new mechanism by which these mutant fibrils regulate and induce ferroptosis in neurons, leading to familial ALS. This research not only provides a new structural basis for understanding the role of SOD1 mutant fibrils in the pathogenesis of ALS but also offers new scientific evidence for the development of ALS therapeutic drugs targeting SOD1 mutant fibrils and the ferroptosis they

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Keywords: Amyotrophic lateral sclerosis, Different types, Model mouse

Activate.

SOD1 Model mouse

SOD1 gene variation is the first ALS pathogenic gene to be located in 1993, and is currently the main target of preclinical studies and clinical trials in most ALS animal models, especially in Asia. SOD1 gene is the gene with the highest frequency of genetic variation in ALS, accounting for 20% of familial ALS and 2% of sporadic ALS Xiaoguang et al. (2024). SOD1 can remove excess superoxide free radicals, regulate cellular respiration and energy excretion and absorption. SOD1 mutations have been shown to affect protein folding, and the consequent increase in toxicity may be due to the accumulation of misfolded proteins within mitochondrial membranes and the production of free radicals, ultimately leading to cell damage and death Vehviläinen et al. (2014).

SOD1-G93Athe transgenic mice were genetically modified to express human SOD1 carrying the G93A mutation (a single amino acid substitution carrying codon 93 glycine to alanine). Due to the loss of motor neurons in the spinal cord, this strain of mice can develop paralysis of one or more limbs, and the lifespan of the transgenic mice is shortened by approximately 50%. While maintaining a live population, Jackson's lab found that male mice were aggressive. There are generally no more than four male rats per cage.

TDP—43

The pathogenesis and recent progress of TDP-43

TDP-43 (TAR DNA-binding protein 43) is a ribonucleic acid-binding protein that is normally mainly located in the cell nucleus and participates in various RNA metabolic processes. In ALS, abnormal aggregation and cytoplasmic deposition of TDP-43 are important pathological features of the disease. The main mechanism of its pathogenesis is that TDP-43 abnormally aggregates in the brain and spinal cord of ALS patients, forming insoluble aggregates, which mainly deposit in the cytoplasm. Decker et al. (2025). This abnormal aggregation may interfere with normal functions within the cell, such as RNA metabolism and protein degradation pathways, leading to an imbalance in the intracellular environment. Secondly, the abnormal accumulation of TDP-43 leads to the decrease of its content in the nucleus, which affects its normal function in the nucleus. TDP-43 is involved in the splicing, stability and transport of mRNA in the nucleus, and its dysfunction may lead to abnormal regulation of gene expression and affect various cellular functions Wang et al. (2024). The accumulation and deposition of TDP-43 can activate the immune system and trigger a neuroinflammatory response. The activation of inflammatory cells will release a variety of inflammatory factors, further damage neurons, accelerate the disease process of ALS.

The latest progress on TDP-43 begins with its liquid-liquid phase separation (LLPS). The LLPS of TDP-43 is an important mechanism for its formation of condensates within cells. Research has found that the phase separation process of TDP-43 is regulated by multiple factors, including RNA binding, protein modification, and cellular environment. A study in 2023 revealed the relationship between the phase separation of TDP-43 and the pathogenesis of ALS. Smith et al. (2003). The study found that the phase separation of TDP-43 can be regulated by RNA binding and protein modification, and these regulatory mechanisms are disrupted in ALS patients, resulting in abnormal aggregation and deposition of TDP-43. By modulating these regulatory mechanisms, abnormal aggregation of TDP-43 can be reduced, thereby alleviating the symptoms of ALS. Secondly, according to the latest research in 2024, Hsp70 can regulate TDP-43 Gu et al. (2021). Hsp70 (heat shock protein 70), a molecular chaperone, can bind to TDP-43 and maintain its dynamic equilibrium within cells. Elevated levels of Hsp70 can inhibit TDP-43-mediated toxicity, and the levels of Hsp70 are significantly reduced in ALS patients with TDP-43 aggregation. Hsp70 can maintain the homeostasis of TDP-43 protein, effectively delaying the maturation and solidification of TDP-43 liquid-liquid droplets and preventing the pathological aggregation of protein particles. These research advancements provide a new perspective on the role of TDP-43 in the pathogenesis of ALS. Future research will continue to explore the mechanism of TDP-43.

