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Review

Unlocking the potential of stem cell therapy for Autism: A new era in neurotherapeutics.

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Abstract

Autism spectrum disorders have distinct core symptoms, including struggles with social interactions and repetitive behaviours. These disorders involve complex neurodevelopmental problems, inflammation, and immune system dysfunction. Due to the underlying neurobiological causes of autism, researchers have explored the potential of cell-based therapies, such as stem cells, to treat the condition. Stem cells exhibit unique immunological properties, making them a promising area of study for autism treatment. This review examines autism's cellular and molecular abnormalities, potential stem cell therapies, animal models, and ongoing clinical trials. Research on autism's genetics shows that no proven cure exists, but studying stem cells has led to promising results, particularly with mesenchymal stem cells and human embryonic stem cells. These cells have been used to reduce autism severity and improve quality of life. Additionally, stem cells have been used to model various autism forms, such as Rett Syndrome and Fragile X Syndrome, allowing researchers to develop novel therapies. However, researchers must consider the ethical implications of their work, particularly when studying children, and prioritize their well-being and safety.

Keywords: Autism Spectrum Disorder, Stem Cells, Cell Therapy, Modelling, Treatment, Hypoperfusion.

INTRODUCTION

Autism spectrum disorders (ASDs)

Autism spectrum disorders are complex neurodevelopmental conditions that involve a wide range of severity, functional disability, and intellectual levels. They begin in the womb and are influenced by multiple genetic and environmental factors. This multifactorial origin leads to disruptions in early embryonic development, causing abnormalities in brain formation and synaptic connections, which progress over time [1].

Due to its diverse nature, the term autism has been used to describe both specific diagnoses and general presentations. In 1980, pervasive developmental disorders were included in the DSM-III to highlight social communication deficiencies. The most recent diagnostic systems, the ICD-11 and DSM-5, use the term autism spectrum disorder, differentiating between individuals using clinical specifiers and modifiers.

The prevalence of autism spectrum disorder has increased among US children, from 1.1% in 2008 to 2.3% in 2018, with higher rates among males. Studies suggest a lower male-to-female ratio due to females disguising their symptoms and less sensitive diagnostic methods. A team of professionals makes the diagnosis based on individual observations, parental interviews, and standardized assessment tools, combining their expertise to agree upon a diagnosis that follows established medical criteria [2].

Autism symptoms involve repetitive behaviors, sensory issues, social communication and interaction problems, and varying levels of intellectual disability. Along with primary symptoms, people with autism often have co-occurring conditions such as anxiety, depression, epilepsy, and attention problems [3].

Two key features characterize autism, regardless of background differences: difficulty with social communication and repetitive behaviors. Diagnosing autism relies on behavioral symptoms since there's no reliable biomarker [4].

Treatment for autism can vary and involves multiple therapies like speech therapy, occupational therapy, and behavior analysis. Medications like psychotropic drugs may also be used. Other options include alternative treatments and therapies that show some promise [5].

This text will discuss the recent developments in stem cell therapy for autism, its possible consequences, and its uses.

Stem cells in autism spectrum disorder

For human diseases that would otherwise be incurable, stem cell therapies are widely regarded as the molecular and regenerative medicine of the future. Additionally, stem cells can be used to create patient-specific cell-based medications. Therefore, stem cells are thought to present fresh approaches to treating ASDs. For stem cell treatments, the immunological and neurological dysregulations seen in ASDs offer particular targets. Stem cells have a number of beneficial properties that point to possible therapeutic usage for ASDs. These are:

(1) the stem cells' capacity for self-renewal, which allows them to produce more stem cells that are exactly the same; and

(2) the differentiation process, which allows the cells to produce more differentiated cells

(3) Paracrine regulatory properties: stem cells produce and release an intricate implantable "biopharmacy" that can control the recipient's cell differentiation, tissue and organ repair, and anti-inflammatory responses.

The stem cell's potential paracrine pharmacology is determined by its cell type and programming. The biopharmacy of stem cells: trophic and immune modulatory human-specific biomolecules may equally be isolated in the laboratory and used as specific therapeutic agents without the actual implantation of the cells into the patient.

