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Research Progress of Non-Coding RNA in Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by motor neuron degeneration. It begins to show some muscle abnormalities, and eventually it is usually due to respiratory muscle atrophy leading to ventilatory dysfunction death. The prevalence of male is higher than that of female, which is divided into sporadic and familial types. At present, only two drugs can be used for treatment. Therefore, it is urgent to find biomarkers that can diagnose ALS or predict the progression of ALS. Studies have shown that miRNA in non-coding RNA as biomarkers can reflect disease progression or disease severity or diagnosis. This review aims to describe the detection of non-coding RNAs in blood or cerebrospinal.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by degeneration of more than upper motor neuron (UMN) and lower motor neuron (LMN). The initial symptoms vary from person to person, and some patients may show bulbar onset, that is, dysarthria and dysphagia. Some patients showed spinal disease, namely limb weakness[1]. Muscle weakness in ALS will gradually develop to other parts of the body. The main cause of death in patients is ventilation dysfunction[2]. During the period from 1995 to 2015, the prevalence of the disease in males was higher than that in female and showed a slightly higher upward trend in time. The median age of male diagnosis was 68.2 years old[3]. ALS is divided into two forms according to the incidence and genetic characteristics[4],The most common form is sporadic amyotrophic lateral sclerosis (SALS), which accounts for 90-95 %, and there is no obvious genetic component. The remaining 5-10 % of cases are familial amyotrophic lateral sclerosis (FALS), because they have related genetic dominant genetic factors[5]. To date, there are only two FDA-approved drugs for ALS treatment, including riluzole and edaravone[6],Their therapeutic effects on ALS patients are limited. The lack of presymptomatic biomarkers and delays in clinical diagnosis significantly limit the therapeutic potential of potential disease-modifying drugs[7].It leads to problems such as untimely treatment of ALS patients. At the same time, it should be noted that in recent years, researchers have been looking for reliable

biomarkers that can diagnose ALS or predict the progression of ALS disease[8]. However, the heterogeneity of ALS patients is large, and a single biomarker is difficult to accurately diagnose ALS in the early stage. In order to diagnose ALS more effectively, a set of biomarkers may be needed[9].This review aims to describe the detection of non-coding RNA in blood or cerebrospinal fluid (CSF) as a biomarker that can be used to evaluate the diagnosis or prognosis of ALS disease or to monitor disease progression.

2. Coding RNA and non-coding RNA

RNA has many forms and complex functions. It is generally divided into two categories: coding RNA and non-coding RNA (ncRNA) according to whether it encodes proteins. Encoding RNA is messenger RNA (mRNA). mRNA is transcribed by DNA and edited to produce mature RNA, which is then translated into amino acids in ribosomes. Non-coding RNA can be transcribed from the genome, but not translated into proteins, and can perform their respective biological functions at the RNA level[10]. Non-coding RNA exists in a variety of forms such as transcription RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA) and microRNA (miRNA)[11]. The team[12] used RNA sequencing (RNA-seq) to investigate small non-coding RNAs (sncRNAs) in human serum, indicating that many RNAs in serum can be used as potential biomarkers. This blood-based biomarker is particularly desirable because serum or plasma is readily available and can be repeatedly sampled.

3. MicroRNA

miRNA is a small non-coding RNA responsible for regulating gene expression and final protein expression and has been used as a biomarker for many cancers and neurodegenerative diseases[13]. Greig et al.[14] first searched for slow and fast-progressing ALS patients and collected serum samples from healthy controls in the BioMOx discovery cohort, and then used the Qiagen auto-mated analysis (QA) to compare 17.5 % of serum samples with annotated sequences on the human genome to reflect the complete state of RNA in the serum. Consistent with previous studies[15-17], it was found that miRNAs accounted for the majority of the comparison readings in all samples. There were 7 miRNAs in an average of 10 reading targets in all sample pools, followed by rRNA and tRNA in general, while other ncRNA types (including piRNA) did not exceed 5 % of all ncRNAs.

