Review

Prospects of Stem Cell Therapy for Autism Spectrum Disorders

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ABSTRACT

Autism is a group of highly complicated neurodevelopment disorders affecting 1 in every 110 children born in USA. The etiology and pathophysiology are poorly understood and it currently has no universally accepted therapy or cure. Stem cell replacement therapy via transplantation potentially reverse brain hypo perfusion and immune dysfunction, which are considered to be two major pathophysiology mechanisms of autism. Recent advances in the in vitro study of disease modeling of autism reveals disease-specific cellular defects and reversible symptoms, opens the possibility of cell therapy and offers new hopes for cures. However, this new therapy is still in its infancy. There are many technological barrier such as immune-rejection, tissue migration and integration, cancer risk, safety concern, proper development in the inner environment and clinical barriers of individual sensitivity and liability, disease complexity, and more, which will need to be overcome before reaching new era of therapy. It will be necessary to conduct in vivo animal studies and then further clinical trials, however, before any potential clinical application in autism and other human disease can be realized.

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INTRODUCTION

Autism is widely regarded as among the most complicated neurodevelopment disorders, with rapid increases in incidence reported recently. Since the last decades of the twentieth century, Autism spectrum disorders (ASD) increased steadily in the USA and around the world. In 2007, it reached to epidemic proportions, with approximately 1 in 166 children in the USA. It reached 1 in 110 children at the end of 2009 (a 57% jump in just four years).[1] Autism has become a huge healthcare burden and threat globally.

Autism is characterized by difficulties communicating and interacting with others, and is often accompanied by significant behavioral challenges. It is a clinical syndrome rather than a disease, with its diagnosis based on psychological testing and DSM-IV-TR criteria. The etiology of Autism is largely unknown, but it has significant genetic and environmental etiological factors.[2] Current treatments for autism can be divided into behavioral, nutritional and medical approaches, although no golden standard approach exists. Behavioral interventions usually include activities designed to encourage social interaction, communication, awareness of self, and increase attention. In recent years, numerous clinical and research organizations and health care providers have put continuous effort exploiting biochemical approaches.[3,4] Only small numbers of the treated children with autism develop into independent adults, however, and medications offer only symptom control and behavioral modification.

Stem cell therapy as a hope of cure for autism has brought great attention the last several years, extensive researches has been conducted and showed promising results. Parents are desperate to try this new therapy because they have no time to wait. Stem cell therapy has a potential to help to open a new era of treatment for this centuries old mystery.

OVERVIEW OF STEM CELL THERAPY FOR HUMAN DISEASES

As bone marrow stem cell transplantation became a gold standard therapy for bone marrow failure, including the most hematologic malignancies the last 20 years, extensive research and preclinical studies reveals that stem cell treatment is also a promising treatment for a range of human diseases. Harris et al estimated, for example, that up to 128 million individuals or almost 1 in 3 individuals in the US might benefit from regenerative medicine therapy (mostly

"stem cell" and "progenitor cell" technologies).[5] In addition to treatment of hematologic disease, stem cells are used for burns, bone grafting in orthopedics and corneal generation from limbal stem cells. Preclinical animal studies show therapeutic effects on spinal cord injuries[6] Parkinson disease,[7] retinal disease,[8] myocardial infarction,[9] type I diabetes,[10] multiple sclerosis, and muscle damage. The induced pluripotent stem cells (iPS) as a source of cell replacement has used human fibroblast cells.[11-12] Stem cells can also alter disease processes without engrafting,[13] as some effects through cytokine production[14] are potentially therapeutic. Stem cells in adult tissues can be targeted by certain drugs, with can activate or change stem cell function.[15]

Although stem cell therapy for human disease is quite promising, the development of this innovative medicine is still in an immature state that is marked by slow progress and mixed results[16] in clinical trials. Consequently, bone marrow transplantation remains the only established use of stem cells approved by the U.S. Food and Drug Administration (FDA) at this time.