TDP-43 model mouse

TDP-43 is a highly conserved protein that is universally expressed in humans and rodents and predominates in the nucleus. The cellular function of TDP-43 remains unclear, but it has been shown to regulate gene transcription, regulate splicing processes, and regulate mRNA stability Wood et al. (2021). The abnormal localization of TDP-43 in the neuronal cytoplasm of ALS patients is related to the loss of nuclear function, which is responsible for regulating the process of mRNA transcription and splice. The formation of TDP-43 cell inclusion bodies induces toxicity in the cells, and then the toxic function of the protein is enhanced Mejzini et al. (2019). Phosphorylated TDP-43 protein aggregation was detected in bone and myocardial tissue of ALS patients Dedeene et al. (2020). Studies have shown that Hsp70 is closely related to TDP-43 and prevents amyloid aggregation in the dynamic, liquid-like phase. Hyperphosphorylation of large amyloid NIs (pTDP-43) is a histopathological marker of ALS Gu et al. (2021). TDP-43 protein plays a key role in ALS. The newly developed B6-hTARDBP mouse model, which can express the human TARDBP gene and TDP-43 protein,

provides an important tool for drug development. This model can be used to construct humanized models of popular pathogenic point mutations, meeting the research needs of emerging therapies. Cyagen Biosciences has successfully developed a humanized B6-hTARDBP mouse model of the mouse Tardbp gene (product number: C001418). This model can be used to construct humanized models of popular pathogenic point mutations to meet the research needs of emerging therapies such as CRISPR, ASO, siRNA, and miRNA. The B6-hTARDBP mouse successfully expresses the human TARDBP gene, and the results of RT-qPCR, Western Blot, and immunohistochemistry (IHC) tests all show significant expression and wide distribution of human TDP-43 protein. Lépine et al. (2022). The listing of this breed of mice brings a new breakthrough for ALS animal experiments.

FUS

FUS pathogenesis and recent progress

FUS (Fused in Sarcoma) is a ribonucleic acid-binding protein that is normally mainly located in the cell nucleus and participates in various RNA metabolic processes, including mRNA splicing, stability and transport. In ALS (Amyotrophic Lateral Sclerosis), abnormal aggregation and cytoplasmic deposition of FUS is an important pathological feature of the disease. The main mechanism of its pathogenesis is that FUS abnormally aggregates in the brain and spinal cord of ALS patients, forming insoluble aggregates, which mainly deposit in the cytoplasm Wang et al. (2023). This abnormal aggregation may interfere with normal intracellular functions, such as RNA metabolism and protein degradation pathways, leading to an imbalance in the intracellular environment. The aggregation and deposition of FUS can trigger oxidative stress responses within cells, increase the production of free radicals, and damage cell membranes, proteins, and DNA. Additionally, the abnormality of FUS can affect mitochondrial function, causing energy metabolism disorders and further exacerbating cellular damage. The aggregation and deposition of FUS can activate the immune system and trigger neuroinflammatory responses.

The activation of inflammatory cells releases various inflammatory factors, further damaging neurons and accelerating the disease progression of ALS.

A 2023 study revealed the interaction between FUS and neuroinflammation Zhou et al. (2022). Research has found that the aggregation of FUS can activate microglia, release inflammatory factors, and further damage neurons. By inhibiting the activation of microglia, the neuroinflammatory response can be alleviated and the disease progression of ALS can be delayed. In recent years, a popular research topic has been the connection between FUS and ferroptosis. Some literature reports suggest that the abnormal aggregation of FUS may further aggravate neuronal damage by activating the ferroptosis pathway. Ferroptosis is a form of iron-dependent cell death characterized by increased intracellular iron content and intensified lipid peroxidation reactions, ultimately leading to cell membrane damage and cell death. The latest research has revealed the specific molecular mechanism by which FUS aggregation activates the ferroptosis pathway by interfering with mitochondrial function and iron metabolism. The aggregation of FUS can activate the NRF2 (nuclear factor erythroid 2-related factor 2) signaling pathway, resulting in iron metabolism disorders and increased lipid peroxidation reactions, ultimately triggering ferroptosis Wang et al. (2023). In 2024, a study also indicated that the aggregation of FUS directly increases intracellular lipid peroxidation reactions, generating a large amount of lipid peroxides. These lipid peroxides further damage the cell membrane, leading to increased membrane permeability and ultimately triggering ferroptosis. Zhang et al. (2024). These research advancements have provided new perspectives on the role of FUS in the pathogenesis of ALS and offered scientific grounds for the development of novel therapeutic strategies. Future studies will continue to explore the regulatory mechanisms of FUS in the hope of identifying more effective treatment methods.

