

WJSC 6th Anniversary Special Issues (2): Mesenchymal stem cells**Mesenchymal stem cells in treating autism: Novel insights**

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Abstract

Autism spectrum disorders (ASDs) are complex neurodevelopmental disorders characterized by dysfunctions in social interactions, abnormal to absent verbal communication, restricted interests, and repetitive stereotypic verbal and non-verbal behaviors, influencing the ability to relate to and communicate. The core symptoms of ASDs concern the cognitive, emotional, and neurobehavioural domains. The prevalence of autism appears to be increasing at an alarming rate, yet there is a lack of effective and definitive pharmacological options. This has created an increased sense of urgency, and the need to identify novel therapies. Given the growing awareness of immune dysregulation in a significant portion of the autistic population, cell therapies have been proposed and applied to ASDs. In particular, mesenchymal stem cells (MSCs) possess the immunological properties which make them promis-

ing candidates in regenerative medicine. MSC therapy may be applicable to several diseases associated with inflammation and tissue damage, where subsequent regeneration and repair is necessary. MSCs could exert a positive effect in ASDs through the following mechanisms: stimulation of repair in the damaged tissue, *e.g.*, inflammatory bowel disease; synthesizing and releasing anti-inflammatory cytokines and survival-promoting growth factors; integrating into existing neural and synaptic network, and restoring plasticity. The paracrine mechanisms of MSCs show interesting potential in ASD treatment. Promising and impressive results have been reported from the few clinical studies published to date, although the exact mechanisms of action of MSCs in ASDs to restore functions are still largely unknown. The potential role of MSCs in mediating ASD recovery is discussed in light of the newest findings from recent clinical studies.

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Key words: Autism spectrum disorders; Autism treatment; Cell therapy; Mesenchymal stem cells**Core tip:** Autism spectrum disorders are still untreatable pathologies. Mesenchymal stem cells possess the immunological properties which make them promising candidates as a novel therapeutic option.

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AUTISM SPECTRUM DISORDERS

Autism spectrum disorders (ASDs) are complex neuro-

developmental disorders. Indeed, this term refers to a heterogeneous group of varied conditions characterized by dysfunctions in social interactions, skills, and communication, restricted interests, and repetitive stereotypic verbal and non-verbal behaviors, influencing the ability to relate to others. Cognitive, emotional and neurobehavioral abnormalities characterize the core symptoms^[1,2]. The prevalence of these disorders has dramatically increased in the last years, with present rates of 11.3 per 1000 (one in 88) children aged 8 years in the United States, according to Centers for Disease Control^[3]. ASDs are presumed to be a lifelong disability with multiple impacts on child and adult health. Indeed, adult autistic individuals show limited independence because of their learning disability. In adulthood, communication is still impaired, as reading and spelling abilities are poor. Stereotyped behaviors and restricted interests still persist. The children affected require special and intensive parental, school, and social support^[4]. ASD results in a substantial impact on a person's quality of life and that of their family^[5]. Given the total lifetime societal cost of caring for one individual with autism, estimated in \$3.2 million^[6], autism should be considered as an urgent public health priority^[2].

Together with the cognitive, emotional and neurobehavioral abnormalities, ASDs are disorders characterized by a broad range of biochemical, toxicological and immune involvement, including: oxidative stress, endoplasmic reticulum stress, decreased methylation capacity, limited production of glutathione, mitochondrial dysfunction, intestinal dysbiosis, increased toxic metal burden, and immune dysregulations including autoimmunity^[7].

Currently, only a handful of medications are licensed for treating a limited number of autism-related symptoms^[8]. Moreover, prescribed pharmaceuticals (*i.e.*, antipsychotics) fail to address the ASD core symptoms, have the potential of markedly adverse effects, and are at best palliative^[9-12]. The alternative treatments for ASDs are diverse and include: behavioral, nutritional, and biomedical approaches. Thus the need for a definitive and effective therapy is an unfulfilled priority for autism research.

MESENCHYMAL STEM CELLS

Presently, cell therapies and cell-based biopharmacies offer a valid intervention for several otherwise untreatable human diseases. Stem cells appear to represent the greatest potential for the future of molecular and regenerative medicine^[13,14]. Among the various stem cell subtypes, mesenchymal stem cells (MSCs) provide a useful tool for the treatment of several diseases associated with inflammation, tissue damage, and subsequent regeneration and repair^[15].

MSCs are multipotent stem cells that possess the capacity to differentiate *in vivo* or *in vitro*, under specific conditions, into cells of connective tissue lineages, including bone, fat, cartilage and muscle^[16]. They are distinct from the hematopoietic lineage, and were initially described by

Alexander Friedenstein in the 1960s after he extracted MSCs from bone marrow^[17]. It is common practice for clinical and research applications, to acquire MSCs from bone marrow aspirates of the superior iliac crest under local anesthesia. The cells are then isolated by their adherence to plastic and amplified through passage in culture, where they exhibit a great replicative capacity^[18].