THE RATIONALE OF STEM CELL THERAPY IN AUTISM

Autism spectrum disorder is a behaviorally defined clinical syndrome that likely involves multifactorial and heterogeneous etiological mechanisms. Evidence of abnormal brain development and function is compelling and well-accepted. Pathophysiological changes remain poorly understood, though abnormalities in cerebral hypoperfusion,[17] inflammations,[18] oxidative stress,[19] increased brain volume,[20] immune dysregulation[21] mitochondrial dysfunction, neurotransmitter abnormality,[22] excess opioid, impaired detoxification, and functional disturbances such as disconectivity[23] offer clues.

In recent years, brain hypoperfusion and immune dysfunctions[17,21] have been generally recognized as two major brain pathologic alterations in autism. The areas affected by hypoperfusion seem to correlate with regions of the brain that show abnormal function of autism. Sasaki et al reported the areas of hypoperfusion were also related to foci observed on EEG.[24] Gupta SK, et al concluded that children with autism have different levels of perfusion abnormities in brain causing neurophysiologic dysfunction that presents with cognitive and neuropsychological defects.[25] It is further indicated that the degree of hypoperfusion correlates with the severity of autism symptoms. Statistically significant inverse correlations occur between extent of hypoxia and IQ. Yang et al recently reported that hypoperfusion in autistic brains may be global. Asymmetric changes of hemispheric hypoperfusion were more obvious in the Asperger group than in the autism group, which indicates at least somewhat different neurobiological mechanisms between these subgroups.[17] Damage from hypoperfusion of temporal areas was associated with onset of autism-like disorders, as Bachavelier et al reviewed.[26] Further studies revealed that improvement of hypoxia ameliorates clinical symptoms in autism, which implies that hypoperfusion contributes to the development or exacerbation of clinical symptoms in autism. Hyperbaric Oxygen Therapy (HBOT) provides invaluable clinical data on the treatment of hypoperfusion. Encouraging results were reported in Jandial et al in 2009, which showed neural proliferation after reperfusion in numerous animal models of cerebral ischemia.[27]

Immune dysfunction in autism, on the other hand, is also widely recognized. Ashwood et al recently reported findings suggested that ongoing inflammatory responses may be linked to disturbances in autistic behavior.[28] Careaga et al proposed that autism may in fact be a systemic disorder with connections to abnormal immune responses.[29] Ashwood et al pointed out such aberrant immune activity during vulnerable and critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of ASD.[30]

In 2007, Ichim et al [31] published their important review article about stem cell therapy for autism; they, proposed a role for stem cell therapy in treating autism. More specifically, they proposed the administration of CD34+ umbilical cord cells and mesenchymal cells as novel treatments for the above two major pathologies associated with autism – hypoperfusion and immune dysregulation.

Treatment with umbilical cord blood CD34+ stem cells in the damaged areas of the brain may trigger or increase angiogenesis, the induction of new blood vessels from preexisting arteries, to overcome ischemia. Cord blood CD34+ cells are known to be potent angiogenic stimulators. Once the hypoperfusion is improved or reversed, it would not only improve nervous system functioning, but would also promote neural proliferation as an apparent self-repair mechanism.

Since immune system is also critical in stem cell administration, mesenchymal cells are considered to be a necessary element in the treatment of immune dysregulation associated with autism. This approach may improve other, nonneurological problems as well, such as "leak gut". Inflammatory bowel disease represents a state of dysregulated inflammation. A small pilot study of mesenchymal stem cells suggested a benefit in Crohn's disease, leading to the launch of multicenter, placebo-controlled studies. Larger trials in graft-versus-host disease have suggested a benefit, possibly due to reparative effects as well as immunomodulatory activity.[32] Other stem cell studies, including the use of placenta-derived stem cells, are being initiated in Crohn's disease. Using these two kinds of stem cells together may potentially heal both the brain and the gut in autism.[33]

THE PRECLINICAL AND CLINICAL PICTURE OF STEM CELL THERAPY FOR AUTISM

Recent studies show that umbilical cord blood CD34+ stem cell and mesenchymal stem cells administration for therapeutic angiogenesis and immune regulation may be effective in treating experimentally in various hypoperfusion

defects such as stroke.[34,35] Angiogenesis is induced through the formation of collateral vessels and has been observed in hypoperfused tissues. Theoretically, the level of angiogenesis needed for autism is lower than that needed for stroke, since ischemia in autism is milder than it is in stroke. Cytokines production by cultured human umbilical cord blood indicates systemic administration of cord blood cells is sufficient to induce neuroregeneration related to brain repair. Cellular therapies utilizing mesenchymal stem cells (MSCs) may provide functional benefits for a wide range of neurological insults.[36] One important concern should be noted involving the autologous reaction. It was believed that allogeneic cord blood cells could not be used without immune suppression, but Riordan et al[37] have successfully demonstrated the feasibility of cord blood cells administration in the absence of immune suppression.