FUS model mouse

FUS is a multifunctional DNA/RNA-binding protein that is mainly located in the nucleus and can shuttle between the nucleus and cytoplasm. FUS is widely expressed in most human tissues, mainly in the nucleus, and shuttles to the cytoplasm to mediate various cellular processes. Under physiological conditions, FUS is mainly nuclear-localized, but in the cytoplasm of brain and spinal cord cells of ALS patients with FUS mutations, it abnormally accumulates. It can be seen that the toxic effect of FUS is related to its abnormal cytoplasmic localization, which may disrupt the nuclear-cytoplasmic balance transport. Geevasinga et al. (2016) FUS gene mutation is the second most common ALS gene mutation after SOD1, so the mislocalization of FUS protein can be used as a new molecular diagnostic marker.

FUS transgenic mouse strains exhibit progressive, mutation-dependent motor neuron degeneration followed by early, structural, and functional abnormalities at the neuromuscular junction.

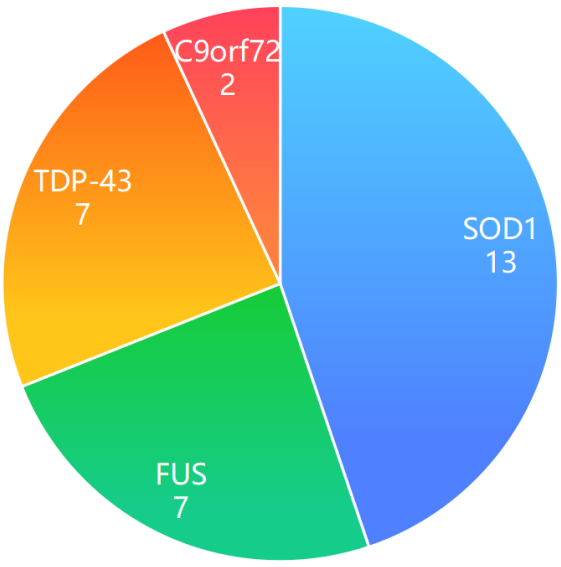
For example, in the FUS-Delta14 knockdown mouse model, the heterozygous animals did not begin to show progressive motor neuron loss and neuromuscular junction denervation until adulthood. The progression of the disease is relatively slow, and more obvious motor dysfunction, such as decreased coordination of limb movement and weakened strength, may begin to appear

symptoms gradually worsen over time, but the overall course of disease may be longer than in SOD1 mice, with some mice surviving for more than 12 months or longer. In the FUS (1-359) mouse model, vascular degeneration occurs before the degeneration of motor neurons.

Comparison of model mice

At present, most models of ALS are realized by gene editing, so many ALS transgenic mice have emerged. Because of its first-mover advantage, SOD1 has developed a large number of ALS model mice, and as of mid-2019, there have been nearly 30 species; There are also more than 30 TARDBP (code TDP-43) related; There are probably close to ten species of FUS; The remaining animal models such as UBQLN2, VCP and VABP are relatively few. According to literature statistics, there were 29 experimental papers on ALS mice at home and abroad in the past 5 years Decker et al. (2025), Wang et al. (2024), Smith et al. (2003), Gu et al. (2021) Wood et al. (2021), Mejzini et al. (2019), Dedeene et al. (2020), Gu et al. (2021), Lépine et al. (2022), Wang et al. (2023), Zhou et al. (2022), Wang et al. (2023), Zhang et al. (2024), Geevasinga et al. (2016), Yinwei et al. (2018), Meyer et al. (2021), Zhan et al. (2023), Shan-Shan et al. (2025), Zeng et al. (2022), Sharma et al. (2016), Devoy et al. (2017), Deĭkin et al. (2014), Milioto et al. (2024), Korobeynikov et al. (2022), Jiang et al. (2021), Shumin et al. (2024), He et al. (2021), Su et al. (2019), Liu et al. (2020), statistics of the species of experimental animals used found that, $SOD1^{G93A}$ is still the most widely used mouse species, with a frequency of up to 13 times, and FUS and SOD1 are the second most frequently used (Figure 1).

Figure 1: Summary of experiment frequency of different model rats



Different mice showed different states, such as motor performance, muscle tone and so on.