Consideration is being given to these paracrine roles of stem cells, such as the secretome or biopharmacy [6, 7]. It has previously been suggested that the trophic and immunomodulatory qualities of stem cells may be used to provide the beneficial benefits of cell-based treatment for ASD. The recipient immune system can be impacted by autologous or donor stem cells via two hypothesized mechanisms:

(1) cell-to-cell contact activation mechanism, which converts pro inflammatory macrophages to anti-inflammatory macrophages; and [8].

(2) paracrine secretome activity. It is important to remember that ASDs are linked to substantial immunological changes and an excess of pro inflammatory cytokines [9].

This article will includes the major types of stems cells embryonic, fetal, and adult that could offer special advantages in cell transplantation for ASD treatment.

Embryonic cells

Embryonic cells, such as embryonic stem cells (ESCs), hold the potential to develop into multiple types of cells due to their ability to differentiate into all three germ layers. This property makes them valuable for research purposes, but their application is hindered by regulatory challenges and the risk of immune rejection, particularly in pediatric populations. Research has shown that ESCs may be useful in treating immune system-related pathologies due to their capacity to give rise to various immune cells and cell types [10].

Currently, the focus is shifting from transplantation to leveraging ESCs as a source of regenerative molecules for therapeutic applications, particularly in developing treatments for autism spectrum disorders.

Induced pluripotent stem cells (iPSCs) mimic the behaviour of ESCs following transplantation, and genetic modifications can unlock their potential to generate more mature cells [11]. However, long-term studies on the safety and effects of iPSCs post-transplantation are still in their early stages. For pediatric populations, it may be advisable to exercise caution in utilizing these cells due to the potential risks involved.

Fetal cells

Within fetal tissues, there is a subset known as fetal stem cells (FSCs). In addition to FSCs, fetal-derived tissues usually comprise committed and differentiated cells. These fetal tissues and the FSCs that are linked to them differentiate into three subtypes: mesodermal, endodermal, and ectodermal (which includes the brain).

They possess immune-regulatory capabilities similar to those seen in mesenchymal stem cells, but they also have a larger capacity for growth and improved flexibility, which makes them highly promising for therapeutic usage. In fact, compared to neonatal and adult cells, FSCs can be reprogrammed to pluripotency more quickly, simply, and effectively. Neurodegenerative disease therapies are particularly interested in early gestational fetal neural tissue, which could also be used as a model for interventions for ASD. This is partly due to the fact that early FSCs express either very little or no MHC I or MHC-II [12].

Fetal mesenchymal stem cells have been shown to have a stable phenotype, exhibit reduced senescence, and have potent immune modulatory activities. Furthermore, unlike ESCs, they are derived from tissues that would otherwise be thrown away and cannot develop into teratomas after transplantation. Unlike MSCs, FSCs exhibit baseline levels of the pluripotency stem cell markers Oct-4, Nanog, Rex-1, SSEA-3, SSEA-4, Tra-1-60, and Tra-1-81 during the first phase of their lives. In contrast, during the second phase, they express mesenchymal stem cell markers, such as CD73, CD90, and CD105, and they are unable to express endothelial or hematopoietic markers, such as CD14, CD34, and CD45 [13].

For patients with neurological disorders, fetal tissue transplantation has emerged as a viable symptomatic therapy and disease management alternative. Human fetal cells isolated from the first trimester can develop a mature neuronal phenotype, survive transplantation, and have a functional effect. Instead of cell replacement, FSC advantages may result from paracrine trophic activities on host tissues, especially immunological, brain, and gastrointestinal organs. Numerous diffusible neurotrophic and growth factors can be produced and released by FSCs [14]. Another important mode of action that may be used in ASD treatments is their ability to inhibit proinflammatory cytokines.

Adult stem cells

Mesenchymal stem cells

In addition to bone marrow, adipose tissue, and birth tissues (umbilical cord blood, umbilical cord tissue, amniotic fluid, and placenta), MSCs are a diverse collection of undifferentiated, multipotent cells. Although MSCs can produce mesodermal tissue types such as bone, cartilage, and fat, their main mode of action is believed to be due to paracrine effects such as chemoattraction, immunomodulation, angiogenesis, apoptosis prevention, support for the growth and differentiation of local stem and progenitor cells, and antifibrosis. MSCs have shown immunomodulatory effects on humoral and cell-mediated immune responses, such as preventing neutrophil recruitment, reducing the generation of pro-inflammatory cytokines, and slowing the proliferation of B-, T-, NK-, dendritic-cell, and microglial cells [15].