In order to achieve a detailed classification of this type of stem cell, the International Society for Cellular Therapy has proposed the following minimal criteria to identify human MSCs: they must grow in standard, plastic-adherent culture conditions; must express the cyto-specific markers CD73, CD90 and CD105, without expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules; and must be capable of *in vitro* differentiation into osteoblasts, adipocytes and chondroblasts^[19].

Interestingly, MSCs seem to be the most promising clinical candidate for immune-modulatory cell-based therapy^[20]. MSCs show immunomodulatory capacities, as they are able to induce tolerance in immunocompetent allotransplants or even xenotransplant recipients^[21]. Interacting with a wide range of immune cells, probably through a cell-to-cell contact mechanism^[22], MSCs are able to modulate T-cell phenotype and immune-suppress the local environment^[23].

Their unique properties of immunomodulation, multipotency, and rapid self-renewal proliferation rate, distinguish them as useful tools for application in immunomodulatory therapy and neurological disorders. In addition, other desirable characteristics of MSCs, *e.g.*, genetic stability, stable phenotype, and easy procedures for collection, storage and shipping from the laboratory to the bedside^[24], direct us to MSC-based therapies as a potent intervention.

In clinical settings, MSCs can be transplanted directly without genetic modification or pretreatments (*i.e.*, immunosuppressants). No host *vs* graft rejection has been observed^[25]. Importantly, there is an absence of uncontrollable growth or tumorigenesis with MSCs, in contrast to the potential problems intrinsic to embryonic stem cells^[26]. Crucially, MSCs create no moral objection or ethical-religious controversies, unlike embryonic or fetal stem cells^[27].

MESENCHYMAL STEM CELLS IN TREATING AUTISM: THE RATIONALE

The potential application of cell therapy, in particular MSCs, for ASDs has already been discussed by our group^[28,29]. After a brief description of MSC-mediated ameliorative effects in ASDs, we will review recent and ongoing clinical trials using MSC transplantation in ASD patients.

We hypothesize that MSCs exert a positive effect in ASDs through the following mechanisms: stimulation of the plastic response in the host damaged tissue (*e.g.*, inflammatory bowel disorders); synthesizing and releas-

ing anti-inflammatory cytokines and survival-promoting growth factors (paracrine and biopharmacy); integrating into existing neural and synaptic network (engrafting), and restoring plasticity^[28,29]. Following transplantation, MSCs target and migrate to the site of injury. In some cases these cells respond to the local environment with appropriate secretion of soluble factors to ameliorate inflammation and promote repair^[30]. This paracrine mechanism offers potential in ASD treatment.

ASDs are characterized by a coexistent, if not etiological, immune system dysregulation^[31]. Changes in innate and adaptive immune responses have been reported in ASD patients^[32]. Characteristically, ASD cases show alterations in both T cell- and B cell-mediated immunity, as well as an imbalance in CD3⁺, CD4⁺, and CD8⁺ T cells and natural killer (NK) cells^[33]. On these bases, the regulatory effects mediated by MSCs present an optimal way to restore immune balance, which cannot otherwise be obtained through pharmaceutical interventions. Through inhibition of the proliferation of CD8⁺/CD4⁺ T lymphocytes and NK cells, suppression of the immunoglobulin production by plasma cells, and inhibition of the maturation of dendritic cells (DCs), MSC transplantation appears ideally suited to provide a unique therapeutic application for ASDs^[34,35].

In addition, MSCs are able to inhibit T lymphocyte pro-inflammatory cytokine production^[36]. MSCs function as an implanted biopharmacy: after homing in to the targeted tissue site, they synthesize and release a broad range of bioactive molecules^[35,37], *i.e.*, anti-inflammatory cytokines, trophic and growth factors, interleukin (IL)-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15, macrophage colony-stimulating factor, Flt-3 ligand, and stem-cell factor^[38], which in turn could be responsible for activating endogenous restorative mechanisms within injured tissues. This strong paracrine activity of MSCs seems to be the most plausible and reasonable mechanism for the functional benefit derived from MSC transplantation. Furthermore, transplanted MSCs can induce the host tissue to upregulate the production of anti-inflammatory molecules, such as IL-10, in this way restoring the pro-inflammatory processes noted in ASDs^[39,40].

MESENCHYMAL STEM CELLS IN TREATING AUTISM: CLINICAL EVIDENCE

Despite insufficient pre-clinical models of MSC therapy for ASDs^[41], several clinical studies on humans have been conducted. Recently, a non-randomized, open-label, controlled, single-center phase I / II clinical trial to examine the treatment safety and efficacy of transplantation of human cord blood mononuclear cell (CBMNCs) and/or human umbilical cord-derived mesenchymal stem cells (UCMSCs) in children with autism has been performed^[42]. Stem cell administration was carried out via intravenous and intrathecal infusions. Autistic children transplanted with cells were followed for 24 wk. According to the authors, the cell treatment was safe, well toler-

ated without immediate or long term side effects, and no allergic, immunological reactions or other serious adverse events were observed at the time of injection or during the whole follow-up period. The cell transplantation showed efficacy; improvements were observed in visual, emotional and intellectual responses, body use, adaption to change, fear or nervousness, non-verbal communication and activity level, as measured by Childhood Autism Rating Scale, as well as in lethargy/social withdrawal, stereotypic behavior, hyperactivity and inappropriate speech evaluated by the Aberrant Behavior Checklist^[42]. They noted that the group receiving CBMNCs and UCMNCs demonstrated a more robust therapeutic effect than the group receiving mono-cell line therapy, which may be attributed to the action of CBMNCs and UCMSCs in synergy. It has been proposed the synergistic mechanism is related to increased cell-mediated perfusion in brain areas and/or the regulation of immune dysfunction.