SOD1: The main pathological features of SOD1 gene include mitochondrial damage, protein folding error and deposition, excitatory poisoning, oxidative stress and so on. The development of disease symptoms in SOD1 mice is relatively typical. In the case of SOD1-G93A mice, for example, it is the type of disease that progresses rapidly, and in the early stage (about 3-4 months), the mice may develop mild muscle weakness in the hind legs, which is manifested by slightly less strength in walking or gripping the hind legs. With the passing of time (about 5-6 months), the muscle atrophy of the hind limb was gradually obvious, and the motor ability of the mice was further decreased, and the hind limb mopping and jumping ability were weakened Zhan et al. (2023).In the advanced stage of the disease (about 8-10 months), mice may completely lose the ability to exercise, and even develop severe conditions such as respiratory failure due to respiratory muscle involvement, and generally die at about 10-12 months. In our research, the blank group and SOD1 mice were respectively given intragastric administration, and it was found that the general state, body weight and muscle strength of the control mice were better than those of the model group.

TDP-43: TThe DP-43 mutant gene mainly phenotypes axon and synaptic defects, and has degenerative changes in motor neurons. In the spinal cord and brain tissue of TDP-43 mice, abnormal phosphorylation and aggregation of TDP-43 protein in neurons are the main pathological features. These aggregated TDP-43 proteins interact with other intracellular components to form inclusion bodies. At the same time, the dendrites and axons of neurons will also appear atrophy and degeneration, affecting the transmission of nerve signals. At the neuromuscular junction, as in FUS mice, structural and functional abnormalities, such as alterations in the synaptic gap and reduced neurotransmitter release, were also observed. TDP-43 mice showed abnormal gait and decreased grip power during exercise Shan-Shan et al. (2025).

In terms of survival time, mice such as TDP-43M337V are usually phenotypically normal at 3 months of age. By about 6 months of age, progressive motor deficits, such as abnormal gait and reduced flexibility of limb movement, begin to appear, accompanied by loss of neuromuscular junction integrity. The disease progresses at a moderate rate and generally does not deteriorate rapidly in a short period of time as in SOD1 mice, with some mice surviving for more than 10 months.

FUS: Histopathologically, the spinal motor neurons of FUS mice showed significant pathological changes. In addition to the aggregation of FUS proteins in the cytoplasm, the deformation of the nuclear membrane of neurons and the abnormal distribution of chromatin were also observed Zeng et al. (2022). At the cellular level, there are changes in organelles such as endoplasmic reticulum

expansion and Golgi apparatus disintegration, which affect the normal functions of neurons such as protein synthesis and secretion. At the same time, structural and functional changes may also occur at the neuromuscular junctions of the peripheral nervous system, such as the reduction of synaptic vesicles and abnormal distribution of acetylcholine receptors.

The disease progresses relatively slowly in FUS mice, and more obvious motor dysfunction, such as decreased coordination of limbs and decreased strength, may begin at about 6 months. The symptoms gradually worsen over time, but the overall course of disease may be longer than in SOD1 mice, with some mice surviving for more than 12 months or longer.

Experimental evaluation method of model mice

With reference to a large number of literatures, it is found that most scholars usually adopt the following methods for evaluation when conducting mouse animal experiments.

Behavioral test:

Starting from the 8th week, general condition grading or grading was performed every day. The standard was referred to Vercelli et al. 's 1-5 grading method or MMT grading.

Vercelli:

5 points: no motor dysfunction

4 points: Abnormal extension or tremor of the hind limb when the mouse is suspended

3 points: obvious hind limb weakness, abnormal gait

2 points: both hind legs are completely paralyzed, crawling only on the front legs.

1 point: Both hind limbs were completely paralyzed, and the mouse could not be turned over for 20 seconds after lying on its back

MMT:

The evaluation method of manual muscle strength is divided into 6 levels from weak to strong. The most commonly used is the Lovett scale: 0, with no visible or felt muscle contractions; Grade 1, slight muscle contraction may be palpable, but no joint movement; Level 2, able to do full range of joint motion in a gravity-free position; Level 3, can resist gravity to do the full range of joint motion, but cannot resist resistance; Level 4, can resist gravity and a certain resistance movement; Level 5, can resist gravity and sufficient resistance of the movement.

Rotating rod experiment

Each mouse was placed on the rotating rod of the rotating rod fatigue tester with a maximum rotating speed of 25r/min (before the experiment, each mouse was trained for 3 days, twice a day, with 180s as the cut-off value). The experiment was repeated three times, with each test interval of at least 1h.

The average persistence time of each mouse was taken. The longer they held on, the better their endurance and balance.