Due to their clinical safety, immunomodulatory properties, ease of extraction from both adult and pediatric tissues, rapid expansion, and storage, these cells are thought to be highly valuable for transplantation. Furthermore, MSCs have the ability to move and settle in the locations of tissue damage after transplantation. Due to their potent anti-inflammatory and immunosuppressive properties, MSCs are very desirable for successful autologous and heterologous transplants that do not necessitate the use of pharmaceutical immunosuppression. They do not give uncontrollable growth or tumour formation In ASD therapy, MSC-mediated immune system modulating activity could be a key mechanism. As noted above, MSCs have a high long-lasting immunosuppressive action via soluble bio factors. MSCs influence the immune system in this way. MSCs have been shown to suppress the production of immunoglobulin by plasma cells, inhibit the maturation of dendritic cells (DCs) without affecting regulatory T cells, downregulate the production of proinflammatory cytokines by T lymphocytes, and inhibit the proliferation of CD8+ and CD4+ T lymphocytes as well as natural killer cells [16].

ASDs have been linked to immune system dysregulation as well as alterations in both innate and adaptive responses. Children with ASD exhibit abnormalities in their CD3+, CD4+, and CD8+ T cells as well as NK cells. Furthermore, proinflammatory cytokines, cannabinoid-type 2 receptor, and caspase proteases are overproduced in peripheral blood mononuclear cells (PBMCs) isolated from children with ASD, likely leading to long-term immunological changes and proinflammatory cellular responses [17]. MSCs have the capacity to influence immune system cells other than T cells, such as NK cells. Large-scale secretion of many bioactive molecules (paracrine activity), such as PGE-2 and IL-10, mediates this MSC trait. T-cell-mediated responses are impacted by these substances.

MSCs may potentially repair damaged brain function, plasticity dysregulation, and impaired cortical organization in ASDs. Postmortem brains from individuals with ASD have been found to exhibit abnormal functioning and changes in the cerebellum. Transplanted MSCs can in fact assist synaptic plasticity and functional recovery, which lends credence to the prospective use of cell treatments for ASDs. Another is MSCs' capacity to move to damage areas and participate in the healing process following implantation is another proposed mechanism of action of brain restoration and tissue repair played by MSCs.

Specific Mesenchymal Stem Cell Subtypes

Adipose-Derived Mesenchymal Stem Cells

Adipose-derived mesenchymal stem cells (AD-MSCs) are prevalent in human adipose tissue. They are easily extracted by minimally invasive methods, such as modest volume lipo-aspiration. These cells have received significant attention for autologous cell treatment. AD-MSCs exhibit anti-inflammatory properties and can develop into adipogenic, osteogenic, chondrogenic, and other mesenchymal cells. Despite clinical experiments using AD-MSCs, their true potential remains undetermined. In humans after reimplantation, differentiation into cell lineages other than adipocytes has yet to be definitively demonstrated. There's no evidence that reinfusing MSCs from fat tissue will solve the problem of them returning to the original site to repair it. Extracting MSCs from fat tissue also raises concerns about purity and the cells' molecular characteristics [18]. These cells may be a mix of different cell types, making it unclear whether they alone cause the observed effects. Before using MSCs from fat tissue to treat ASD, more research is needed to understand their biology and any potential risks associated with their use.

Umbilical cord derived MSCs

Umbilical cord-derived stem cells, mainly mesenchymal stem cells, are obtained from umbilical cord tissue and are abundant because discarded cords and placentas are abundant. These hematopoietic stem cells and those in the stroma of the umbilical cord's Wharton's jelly have potential applications, particularly in low immunogenicity. Wharton's jelly cells have low levels of HLA-ABC and no HLA-DR and can inhibit proliferation of lymphocytes [19]. They show immunomodulation properties, provide trophic support, and have potential in CNS regenerative medicine and ASDs.

Neural cells

Researchers have found promising results with another type of stem cell called Neural Stem Cells or Neuroprogenitor Cells. These cells are capable of generating multiple cell types within the central nervous system and can be isolated from both fetal and adult stem cells [20]. They have the potential to repair damaged neural tissue, reconstruct neural circuitry, and treat nervous system diseases. However, for clinical applications in neurodegenerative diseases or autism, more investigation is needed to address issues such as a reliable autologous source and regulation of neural plasticity and differentiation.