Autism in vivo studies are a step behind. It is equally important to use stem cells in disease modeling which is particularly relevant to diseases of complex etiology[38] such as autism. In recent years, stem cell research in the USA has been helpful in developing new medications for autism, with a number of in vitro studies reported. Autism cells have been successfully recreated from stem cells in lab studies. A collaborative effort between researchers at the Salk Institute for Biological Studies and the University of California successfully used human-induced pluripotent stem (iPS) cells derived from patients with Rett syndrome to replicate autism in the lab and study the molecular pathogenesis of the disease.[39-40] This study revealed disease-specific cellular defects and reversible symptoms that may be treatable. More recently Vaccarino FM[41,42] et al indicated exciting advances based on the use of induced pluripotent stem cells iPSCs, which holds promise for improving early diagnosis and, possibly, treatment of psychiatric disorders such as autism. Specifically, examination of iPSCs from typically developing individuals may reveal how basic cellular processes and genetic differences contribute to individually unique nervous systems. Gaspard N et al concluded that stem cell-derived neural progenitors and neurons could help to rebuild damaged brain circuitry, opening the possibility of cell therapy.[43]

What about the clinical picture? Research in several countries, such as China, Mexico and India, include the use of cord stem cells to treat autism. The protocol includes involves several intravenous infusions over the course of a year, which are not covered by insurance. A typical protocol, for example, involves 4-5 intravenous injections of 20 million stem cells over the course of a week, along with stem cell growth factors, at a cost of about $25,000 for one course of treatment. Data from Mexico reported[44] that 19 US patients under supervision of David Howe, MD, US licensed physician, traveled to Moscow to receive treatment with mesenchymal and neuronal cells for a number of conditions, including one autism patient. Improvement in patient status was reported in 17/19 (89%) patients. None of the patients developed tumors; Chaitanya Stem Cell Therapy Center in India[45] claims to have successfully treated 300 cases since last 28 months for cerebral palsy, Autism, Mental retardation, Spinal Cord Injury and Paraplegia, and Diabetes. China is another major stem cell treatment source.[46]

Depite these anecdotal cases and reports about autistic children who benefitted from stem cell therapy, no known clinical trials are under development. Biohellenika supported, free of charge, the therapy of a child who was treated with mesenchymal stem cells derived from the child's own adipose tissue,[47] and reported positive short term benefits. Unfortunately, positive treatment reports are little more than unsubstantiated rumors at this point,[48,49] owing to a lack of credible, peer-reviewed articles or even case reports.[50] Hopefully, this picture will change. Because of epidemic nature of autism and the sound rationale of stem cell therapy, autism is listed as top three candidates in adult stem cell treatments the next ten years.[51]

BARRIERS TO SUCCESS

As mentioned above, stem cell therapy provides intriguing treatment possibilities for many human diseases, including autism. However it is still in its immature stage. There are many barriers to overcome on the path to clinical feasibility and treatment success. First of all, stem cell therapy as a new renovation has a lot of technical complexities to be addressed when used in human body. Immuno-rejection of stem cell transplants is a great challenge in clinical treatment. There is a need to establish cell survival rates after immediate or subsequent immune-rejection, for example, or after graft-versus-host disease. Individualized iPSC tissue offers the possibility of personalized stem cell therapy in which graft rejection would not occur, but achieving this on a large scale is problematic because of inefficient reprogramming techniques and high costs. The creation of stem cell banks comprising HLA-typed hESCs and iPSCs may help overcome the immunological barrier by providing HLA-matched (histocompatible) tissue for the target population.[52] Immune modulation offers therapeutic benefit for immune rejection reactions.[53] Neural stem cells have unique characteristics that help them modulate the host immunological defense, but, under some conditions, may still trigger a rejection process.[54]

Interactions with surrounding tissue could also be complicated for surviving transplanted stem cells. MRI studies could track the grafted cell migration[55] and the surrounding tissue which may negatively affect graft survival or the functional recovery of the tissue. Kim et al[56] described procedures to direct the differentiation of human embryonic stem cells and human induced pluripotent stem cells into forebrain neurons that are capable of forming synaptic connections, and that are able to induce presynaptic differentiation in human induced pluripotent stem cell-derived neurons.

