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Review

Perspectives on the use of stem cells for autism treatment

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ABSTRACT

Autism spectrum disorder (ASD) is a defined condition characterized by impairments in social interaction, communication, and often repetitive behaviors and patterns. It has a multifactorial etiology, meaning that each case may present differently from others. In individuals with autism spectrum disorder, deficits in social communication are often accompanied by symptoms related to repetitive behaviors or specific areas of interest. With the rapid increase in the prevalence of ASD today, attention has shifted towards stem cells as a potential new treatment option. Currently, there is no accepted treatment for autism spectrum disorder. The existing treatments for autism do not directly alter the underlying molecular basis but rather aim to address the social and behavioral dysfunctions resulting from disruptions in these pathways, providing various interventions and support that have an impact on the quality of life. This review provides an overview of stem cell types, studies related to the use of stem cells, and an exploration of stem cell applications in cerebral hypoperfusion, demonstrating that the potential treatment of individuals with autism using stem cells holds promise for the future.

Keywords: Autism spectrum disorder, cerebral hypoperfusion, cord blood, mesenchymal stem cells, stem cell therapy.

Autism spectrum disorders (ASDs) have become a subject of increasing interest in recent years due to their higher prevalence. The growing number of reports linking measles and mumps vaccines to autism, as well as reports associating autism with inflammatory bowel disease, has also contributed to increased public concern.[1,2]

Autism spectrum disorders encompass a group of neurodevelopmental pathologies, including autism, Asperger's syndrome, and Rett disorder. Autism is a spectrum disorder, meaning that its symptoms and severity can vary from person to person. It is a defined disorder characterized by impaired social interaction, communication difficulties, and often repetitive behaviors and patterns. Children with ASD typically exhibit repetitive behavior and speech patterns, have difficulty understanding gestures and facial expressions, and show deficits in social interactions and verbal/nonverbal communication. Additionally, it is associated with anxiety, attention deficit hyperactivity disorder, motor impairments, intellectual disabilities, and gastrointestinal problems. Individuals with autism may have restricted, repetitive, and intense areas of interest and may show little interest in activities outside of their limited interest areas.[3]

The etiology of ASD is not fully understood. However, genetic, epigenetic, immunological, neurological, vascular, and environmental risk factors can contribute to the development of the disorder. For instance, genomic and transcriptomic analyses have revealed mutations and alterations in gene expression patterns for synaptic scaffolding proteins such as Shank3, translational regulator Fragile X messenger ribonucleoprotein 1, or methyl-CpG binding protein 2. These changes can alter the structure of neurons and synaptic terminals and may explain some characteristic defects in synaptic function, glial activation, and cytoarchitecture organization in the brains of individuals with ASD.[4-7] Many risk factors have been identified for ASD, primarily associated with maternal exposures before and during pregnancy. These include

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exposure to chemicals (e.g., toluene, pesticides), heavy metals (arsenate, mercury, lead), perinatal trauma, maternal infections during pregnancy, hypoxia, and preterm birth.[8-12]

Defects such as immune dysregulation, T-cell deregulation, excessive cytokine production, and significantly low plasma levels of transforming growth factor play a role in the severity of ASD.[13-16] Children with ASD have been observed to have gut immune dysregulation and gastrointestinal symptoms.[17-20] Based on the Childhood Autism Rating Scale (CARS), serum levels in individuals with severe autism were found to be significantly higher compared to those with mild to moderate autism.[21]

The increasing prevalence of autism, which is approximately four times more common in males than females, has created a significant economic burden in terms of special education, healthcare expenses, and parental productivity loss.[22,23] The current pharmacological treatments for patients with ASD primarily target comorbid conditions associated with the disorder but have not been demonstrated to effectively mitigate core symptoms such as social interaction and communication impairments.[24-26] Furthermore, these medications (e.g., selective serotonin reuptake inhibitors, antipsychotics) may cause side effects such as emotional blunting and weight gain, which can significantly reduce the quality of life for patients.[27,28]

Given the rapid increase in the prevalence of ASD and the lack of effective pharmacological treatments for ASD, the need for novel therapeutic approaches is growing rapidly.