Different stem cells and related sources for the treatment of autism and their mechanism of action

Type of stem cells	source	Mechanism of action
Fetal cells	Fetus, amniotic fluid, umbilical cord, fetal blood, placenta	Immunomodulatory capacities Secretion of neurotropic factors Suppression of proinflammatory process
Mesenchymal stem cells	Bone marrow, umbilical cord	Neuroprotective functions. Hypoimmunogenic and immunosuppressive properties. paracrine secretion of several anti-inflammatory and survival promoting.
Adipo-derived stem cells	Adipose tissue	Secretion of trophic factors. Immunosuppressive and hypoimmunogenic effects.
Umbilical-cord and amniotic fluid-derived stem cells	Umbilical cord, placenta, amniotic fluid	Low immunogenicity and immunomodulation properties. In vitro growth capacity.
Neural stem cells	Brain (subventricular zone of lateral ventricles and subgranular zone of hippocampus).	Maintainance of homeostasis. Secretion of neurotrophic factors. Neuroprotective effects. Differentiation into neural-type cells.

Mechanisms of the therapeutic effect

At least two potential key-action mechanisms of stem cells can be useful in treating autism spectrum disorders (ASD). They include the paracrine effect and immunomodulatory properties. In ASDs, there are abnormalities in the immune system, with strong production of pro-inflammatory cytokines. This results in an imbalance in innate and adaptive immunity, with alterations found in various types of immune cells, including CD3+, CD4+, CD8+, and natural killer cells.

Abnormalities in immune responses, such as an overproduction of pro-inflammatory IL-1β cytokine, confirm immune system disruptions in ASDs [21]. However, stem cells can potentially restore these ASD-induced immune alterations by inhibiting the overactivation and proliferation of immune cells, and by increasing the production of anti-inflammatory molecules. Research has shown that stem cells can moderate the immune system through soluble factors released in response to local chemical signals. Another theory is that stem cells can address ASD-related immune and inflammatory issues by enabling cell-to-cell contact, allowing them to switch pro-inflammatory cells to their anti-inflammatory counterparts.

Clinical trials on stem cells and autism

In order to confirm the safety (in the first place) and effectiveness of the cellular therapy, clinical trials on stem cell transplantation in ASDs are crucial.

To date, a number of clinical trials have been conducted to show the safety and effectiveness of using stem cells to treat autism. An open-label proof-of-concept study was carried out by Sharma et al. on the utilization of autologous bone marrow-derived mononuclear cell (BMMNC) transplantation in 32 individuals with a confirmed diagnosis of autism (median age at intervention 10.5 years, male: female 3:1). Intrathecal cellular treatment was part of the program, which was followed by occupational therapy, speech therapy, a sensory integrated approach, psychological intervention, and nutritional advice. Multipotent adult progenitor cells, endothelial progenitors, and HSCs and MSCs make up the heterogeneous mixture known as mononuclear cell fraction [22].

After being extracted from the bone marrow aspirate, these cells were counted using the CD34+ marker and their vitality examined. The cells were injected intrathecally the same day, and to increase the injected cells' survival, methyl prednisolone was administered intravenously. In order to prove the safety of stem cell transplantation, long-term adverse effects were tracked. Minor side effects included aspiration, nausea, vomiting, and injection side discomfort. These incidents were described as procedure-related rather than problems linked to cellular transplantation. One significant adverse event associated with the cell treatment was a slight increase in hyperactivity, and three individuals experienced seizures. Indian Scale for Assessment of Autism (ISAA) results following cellular therapy showed improvements in the areas of reciprocity and social connections (better eye contact, sociable grin, and interacting with others), cognitive factors (focus, attention, and reaction time), and speech and language patterns (decrease in echolalic speech, repetitive, stereotyped language use, making strange noises or infantile squeals, difficulty starting or maintaining conversations with others, difficulty understanding the pragmatics of the conversation, and speech regression).