The risk of tumors is a significant safety issue and threat, as are viruses used in some therapies that can develop in recipient's bodies. This is of particular importance when using pluripotent cells[57,58] The pluripotent cell methods of greatest efficiency for reprogramming cells are currently retrovirus or lentivirus-based, and, therefore, run the risk of

mutagenesis by virtue of viral integration into the host genome.[59] Progress in reducing the number of gene products needed for reprogramming, and in the use of either non-integrating viruses or small molecules to supplant retrovirus-based reprogramming, is ongoing.[60] These developments may mitigate the concerns about insertional mutagenesis, but will not entirely assuage concern for altered growth control of modified cells, particularly those with pluripotency.

Generating the proper cell type from pluripotent cells remains a significant challenge for some cell types. Protocols have now been devised to create some neural cell types of clear clinical importance.[61] However, for other tissues, the cell types created most closely resemble embryonic blood cells and are not capable of engrafting the bone marrow without further and undesirable genetic manipulation.[62] Achieving the right stage of differentiation is another consideration in development of the stem cell derived cell therapies. It may be most desirable to generate progenitors, rather than fully mature terminally differentiated cells in some tissues, so that the replaced cells do not quickly senesce and die.

Furthermore, autism as a group of highly complicated neurological disorder is more genetically labile than others. For example, secondary malignancies (SMs) in Hodgkin lymphoma (HL) are thought to be related to exposure to chemotherapy and radiation therapy, and tend to occur a decade after initial therapy. Chandrakasan et al, for example, reported a 14 year old autistic male who developed malignant fibrous histiocytoma (MFH) two years after autologous stem cell transplantation for advanced stage HL. The MFH and post-surgical reactive tissues exhibited multiple clonal abnormalities. In addition, PHA-stimulated peripheral blood lymphocytes showed increased frequency of non-clonal chromosomal aberrations. The potential role of genomic instability in early onset of SM in this patient was discussed.[63] In light of likely etiological heterogeneity, it is possible that only some cases of autism will respond positively to stem cell therapy, such as those with evidence of hypoperfusion and immune dysfunction.

It is needed to point out those stem cell technology based therapy protocols, we reviewed as promising as they are, are actually examples of a larger group of strategies (such as gene transfer, or using antibodies to induce endogenous stem cells to form blood vessels or neurons) that may one day help neurons ameliorate abnormalities that underlie autism.

Lastly, social and ethical impacts are important considerations. As mentioned above, stem cell therapy is in its early stage and mostly not approved by FDA and can be only done outside of USA. The technology and protocol is not well established. It's very costly, and not necessarily safe (e.g. stem cells may be contaminated with various pathogens).

CONCLUSION

Autistic Spectrum Disorders encompass a wide range of disorders or conditions that are not yet clearly defined or recognized. More work need to be known before the pathology is clear and treatment can be proposed. While the rationale for using stem cells to treat autism is indeed promising, stem cell medicine, or in general, regenerative medicine, is still in an immature and primary stage. In vitro and in vivo animal studies will need to be furthered to better understand the pathogenesis of autism and screen new medications, and clinical trials with sufficient patient numbers are needed to assess treatment efficacy. When patients and their families consider new treatments, the proposals need to be interpreted in a discerning manner that can be balanced with scientific evidence. We propose more effort involve improvement of technology, development of vivo animal models and development of protocols for clinical trials. We foresee a potential for significant progress in the next decade as stem cell research and regeneration medicine continue to mature.

FINANCIAL DISCLOSURE

Authors declare no financial interests related to this work.

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