4. Related down-regulated miRNAs

Freischmidt 's team[18] found that 56 % of the miRNAs associated with TDP binding showed most of the down-regulation in CSF and serum, which may be due to the impaired TDP-43 function or the change of TDP-43 subcellular distribution in ALS patients. We found that most of the TDP-43 binding miRNAs changed in CSF and peripheral blood, indicating that ALS has a systemic epigenetic disorder. We have learned that increased miR-146a-5p in patients with active multiple sclerosis is a key regulator of the innate immune response, which regulates and maintains immune function[19]. However, the current study found that the expression levels of miR-150-5p and miR-146a-5p in cerebrospinal fluid of patients with sporadic ALS were decreased, which may be due to the specific time point when the highest level of neuroinflammation was not reached at the time of sampling or these miRNAs have other mechanisms or effects[20] In addition, Wei et al. found that miR-378a-3p regulated skeletal muscle growth and promoted myoblast differentiation through post-transcriptional down-regulation of histone acetylase 4 (HDAC4), and found that it was reduced in cerebrospinal fluid samples of sALS patients[21]. Freischmidt et al.[22] showed that circulating miRNAs in the serum of patients with sporadic ALS were highly heterogeneous compared with familial ALS, and two miRNAs, miR-1234-3p and miR-1825, could be identified. They were continuously down-regulated

in sporadic ALS, but miR-3665, miR-4530, and miR4745-5p were found in this study. There was no expression difference. This may be because the sample size of the study is too low.

5. Related up-regulated miRNAs

Waller's team[23] showed comparing sporadic ALS patients with healthy controls and patients with simulated ALS disease, it was found that serum miRNAs were differentially expressed in each group of patients. In another patient cohort, compared with the control group, miR-206 and miR-143-3p increased, while miR-374b-5p decreased. Later, in the longitudinal study, it was found that both miR143-3p and miR374B-5p became more differentiated, indicating that their negative effects on myoblast differentiation were related to the increased expression levels related to muscle denervation, indicating that these specific miRNAs could potentially serve as longitudinal biomarkers for ALS. Similarly, in the current study[20], miR-143-3p was also increased in the cerebrospinal fluid of sALS patients. Studies have shown that overexpression of miR-143-3p is associated with anti-proliferative and pro-apoptotic effects of cancer[24]. Therefore, it is possible that the increased expression of miR-143-3p in cerebrospinal fluid of SALS patients is due to the by-products produced by the death of motor neurons in ALS patients, but other studies are still needed to further prove it. In the study of Toivonen et al.[25], it was found that the expression of miR206 and miR106b in serum was up-regulated in the ALS model established by SOD1-G93A mice, indicating that the lack of miR206 may accelerate disease progression.

The study[26] found that miR-9 and miR-124a were significantly up-regulated in the brainstem motor nucleus and primary motor cortex of the brain of late G93A-SOD1 ALS mice, and the expression of miR-125b was also increased. Among them, miR-124[27] was found to be an important regulator of the time progression of adult neurogenesis in mice, and miR-9 was involved in different stages of neuronal differentiation[28]. It plays an important role in CNS development, indicating that both non-coding RNAs are associated with neural activity. At the same time, Parisi et al.[29] showed that miR-125b induced down-regulation of IL6/STAT3 and increased production of TNF-α leading to the emergence of harmful microglia, indicating that miR-125b is associated with neuroinflammation in ALS. It is known that the pathogenesis of ALS is related to the death of motor neurons and glial proliferation, and the increased expression of neurological markers miR-124 and miR-9 in cerebrospinal fluid and glial marker miR-125b can be used as biomarkers of brain injury [30]. Studying whether the expression of these miRNAs in CSF continues to increase during disease progression is critical for the value of miRNAs as useful biomarkers for disease progression and their potential as prognostic indicators.

B DE Felice et al [31] showed overexpression of miR-338-3p has been found in blood leukocytes. In other studies[20], upregulation of miR-338-3p was also detected in the cerebrospinal fluid, serum, and spinal cord of SALS patients using RT-qPCR compared to controls and other patient groups (including patients with Alzheimer 's disease and Parkinson 's disease).

6. Outlook

Sheinerman[32] Individual RT-qPCR was used to measure the levels of 37 microRNAs in the plasma of the participants. The data showed that the discrimination accuracy between ALS and the control group reached AUC0.93. The accuracy of ALS and AD was 0.93 (AUC, 0.98), which was higher than that of AD and FTD (AUC, 0.87). This verifies the possibility of using microRNA diagnosis to detect and distinguish neurodegenerative diseases. There are also studies [14,33] on other non-coding RNAs, such as piRNA (Piwi-interacting RNA), long non-coding RNA (lncRNA), etc.as ALS biomarkers. The research on biomarkers related to ALS is to diagnose and treat patients as early as possible, judge the severity of the disease and monitor the development of the disease, so as to give

patients the treatment of the nervous system as soon as possible, and lay a certain foundation for the development of new medical methods. Due to the heterogeneity of ALS patients, it is necessary to carry out multi-faceted monitoring. Biomarkers are only one aspect, and they need to be combined with other aspects such as biochemistry in the later stage to help patients diagnose and treat.

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