It was noted that there was a decrease in inappropriate emotional reactions, exaggerated emotions, self-stimulating emotions, and becoming enthusiastic or upset without obvious cause. Changes in the disease's severity, general improvement, and therapy effectiveness were all rated using the CGI scale. Interestingly, following six months of cellular therapy, functional neuroimaging using positron emission tomography (PET) scans revealed increased 18F-fluorodeoxyglucose (18F-FDG) uptake in the frontal lobe, cerebellum, amygdala, hippocampus, para hippocampus, and mesial temporal lobe [23]. Recent studies have shown hypoperfusion in important brain regions of individuals with ASD. Prior to cell transplantation, hypometabolic areas exhibited elevated metabolism following cellular delivery, most likely as a result of better oxygenation and neuronal activity. The authors list the short sample size, lack of randomization, and other limitations as general and controlled group.

Stem cell and autism: animal models

Animal models play a significant role in investigating the potential of stem cells for developing therapeutic strategies for ASDs, providing unique insights that cannot be achieved through clinical trials. However, lifelong neurodevelopmental pathologies such as ASDs are uniquely human behaviors and cannot be fully replicated in animal models, which can only provide basic information. Research has primarily utilized the black and tan brachyuric (BTBR) inbred mouse strain, which spontaneously develops behavioral deficits and brain abnormalities reminiscent of ASDs. When human mesenchymal stem cells (MSCs) were transplanted into BTBR mice, cell therapy improved repetitive behaviors, social behavior, and cognitive rigidity in the transplanted mice [24]. Similarly, transplantation of human adipose-derived stem cells (ASCs) in the valproic acid-induced autism mouse model resulted in improved motor coordination, social behavior, and anxiety. Additionally, human ASCs were found to increase the expression of phosphatase and tensin homolog, VEGF, IL-10, and p-AKT/AKT ratio in the brains of VPA mice. Furthermore, research has demonstrated that mouse-derived MSCs can promote neurogenesis, maturation of newly formed neurons, and improve cognitive and social behaviors in the VPA-induced autism model. Offspring of immune-activated mothers develop altered stem cell differentiation and impaired neurodevelopmental outcomes [25]. Transcriptome analysis has also revealed differential expressed genes in dental pulp stem cells from idiopathic ASD subjects compared to controls, highlighting the biologic mechanisms of ASDs. These findings provide valuable insights into the potential therapeutic applications and limitations of stem cell transplantation in ASD treatment.

Stem cell therapy for autism

Scientists exploring potential autism treatments have found some promising research in stem cell therapy. Studies have shown that a specific type of stem cell called mesenchymal stem cells may help individuals with autism. These cells have the ability to be easily obtained from various tissue types and can be transplanted to patients without the need for genetic modification, resulting in positive outcomes with minimal side effects. Combining mesenchymal stem cells with umbilical cord stem cells or using human embryonic stem cells may be a more effective treatment for autism [26].

Research on the use of human embryonic stem cells has shown improvements in behavioral areas such as eye contact, social interaction, and following commands in patients. Multiple studies have demonstrated the safety and effectiveness of using stem cells to treat autism, particularly in improving communication skills. Additionally, the use of autologous bone marrow cells containing mesenchymal stem cells has been shown to improve the quality of life of autistic individuals by reducing inflammation and impairment [27]. However, further research is needed, particularly to ensure the safety and effectiveness of stem cell therapy in treating autism by conducting large-scale studies, identifying optimal administration methods and dosages.

Mesenchymal stem cells in treating autism

Our group previously discussed the potential application of cell therapy, specifically mesenchymal stem cells (MSCs), for autism spectrum disorders (ASDs). These cells have a paracrine mechanism where they respond to the local environment by secreting factors to alleviate inflammation and promote repair, offering a potential treatment for ASDs. ASDs are characterized by immune system dysregulation, involving changes in both innate and adaptive immune responses. MSC transplantation could restore immune balance, which cannot be achieved through pharmaceutical interventions. Through the inhibition of specific immune cells and suppression of various cytokines, MSC transplantation could provide a unique therapeutic application for ASDs. MSCs function as an implanted biopharmacy after homing into target tissue, synthesizing and releasing various bioactive molecules, including anti-inflammatory cytokines and growth factors. This strong paracrine activity of MSCs seems to be the most plausible mechanism for the functional benefits derived from MSC transplantation, and transplanted MSCs can induce the host tissue to upregulate anti-inflammatory molecules, restoring pro-inflammatory processes noted in ASDs [28].

