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Targeting Chorea in Huntington's Disease: Emerging Therapeutic Strategies

Zichen Wang

Department of Biochemistry, University of Toronto, Toronto, Canada
purple.wang@mail.utoronto.ca

Abstract. Huntington's disease (HD) is a currently incurable neurodegenerative disorder caused by an autosomal dominant mutation in the HTT gene, leading to the production of mutant huntingtin protein (mHTT) with an expanded polyglutamine (polyQ) tract. This aberrant protein aggregation results in progressive neuronal dysfunction, particularly in the striatum and cortex, manifesting as involuntary choreiform movements (resembling dance-like behaviors), cognitive decline, and psychiatric disturbances. Despite advances in symptomatic management—such as antidepressants, dopamine-modulating agents, and physical therapy—existing treatments fail to halt disease progression or reverse neuronal damage.In recent years, novel therapeutic strategies have emerged, offering hope for disease modification rather than mere symptom alleviation. One promising approach involves mini-intrabodies, engineered antibody fragments designed to selectively bind and neutralize mHTT. These intrabodies facilitate the degradation of toxic protein aggregates via lysosomal pathways, effectively reducing neuronal toxicity. Other cutting-edge interventions include antisense oligonucleotides (ASOs) to suppress mHTT expression, CRISPR-based gene editing to correct the HTT mutation, and stem cell therapy to replace damaged neurons.This article evaluates these innovative strategies, with a focus on lysosome-targeted mini-intrabodies as a potential curative approach. By analyzing preclinical and clinical advancements, we aim to highlight future research directions that could transform HD treatment from palliative care to definitive therapy.

Keywords: huntington, therapeutic strategies, targeting therapy

1. Introduction

Huntington's disease is a monogenic dominant neurodegenerative disorder caused by the accumulation of mutant huntingtin protein. Patients with this disease exhibit symptoms such as neuronal damage, movement disorders (dystonia), and cognitive decline. The majority of patients die within 10 to 25 years after the onset of symptoms. The genetic defect kills the neurons in the brain, and death is not the end of Huntington's chorea. One or more of the patient's descendants will inevitably develop the disease. Huntington's chorea most commonly occurs between the ages of 30 and 50. The accumulation of proteins has the most significant impact on neurons in the striatum and cortex, which control human activities, cognition, and spirit. The symptoms of the disease revolve around these three parts, but they are not so obvious in the early stages. In 50% of cases, emotional

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instability, anxiety, and mild depression are the first symptoms. During the early stage of the disease, a large accumulation of huntingtin protein leads to damage to neurons in the striatum and cortex, which control human activities, cognition, and spirit. Later symptoms also revolve around these three parts. At the beginning, involuntary twitching of the face, fingers, and toes occurs. Due to the relatively small number of damaged neurons at the beginning, these movements are not obvious, and patients often do not notice their abnormalities. In the middle stage of the disease, patients develop dystonia, causing twisting and repetitive movements throughout the body, resembling dancing. This is also the origin of the name "dancing disease." The neurons in the brain are also severely damaged, which leads to the inability of patients to think, plan, and engage in complex interactions at this stage. In the late stage, muscle spasms and twitches have spread to the mouth and throat, and the patient's respiratory function is severely affected. The patient gradually loses the ability to eat and drink, and this severe damage increases the risks of malnutrition and aspiration pneumonia and may lead to asphyxiation and death at any time. Current medical treatments include symptomatic drug therapy and non-drug intervention. Antidopamine drugs in drug therapy can alleviate chorea, but they may aggravate cognitive impairment. Antidepressants can manage mental symptoms, but they cannot improve the disease progression. Non-drug intervention includes deep brain stimulation therapy, which can improve motor function temporarily but has a gradually declining long-term efficacy. So far, all treatment methods cannot reduce the load of huntingtin protein and neuronal death. Based on this, this article will focus on summarizing the targeted therapies for mHTT clearance in the new era, which represents a disruptive direction for the treatment of Huntington's disease.