Suspension test

Each animal was placed in the center of a 60cm x 40cm metal mesh. After the mice grasped the metal mesh, they rotated it 180° to an inverted level. The amount of time the mice hung on the metal mesh was recorded (the mice were trained before the test, and 180s was set as the upper limit of the test time). The experiment was repeated twice for each mouse, and the average hanging time of each mouse was taken. The longer the hanging time, the greater the grasping power of the mice's limbs.

Grip test

Gently place the mouse in the center of the instrument grip plate, and when the mouse grips the grip plate firmly, gently pull the mouse tail with even force. Each animal was tested 3 times, and the maximum result was taken 3 times. The higher the grip value, the greater the muscle strength of the limbs.

Rotation experiment

The experiment began at the 9th week. The first 5 days of the experiment were the adaptation and learning stage of transgenic mice, and then the experiment was measured once a week. The rod rotator starts at 1 RPM and reaches 15 RPM within 3 minutes, and records the time (in seconds) that the mouse keeps moving on the roller without falling, with the longest one recorded.

Suspension rope test

This test was used to assess the muscle strength of mice, which was measured one day after the mice turned the rod. The mice were hung upside down on the cage cover with a height of 60cm and soft bedding at the bottom, and the longest time of the mice hanging upside down was recorded, and the longest time was recorded after three tests.

Daily observation and record

Observation content: The fur, eyes, mouth, ears, limbs and anus of the mice were observed regularly to check for any abnormal conditions, such as dull fur, bleeding, dirt, hair removal, eye secretions, tears, cataracts, corneal damage, mouth salivation, bleeding, ear trauma, ear curvature, ear inflammation, etc. There is no trauma, bending, dislocation, swelling, joint inflammation in the limbs, and there is no excretion residue, bloody stool, rectocele, etc.

Table 1: Comparison of the three model mice.

	SOD1	FUS	TDP-43
Feeding environment	In a constant temperature (25-27 ° C), constant humidity and Specific pathogen free (SPF) environment	**Temperature and humidity:** The feeding environment should be controlled at a temperature of 18-29 ° C and relative humidity of 40-70%. Under ideal conditions, the temperature is controlled at 18-22 ° C and the humidity is controlled at 50-60%	
		Light-dark cycle: Maintaining a 12-hour light-dark cycle ensures that the light-dark cycle is strictly followed, as examining mice after the dark cycle has begun can disrupt their normal circadian rhythm and affect their metabolism	
Feeding method	**Breeding density:** When maintaining live populations, Jackson's lab found that male SOD1-G93A transgenic mice were aggressive and recommended that no more than four males be kept per cage	Cage location and density: Cage preparation: According to the type and number of mice introduced, prepare the appropriate cage number in advance	
	Reproduction mode: In order to maintain the stable transmission of the mutant gene of B6SJL-TGN (SOD1 G93A) 1Gur transgenic mice, the B6SJL SOD1 G93A/+ semi-zygotic male mice can be mated with the B6SJLF1/J female mice, and the offspring mice can be genetically identified to determine whether they carry the human mutant gene		
	Daily observation and recording: During the experiment, the animals were observed every day and weighed once a week	Feeding density: The same number of mice should be housed in each cage. Although C57BL/6J mice do not need to change padding as frequently as other transgenic diabetic mice, they develop polyuria after obesity and diabetes, and the mouse cage may also need to change padding more frequently. It is generally recommended to appropriately reduce the feeding density to avoid stress reactions caused by competition for resources among mice	
Eating habit	**General feeding:** Under normal circumstances, SOD1 model mice can be fed sterilized SPF grade pellet rat feed	In general, FUS model mice can be fed a conventional growth and breeding diet, usually with a fat content of about 6%. This feed can meet the basic growth and physiological needs of mice.	TDP-43 model mice are usually fed standard rodent feed, which is able to meet the basic nutritional needs of mice. For the most part, these mice did not require special dietary adjustments
	Special research needs: High energy diet: Studies have shown that a high energy diet is beneficial to SOD1 transgenic mouse models. For example, it was found that SOD1 mice given a high energy diet had a longer survival		
	Ketogenic diet: The ketogenic diet can be used as a potential new treatment for ALS. The study showed that the SOD1-G93A transgenic ALS mice fed the ketogenic diet lost 50% of baseline motor capacity after 25 days later than the disease control group, and at the end of the study, the animals ed the ketogenic diet weighed 6 grams more than the disease control animals, and had more motor neurons in their spinal cord slices	**Special dietary needs**: In some specific studies, diet may need to be adjusted for experimental purposes. For example, if the study involves metabolic aspects, a high-fat, high-sugar diet may be used to induce a specific metabolic state	**Special dietary needs:** In some specific studies, diet may need to be adjusted for experimental purposes. For example, if the study involves metabolic aspects, a high-fat, high-sugar diet may be used to induce a specific metabolic state
		Water and food supply: Drinking water: pH2.5-3.0 acidified water, high-pressure sterile water or purified water can be used.	**Water and food supply:** Drinking water: pH2.5-3.0 acidified water, high-pressure sterile water or purified water can be used
	High-fat/high-sucrose diet: In studying obesity	**Food supply:** The mice are fed in a free-feeding manner, and the daily need to ensure that enough food is provided, and the supply of water and food is frequently checked to ensure that the mice can obtain water and food normally. In obese mice, special attention is needed because they may have more difficulty finding food and water	**Food supply:** The mice are fed in a free-feeding manner, and the daily need to ensure that enough food is provided, and the supply of water and food is frequently checked to ensure that the mice can obtain water and food normally. In obese mice, special attention is needed because they may have more difficulty finding food and water