Immune modulation by mesenchymal stem cells

Researchers expect treating immune deregulation in autism to not only alleviate gastrointestinal and systemic symptoms but also profoundly impact neurological function. Reports suggest that reducing intestinal inflammation through antibiotics or dietary changes can temporarily improve neurological symptoms. However, no clinical agent has been developed to suppress inflammation at the root of the immune abnormality. Mesenchymal stem cell administration is a potential treatment for this purpose. Mesenchymal stem cells are a type of cell found in bone marrow, blood, and connective tissue that can differentiate into various connective tissues. They have the ability to secrete immune-inhibitory factors and present antigens to T cells, allowing for antigen-specific immune suppression. This characteristic enables the use of mesenchymal stem cells in allogeneic form without fear of immune rejection. Mesenchymal stem cells exert immune inhibitory effects through two main mechanisms: presenting antigens to T cells but providing a coinhibitory signal instead of a costimulatory signal, and producing PGE-2 and interleukin-10 [29]. These cells also possess inherent immunosuppressive properties through the production of other factors such as indoleamine 2,3,-dioxygenase and galectin-1. Furthermore, they can non-specifically modulate the immune response by suppressing dendritic cell maturation and antigen-presenting abilities. Mesenchymal stem cells' immunosuppressive activity is not dependent on prolonged culture, as functional induction of allogeneic T cell apoptosis has been demonstrated using freshly isolated, irradiated cells. These cells have potential therapeutic applications in treating immune-related disorders such as autism. Studies have shown that mesenchymal stem cells can stimulate the expansion of certain immune cells which suppress reactions, and they have potential for treating multiple sclerosis by inhibiting immune responses [30]. Another study showed these cells can be infused safely at a certain dose. Because of their unique immune-suppressing and cell-generating abilities, these cells may also help treat the potential low immune cell count associated with autism.

iPSCs: the new frontier cell therapy

Induced pluripotent stem cells (iPSCs) are a relatively new type of stem cells that can be reprogrammed from any cell type in the body using specific genes. However, early methods using integrating vectors carried risks of harmful mutations. New techniques such as using small molecules, viruses, or RNA have been developed to create safer, mutation-free iPSCs, which resemble embryonic stem cells. They can self-renew, express stem cell markers, and develop into different cell types. iPSCs are created from a patient's own cells, offering an unlimited source for autologous therapy. Besides regenerative therapy, patient-specific iPSCs are used in disease modeling, toxicity testing, and drug studies, providing a model for diseases such as Parkinson's, Huntington's, and diabetes.

Disease-specific iPSCs from patients with various conditions including adenosine deaminase deficiency and thalassemia are being used to test the effectiveness of drugs. With promising results from preclinical trials, iPSCs are being considered as a potential treatment for disorders such as neurodegenerative diseases, heart disease, and sickle cell anemia. Studies have shown the efficiency of iPSCs in differentiating into various cell types and treating various conditions in vivo. In experiments using severely damaged spinal cord in mice, injections of brain cells generated from human stem cells have allowed mice to recover mobility without tumor growth [31].

The brain cells generated in this way are able to change into different types of brain cells, promote blood vessel growth, and repair damaged tissue, which likely contributed to these mice recovering. Similarly, in experiments using primates with Parkinson's disease, human stem cells were able to produce brain cells that survived for extended periods and improved the animals' motor skills. These human stem cells have also been used to treat conditions like Huntington's and Amyotrophic Lateral Sclerosis, and have shown promise in treating autism. However, despite promising results, stem cells must still address the challenges of growing tumors or triggering immune system reactions when transplanted into humans. Before using stem cells in clinical trials, scientists must develop more effective ways to create them, use more specialized cells rather than stem cells, and thoroughly test the cells before use. Additionally, it has been observed that cells grown from stem cells can trigger a small immune response in recipients who have the same genetic makeup. Researchers hoping to understand the causes of autism are also studying stem cells derived from autistic individuals, which may help in developing more effective treatments for the disorder [32].