CLASSIFICATION OF STEM CELLS

Today, stem cells are classified into various types based on their sources, origins, and mechanisms of action. Umbilical cord blood and bone marrow are among the most commonly used sources of stem cells. Of these, cells derived from umbilical cord blood are frequently utilized due to their ease of accessibility and the minimally invasive nature of the collection process. Umbilical cord blood contains multiple types of stem cells, including hematopoietic stem cells, mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs).[29,30] Stem cells obtained from cord blood offer several advantages, such as greater compatibility flexibility, ease of collection, lower risk of infection, and convenient storage options.[29-33]

In bone marrow, the cell count is higher, making it sufficient for use in adult patients. It is predominantly used in the treatment of blood disorders, such as leukemia, and autoimmune diseases. Bone marrow stem cells are harvested through surgical procedures performed under general anesthesia. However, the risk of donor-related infections is relatively higher compared to the use of umbilical cord blood.[30,34]

Mesenchymal stem cells can be isolated from almost any tissue, including bone marrow, umbilical cord, placenta, and adipose tissue. These cells adhere to plastic surfaces and possess the ability to differentiate into multiple cell types (multipotency).[35] Mesenchymal stem cells are particularly notable for their paracrine properties, defined as the secretion of molecules that influence neighboring cells. Their paracrine features include the secretion of growth factors (e.g., vascular endothelial growth factor and transforming growth factor), cytokines and chemokines (e.g., interleukin-10, interleukin-6, and monocyte chemoattractant protein-1), as well as exosomes and microvesicles.[35-38] Through the secretion of these molecules, MSCs accelerate tissue repair, modulate the immune system, and stimulate angiogenesis. Numerous studies have demonstrated that therapies involving MSCs can be used safely, underscoring their potential in regenerative medicine and immunomodulation.[35]

Neural stem cells are stem cells with a limited differentiation capacity, capable of differentiating only into neurons and glial cells. Their key characteristics include self-renewal capacity, multipotent differentiation potential, and adaptability.[39,40] Neural stem cells hold potential for applications such as replacing lost neurons in neurodegenerative diseases like Parkinson's and Alzheimer's and improving functions lost due to spinal cord injuries.[41,42] Due to the challenges associated with obtaining these cells from brain tissue and the spinal cord, alternative sources are often sought for therapeutic use.

Induced pluripotent stem cells are generated by reprogramming somatic cells into embryonic stem cell-like pluripotent cells through genetic

engineering techniques. This process can involve the use of viral vectors or non-viral methods. However, the use of induced pluripotent stem cells carries certain challenges and risks, including low efficiency, genetic alterations, and the potential for tumor formation.[43]

STEM CELL THERAPY FOR AUTISM SPECTRUM DISORDER

Clinical studies on stem cell transplantation in ASD are crucial to validate the safety and efficacy of cellular therapies. Due to the variations in stem cell types, administration methods, dosage, and treatment duration, further data collection is essential.

Stem cell therapy trials for ASD were first introduced in the early 2000s, and clinical trials gained significant momentum around 2010. To date, these studies have yielded promising results in alleviating autism symptoms. In one study involving 25 children with ASD, participants received a single intravenous infusion of umbilical cord blood containing 1-5×10^7 cells per kilogram of body weight. Clinical evaluations were conducted prior to the infusion, as well as at six and 12 months post-infusion. The study findings demonstrated improvements in the overall severity of autism and degrees of recovery. Objective eye-tracking measurements indicated increased attention to social stimuli, while standardized assessments showed enhancements in expressive vocabulary, communication skills, and autism symptomatology.[44]

In another study conducted between 2017 and 2019, thirty children with ASD who had CARS scores >37 received bone marrow mononuclear cell transplantation. As a result of this study, a significant reduction in ASD severity was observed, with the median CARS score decreasing from 50 (range 40-55.5) to 46.5 (range 33.5-53.5). Additionally, adaptive capacity improved, and the median Vineland Adaptive Behavior Scale score increased from 53.5 to 60.5. This intervention, when combined with educational interventions, was found to be safe and well-tolerated.[45]