<table>
<tr><td rowspan="2">Physiological level</td><td rowspan="2">Muscle weakness: As the disease progresses, the muscle strength of the limbs of mice will gradually weaken, and it is difficult to carry out normal limb movements, such as climbing, running, and grabbing food. For example, in the rotating rod experiment, SOD1 mice spent significantly less time on the rotating rod, showing decreased muscle strength and coordination.

Muscle atrophy: the muscles of the limbs, especially the muscles of the hind limbs, will atrophy significantly with the development of the disease, and the muscle volume will decrease, which is due to the damage of motor neurons, which cannot normally innervate the muscles, resulting in the loss of nutritional support and functional stimulation of the nerves and gradually atrophy.

Motor neuron degeneration: The number of motor neurons in the anterior horn of the spinal cord is gradually reduced, the neuronal cell body is atrophy and deformation, and the dendrites and axes are prominent and damaged and degraded, affecting the transmission of nerve signals, and thus causing the muscles to be unable to receive normal motor instructions</td><td rowspan="2">In the mouse model of FUSDelta14, heterozygous animals usually begin to show progressive motor neuron loss and neuromuscular junction denervation in adulthood, and then gradually develop symptoms such as reduced motor coordination and strength.</td><td>Motor dysfunction: Progressive gait disorders, such as walking instability, tailing, and mild defects in hindlimb reflexes, appear at 3-4 months of age. With the development of the disease, the hindlimbs gradually become paralyzed, making it difficult to walk and move normally. Some mice will have a spasmodic and trembling gait at 18 months of age.</td></tr>
<tr><td>Cognitive dysfunction: Some TDP-43 gene mice will have cognitive dysfunction, showing similar symptoms to frontotemporal dementia, such as reduced learning and memory ability, spatial disorientation. For example, in the water maze experiment, genetically modified mice took significantly longer to find a hidden platform, indicating impaired spatial learning and memory.</td></tr>
<tr><td rowspan="2">Matters needing attention</td><td rowspan="2"></td><td rowspan="2"></td><td>Behavioral and neurological phenotypes: TDP-43 model mice often exhibit neuronal degeneration and corresponding motor dysfunction, which are major features of ALS and FTLD. Mice may exhibit behavioral and cognitive changes, such as impaired gait and impaired coordination</td></tr>
<tr><td>Weight change: In some TDP-43 model mice, weight gain may be observed, which may be related to different genetic backgrounds</td></tr>
</table>

Number marking: Understand the method of mouse number marking to facilitate accurate identification of mice. Common numbering methods include severed toe numbering, ear marking, and dyeing.

Recording information: The basic information of mouse number, number, gender, week age, genotype and so on were tested to see if they were consistent with the label

CONCLUSION

Amyotrophic lateral sclerosis (ALS), the most common motor neurone disease, progresses rapidly and is highly fatal, and effective drugs are lacking. The current research on the pathogenesis of ALS is still unclear, and in-depth mechanism exploration and animal experiments are needed. There should be a certain understanding of the mechanism and the latest progress, and it is crucial for the selection of model mice.

In this paper, the mechanism progress and the latest research are discussed, and the common ALS model mice in the market are analyzed and compared, which can be selected for ALS animal experiments.

DECLARATIONS

Author contributions

Conceptualization (TQW), formal analysis (TYL), Supervision (RQZ), and writing – review and editing (YWZ). All authors read and approved the final manuscript for submission.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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