2. Existing treatment schemes for Huntington's disease

At present, the treatment of Huntington's chorea includes dopamine drugs, antidepressants, antipsychotics, rehabilitation training, physical training and speech therapy. Among them, dopamine drugs can inhibit abnormal dance movements by regulating dopaminergic system. For example, as a dopamine drug, busulfazine is a specific VMAT2 inhibitor, which can reduce the release of synaptic dopamine to delay the symptoms of dancing, but 7% of patients have a tendency to depression [1]. Drugs for depression, anxiety and psychosis, such as SSRI, are usually the first choice for the treatment of depression prescribed by doctors, and their side effects are smaller and lighter. They can improve depression with 20-40mg/d, and their function is to increase the level of serotonin in the brain, which is a neurotransmitter and plays an important role in regulating mood, appetite, sleep and memory [2]. However, antipsychotics may increase cognitive decline, and some cohort studies show that the annual growth rate of MMSE increases by 0.8 points. Huntington's Dance Association of the United States said that exercise and physical exercise can alleviate symptoms and maximize their functions. 150 minutes of aerobic exercise, such as walking, and fixed bicycles can exercise patients' leg muscles, which can effectively solve the problem that Huntington's Dance patients have difficulty in maintaining their weight, and the exercise plan can help increase their appetite [3]. Speech therapy tends to alleviate social problems. Continuous vocalization and exhaling through the mouth can strengthen the respiratory muscles. Speech therapists can instruct Huntington's patients how to use compensation strategies to improve their language clarity. These strategies include exaggerating mouth movements when talking and finding a quiet environment when talking [4].

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3. A new strategy for treating Huntington's disease

So is Huntington's disease really incurable and can only be alleviated? According to a recent study published in Advanced Science, an intracellular antibody called Mini-intrabody seems to bind mHTT and bring it into lysosome for degradation, so that excessive Huntington protein can be digested [5]. Intracellular antibody is an artificially modified antibody, which can be distributed in cells and target special protein. Therefore, Mini-intrabody binds to mHTT and is transported to lysosomes for degradation under the influence of this intracellular antibody. This method is more focused on the redundant protein rather than the disease gene, but it can effectively reduce the toxicity of the mutant protein. The mice with Huntington's disease were given brain stereotactic injection and orbital intravenous injection to deliver AAV-SM3. The data showed that the injected mice had better exercise tolerance, average speed, muscle strength and exercise ability than the uninjected mice. And the content of mHTT in vivo decreased significantly. The lysosomes of transfected cells were purified and it was confirmed that there were a lot of MHTT in lysosomes [5]. The study of this method provides a new therapeutic strategy for the treatment of Huntington's disease in adulthood, especially for the treatment of the later stage of the disease. Other treatments that can be expected include stem cell therapy and gene therapy. The former is more direct, and stem cells can directly replace apoptotic or dying cells to maintain body function. Since 1990, many experiments of fetal tissue transplantation have been carried out in Huntington's disease patients. Although none of them has fully recovered, these studies show that fetal tissue transplantation can improve cells and behavior [6]. However, these improvements cannot be maintained for a long time. In most patients, the clinical improvement is not affected by neurodegeneration in the late transplantation area, but the area around the brain is still deteriorating. Transplantation of nerve tissue alone can't improve symptoms, but the strong migration ability and paracrine function of stem cells can affect the whole brain, so stem cell transplantation provides an alternative treatment strategy for Huntington's disease. The latter is a representative gene therapy drug-AMT-130 [7] developed by Dutch biotechnology company Uniqere. Its core mechanism is to deliver artificial microRNA through AAV5 vector, targeting the first exon of Huntington gene, reducing the production of mHTT, and solving Huntington's chorea from the root. The way of administration is usually neurosurgery, that is, AAV is injected directly into the striatum after craniotomy. However, in 2023-2024, the published data showed that the overall therapeutic effect of AMT-130 was not good, and the symptoms were not improved obviously, the content of mHTT was not effectively reduced, nerve injury and brain atrophy occurred [7]. At present, the current technology can't keep the expression of miRNA, which leads to the unstable knock-down of mHTT. Huntington's disease is a chronic progressive disease and needs continuous and stable gene suppression. Therefore, gene therapy can only be used as a preparatory scheme for Huntington's disease treatment. In the future, it is necessary to optimize the vector design and target the miRNA to improve the effectiveness of gene therapy.