In a study testing allogeneic human cord tissue-derived mesenchymal stem cells, four doses of umbilical cord blood mononuclear cells (CBMNCs), administered both intravenously and intrathecally, as well as a combination of CBMNCs and intrathecal umbilical cord tissue-derived mesenchymal stem cells (UCMSCs), were evaluated. Six months after treatment, both treated groups showed greater improvements in ASD measures compared to the placebo group. However, the combination of CBMNCs and UCMSCs demonstrated a larger therapeutic effect than CBMNC transplantation alone. No safety issues were recorded during the infusion or throughout the entire process.[46] In another study using cord tissue-derived MSCs, intravenous administration of 36 million cells over a 9-month period in 20 children resulted in improvements in the Autism Treatment Evaluation Checklist.[47]

CEREBRAL HYPOPERFUSION AND AUTISM SPECTRUM DISORDER

The brain, one of the most metabolically active organs, consumes about 20% of the available oxygen for its normal function. The mammalian brain is highly sensitive to hypoxia. Therefore, timely regulation of oxygen distribution is crucial for its function and survival. The autoregulation of cerebral blood flow is dependent on multiple systems. Disruptions in these mechanisms can lead to an inability to meet oxygen demands, resulting in ischemia. In individuals diagnosed with ASD, studies have observed cerebral hypoperfusion, which has also been linked to the severity of autism.[48] Hypoperfusion is an important issue for better understanding ASD.

The temporal lobe or temporal cortex plays a crucial role in various functions, including speech, memory, and hearing. Hypoxia associated with autism is linked to functional changes in temporal neurons.[49] Additionally, this hypoperfusion may contribute to these impairments by allowing the accumulation of abnormal metabolites and neurotransmitters.[48] Investigating the causes and treatment of hypoxia observed in this region in individuals with autism could help us better understand the underlying reasons for difficulties such as face recognition, language perception, and communication skills, which are common clinical symptoms of autism.

In the pathological profile of ASD, cerebral hypoperfusion and insufficient blood flow

in the brain have been observed.[50] Chronic hypoperfusion leads to the breakdown of white matter, which is characterized by oligodendrocyte loss, neuroinflammation, and a decrease in myelin density.[51] When comparing individuals diagnosed with ASD to healthy individuals, positron emission tomography and single-photon emission computed tomography scans have revealed that approximately 75% of children with ASD exhibit individual-based hypoperfusion.[52-54] Across all findings, mixed hypoperfusion was observed in areas including the prefrontal cortex, medial frontal cortex, and anterior cingulate cortex. In another study by Degirmenci et al.,[55] when comparing 10 children diagnosed with ASD to five age-matched non-autistic children, statistically significant hypoperfusion was observed.

In children with autism, reduced central nervous system circulation and subsequent hypoxia have been observed. Studies have shown that temporal lobe areas, which are associated with autism symptoms such as face recognition and language perception, are hypoperfused in children with autism but not in control children.[48] While healthy children exhibit increased blood flow when engaged in tasks requiring attention and sensory input, no physiological response is seen in children with ASD when performing tasks such as speaking or focusing.[56] This lack of compensatory response in the autistic brain may be related to a deficiency in signals/receptors involved in brain vasodilation.[57] Communication difficulties, impaired facial recognition, and emotional deficits in individuals with ASD may stem from disruptions in complex emotional inputs within hypoperfusion areas. In a study by Ohniski et al.,[57] it was found that not only was regional cerebral blood flow consistently reduced in ASD, but cerebral hypoperfusion was also linked to the symptomatology. Each syndrome was associated with a perfusion model in the limbic system and medial prefrontal cortex, and these abnormalities were connected to cognitive dysfunctions observed in ASD, such as abnormal responses to sensory stimuli and repetitive compulsive behaviors.