Stem cell modeling of autism

Disease modeling is a crucial tool for scientists to develop drugs for various disorders. The unknown pathophysiology of Autism Spectrum Disorder (ASD) has led to the development of a modeling system for autism. Human-induced Pluripotent Stem Cells (iPSCs) are used to model autism and elucidate disease mechanisms and discover new therapies. The use of iPSCs has several advantages, including the ability to differentiate into all three germ layers, self-renew, and express stem cell markers, unlike human Embryonic Stem Cells (hESCs). iPSCs can be patient-specific and retain the original genetics from the patient they were derived from. Scientists have successfully generated iPSCs from patients with Rett syndrome and have been able to view and understand the neuronal phenotype of this disorder [33]. The cells had changes in voltage-gated $Na+$ channels, impaired action potential generation, and other abnormalities. A similar experiment using iPSCs to study Rett syndrome found two key findings: a down-regulation of genes responsible for neuronal development and a deficit in neuronal markers directly tied to neuronal differentiation. Modeling Angelman Syndrome with iPSCs has led to the discovery of impaired neuronal maturation, including a depolarized resting membrane potential and decreased excitatory synaptic activity. Researchers have also discovered the role of UBE3A on calcium- and voltage-dependent big potassium channels, driving the development of drug targets against these channels. Fragile X Syndrome can be modeled using iPSCs, which have confirmed the role of the FMR1 gene in the phenotype [34]. The phenotype of iPSC-derived neurons included reduced length, altered calcium influx, and fewer pre- and postsynaptic protein levels. Drug-screening studies have identified several compounds that increase FMR1 gene expression, leading to advancements in the development of drug therapies for Fragile X Syndrome.

Scientists use iPSC modeling to study idiopathic autism, particularly where genetics links are unclear. Studying such cases can lead to discovering related genetics and potential treatments. In idiopathic ASD patients, grown iPSC showed an imbalance of inhibitory to excitatory neurons and excessive gene FOXG1 expression, connected to severity and head size [35]. Similar results were found in non-syndromic autism with iPSC-derived neurons, showing reduced synaptic activity and decreased firing [36]. The latter study tied neuron deficits to interleukin-6 and successfully treated patients by blocking its levels. These experiments demonstrate that iPSC modeling can aid in understanding unclear idiopathic autism cases despite the unknown genetic causes.

Treatment of hypoperfusion of brain by umbilical cord blood cd34+ stem cells in autism

Using umbilical cord blood stem cells may treat problems caused by inadequate blood flow by creating new blood vessels. This process, called therapeutic angiogenesis, can occur due to certain genes being triggered by low oxygen levels. After an injury, the body moves stem cells from bone marrow to create new blood vessels. Brain damage also triggers a similar process, and studies have found a connection between new blood vessel creation and brain repair [37]. Researchers are exploring ways to enhance this process, such as using natural factors to promote healing or giving patients specific proteins called cytokines. Some people have used umbilical cord blood cells to treat conditions like heart problems and poor circulation, as they are abundant and effective in creating new blood vessels [38].

Researchers have successfully used cord blood to stimulate blood vessel growth in various models of ischemia or reduced blood flow. Studies show that a specialized sub-group of cells within cord blood can develop into blood vessel cells and expand up to 40-fold. This sub-group in cord blood is 10 times more concentrated than in bone marrow. Research also found that administering cord blood cells to animals with reduced blood flow improved their conditions and promoted regrowth of damaged areas.

Due to the potency of these cells, researchers suggest they could be useful in treating autism, which is characterized by lower levels of blood vessel growth compared to stroke. However, cord blood typically contains a low number of these specialized cells, making it difficult for large-scale use. To overcome this, researchers have developed methods to expand these cells in the lab, achieving up to 60-fold growth [39]. Studies have treated over 100 patients with these expanded cells, and while there are concerns about immune reactions, data suggests that using these cells without immunosuppression is feasible. The authors of the paper argue that administering cord blood cells without immunosuppression is safe and has been used in over 500 patients without any adverse reactions [40]. They believe that expanding cord blood-derived cells may be an effective tool for promoting new blood vessel growth in autistic patients.

CONCLUSION

. This review examines autism's cellular and molecular abnormalities, potential stem cell therapies, animal models, and ongoing clinical trials. Research on autism's genetics shows that no proven cure exists, but studying stem cells has led to promising results, particularly with mesenchymal stem cells and human embryonic stem cells. These cells have been used to reduce autism severity and improve quality of life. Finally, stem cells have been used to model various autism forms, such as Rett Syndrome and Fragile X Syndrome, allowing researchers to develop novel therapies. However, researchers must consider the ethical implications of their work, particularly when studying children, and prioritize their well-being and safety.

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