4. Missing part of existing treatment scheme for Huntington's disease

At present, the treatment of Huntington's disease mainly focuses on controlling symptoms rather than completely curing them, and because the symptoms in the initial stage of the disease are not obvious, it will be in the middle and late stage once found, which also leads to insufficient intervention in the early stage of the disease, which will also affect the difficulty of follow-up treatment. And in many cases, people often don't realize that this is Huntington's disease. In a normal family in America, James took his elderly father to see a doctor. At first, they thought it was

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his father's knee, because he always felt uncomfortable with his knee, and something kept moving his knee. The doctor said it was osteoarthritis, so James's father stayed in bed for several months. Cases like this are not uncommon. There are 6,000 to 10,000 people suffering from Huntington's disease in Britain, and about 150,000 people may pass it on to future generations. Therefore, it is urgent to cure Huntington's disease at present.

5. Future prospect of Huntington's disease treatment

Huntington's disease (HD) remains a devastating neurodegenerative disorder with no cure, necessitating a multidisciplinary approach to future treatment strategies. The primary pathological hallmark of HD is the accumulation of mutant huntingtin protein (mHTT), which leads to progressive neuronal dysfunction and death. To develop more effective therapies, basic research must be intensified, focusing on elucidating the mechanisms of toxic protein aggregation, its impact on cellular homeostasis, and the molecular pathways underlying neurodegeneration. A deeper understanding of these processes will facilitate the discovery of novel drug targets, enabling precision medicine approaches such as small-molecule inhibitors, gene-silencing techniques, and protein degradation therapies.

Among emerging treatment strategies, mini-intrabodies show promise by selectively binding and promoting the lysosomal degradation of mHTT. However, to maximize therapeutic efficacy, combination therapies should be explored, integrating stem cell transplantation, CRISPR-based gene editing, and antisense oligonucleotides (ASOs) to simultaneously target different aspects of the disease. Additionally, accelerating clinical trials is crucial—researchers must optimize translational pipelines to bridge the gap between preclinical studies and real-world applications, ensuring that breakthroughs in the lab reach patients faster.

Beyond biomedical interventions, mental health and social support must be prioritized. Many HD patients suffer from depression, anxiety, and social isolation, often exacerbated by the disease's hereditary nature and progressive disability. Governments and healthcare systems should implement comprehensive psychosocial support programs, including subsidized mental health counseling, caregiver training, and financial aid to alleviate economic burdens. Public awareness campaigns can also help reduce stigma, encouraging earlier diagnosis and better social integration for patients.

In conclusion, the future of HD treatment lies in three key pillars: (1) advancing basic research to uncover disease mechanisms, (2) developing innovative combination therapies for clinical application, and (3) ensuring holistic patient care through psychological and socioeconomic support. Only by addressing all these dimensions can we hope to improve both the quality and longevity of life for HD patients and their families.

6. Conclusion

Huntington's disease is a severe neurodegenerative disorder. Patients with this disease will exhibit mild muscle twitching within a certain period of time. As the condition worsens, they will experience uncontrollable dance-like movements and progressive cognitive decline. After about four to five months, patients will be unable to perform normal activities and think. The existing treatment methods include antidepressants, dopamine agonists, and exercise therapy. These methods have alleviated symptoms to some extent and improved the quality of life. However, there are still some issues, such as unstable efficacy, strong side effects, and long treatment cycles. The new treatment strategy of microbody antibodies is emerging. It can directly address this problem by constructing endosomes to bind to the Huntington protein and transporting it to lysosomes for the breakdown of

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the mutant protein. Its advantages of directly targeting the cause, high specificity, and potential long-lasting effects make it stand out in a treatment plan. Stem cell therapy and gene therapy have certain limitations and can only be used as adjunctive treatment strategies in the future. Future research directions will focus on studying protein targets within cells and combining mini-endosome therapy with new therapies such as gene therapy and stem cell therapy to develop combined therapies to break through the "irreversibility" and "untreatability" problems of Huntington's chorea and to improve the health status of patients. The government and society can also provide psychological counseling and economic subsidies to patients to enhance their health conditions.

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