Although the exact cause of cerebral hypoperfusion in patients with ASD is not fully understood, decreased blood flow and oxygen restriction may explain at least some of the symptoms present in these patients.[57] The low blood flow observed in the autistic brain may be related to inflammatory responses seen in these individuals.[58,59] Furthermore, significantly elevated levels of 6-keto-prostaglandin in the urine of ASD patients have been detected, leading to increased oxidative stress as well as platelet and vascular endothelial activation in these individuals.[60] According to the data, low blood flow may be a result of inflammation in the endothelial lining.

UMBILICAL CORD BLOOD CD34+ STEM CELL THERAPY FOR ADDRESSING HYPOPERFUSION DEFECTS

Due to the complexity of ASD, attempts to halt pathophysiological deterioration may potentially aid in alleviating symptoms in individuals. However, if temporal lobe ischemia is merely a manifestation of a process, preventing hypoxia may not necessarily lead to therapeutic outcomes. A study by Bachavelier[61] suggested that damage leading to hypoperfusion could be associated with the onset of autism-like disorders, which may help clarify this issue. Furthermore, damage or removal of the temporal lobe has been observed to induce autistic-like traits such as expressionless faces and reduced eye contact, suggesting that temporal lobe ischemia could potentially be causal.[62-64]

In ischemic conditions, therapeutic angiogenesis can be used to stimulate the formation of new blood vessels from pre-existing arteries.[65] The process of angiogenesis, known as the formation of new blood vessels by the body, is particularly important in situations such as tissue repair, tumor growth, and embryonic development. This angiogenic response is triggered by signals resulting from conditions like inflammation and hypoxia. Cells secrete angiogenic factors such as vascular endothelial growth factor, insulin-like growth factor-1, and angiopoietin, and it has been observed that these factors play a role in neurogenesis following ischemia.[66] These factors stimulate the endothelial cells of existing blood vessels, causing them to proliferate and migrate, leading to the formation of new blood vessel sprouts. These cells then move onto the extracellular matrix and form new vessels, which mature over time. The angiogenic response has

been observed to occur following myocardial infarction, where bone marrow angiogenic stem cells are mobilized into the systemic circulation, as well as after cerebral ischemia, such as stroke.[67]

To enhance angiogenesis in ischemia, cells with the potential to differentiate into endothelial cells can be used. For the purpose of stimulating angiogenesis, cord blood contains CD34+ cells that have high activity in terms of proliferation, cytokine production, and endothelial differentiation.[68,69] Studies have shown that EPCs, which are found in the CD34+ cell population and enriched in CBMNC, have the ability to stimulate angiogenesis in ischemic tissues.[70] CD34+ progenitor cells found in CBMNCs have the potential for endothelial development and have been proven to transform into new endothelial cells to repair damaged endothelial walls or form new vascular structures.[69] Recently, CD34+ cells have been used in myocardial ischemia and peripheral artery disease, yielding promising results.[71,72]

The concentration of the endothelial progenitor fraction in cord blood CD34+ cells is approximately 10 times higher than that of CD34+ cells obtained from bone marrow.[73] Additionally, CD34+ cells have been observed to induce neuroregeneration.[74-76]

Considering the potential of CD34+ cells derived from umbilical cord blood to promote angiogenesis in ischemic areas, preclinical studies conducted in various ischemic animal models aimed at increasing angiogenesis around the degeneration regions caused by cerebral hypoperfusion and hypoxia in individuals with autism have shown functional improvements. These findings suggest that umbilical cord blood CD34+ cells may be beneficial in improving hypoxia.[46]

In conclusion, in the coming years, it is certain that the role of stem cells in treating neurodevelopmental disorders such as ASD will gradually increase. Stem cell therapies hold promise for ASD and are considered to have potential therapeutic targets. However, due to variables in clinical studies, such as the diversity of stem cell types and doses, developing a well-defined application protocol to maximize therapeutic efficacy currently appears challenging. Further research is needed, as there is still limited knowledge about long-term outcomes, and follow-up periods after existing clinical trials are generally short. Therefore, the long-term safety and efficacy of stem cell therapy must be thoroughly evaluated. Based on this information, stem cell therapy is not yet a fully effective treatment option for ASD.

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