Intrathetically transplanted autologous bone marrow-derived mononuclear cells were efficacious in improving the quality of life in a 14-year-old boy with severe autism^[43]. A detailed cell-sorting analysis was not done, but the cell extract contained a percentage of MSCs. We know bone marrow is comprised of a heterogeneous population of stem cells, encompassing hematopoietic stem cells, MSCs, endothelial progenitor cells, and very small embryonic-like stem cells. The bone marrow cell transplantation was safe, the patient had no noted side-effects and showed some immediate improvements within a week (eye contact and attention, fine motor activities). Significant improvements were observed over a period of 6 mo to 1 year (social interaction and emotions, impulse control, reading skills, tracing, recognition of all shapes and following commands, and hyperactivity). Interestingly, comparisons of pre/post cell therapy brain positron emission tomography scans revealed a markedly increased uptake in bilateral temporal lobes and bilateral calcarine cortices with mild increased uptake in the left medial pre-frontal cortex^[43].

Transplanted stem cells therefore seemed to ameliorate neural hypoperfusion in the previous case report. Hypoperfusion may be a consequence of focal inflammation and would likely result in low-grade ischemic consequences: hypoxia, abnormal metabolites, neurotransmitters dysregulation, and potential neural tissue damage.

In the light of these encouraging, but limited observations, the authors launched an open-label proof-of-concept study using autologous bone marrow-derived mononuclear cell transplantation in 32 patients with autism^[44]. The average number of intrathecally injected cells was 8×10^7 cells. Cell treatment was determined to be safe and adverse events were transient (hyperactivity). They hypothesize that the intrathecal administration route is able to enhance homing of the transplanted cells into the central nervous system. Clinical improvements after cellular therapy were observed in social relationships and reciprocity, emotional responsiveness, communication and behavior. As a putative mechanism of action,

the authors further hypothesized that cellular transplantation was able to restore function to ASD patients by neuroprotection, neural circuit reconstruction, neural plasticity, neurogenesis, and immunomodulation.

The hypothesis that intrathecal administration increases the efficacy of stem cell therapies is not actually evaluated by these various studies. Clearly, it is a testable hypothesis and future studies should include arms with and without intrathecal administration to compare the therapeutic efficacy of the more invasive intrathecal implantations.

PROBLEMS

Despite these early clinical trials with MSCs, there are no apparent pre-clinical studies on the use of MSCs in ASD models^[41]. Thus, more research into the mechanisms of action post transplantation is required to adequately understand the route, dosing and safety. However, the parental perspective is unlikely to wait on more detailed scientific studies. Stem cells are readily available from many centers in numerous countries, with various cell types and methodologies being utilized. Families recognize the devastating nature of autism on their children and are already seeking stem cell therapies. Based on a simple scan of the internet sites advertising cell therapies, it appears hundreds of ASD children have already been treated.

Another complexity in the research arises from stem cell sourcing. Some protocols use allogeneic (derived from a different person or collection of donors), while others use autologous donor (self-derived) cell types^[15]. Some protocols for ASD also use expanded autologous MSCs (United States Patent Application: 20060182724). This adds another dimension to the discussion and a potential source of laboratory contamination. Expansion requires medium for growth from which the cells must then be isolated, and any medium washed sufficiently to prevent a reaction in the recipient. Typically bovine serum is used. This creates the further risk of prion infection of the medium. To avoid this, one group has proposed using pooled human serum^[45]. This xeno-free methodology has many desirable features, but retains the concerns about human pathogen transmission. The group, however, screened extensively for contamination and it appeared they were able to ascertain that the samples were free of any disease vectors. This process should be considered for any use of expanded MSCs for ASD therapies.

Another challenge in the standardization of dosing derives from the varying efficacy amongst allogeneic donors in terms of: vitality, potency, and expansion potential. Every donor is different and this could affect efficacy and also paracrine effects. Indeed, it seems that the secretion of bioactive molecules could differ by a factor of 10 between different donors of matched age and gender^[15]. Recently, in order to increase the adequate supply of stem cells from donor tissues, it has been demonstrated that a 3D co-culture system with murine-derived hematopoietic stem cells co-cultured with MSCs produces 3D-microag-

gregates of stem cells. These 3D-microaggregate systems support the expansion of approximately twice as many hematopoietic stem cell candidates as the 2D controls. In addition, the MSCs maintained in 3D aggregates are able to express significantly higher levels of hematopoietic niche factors compared with 2D cultures^[46].

Finally, there are complex hurdles to overcome from the legal and regulatory restrictions placed by governments seeking to control cell therapies^[27]. Several countries (*i.e.*, United States and EU area) have attempted to create uniformity within the regulations governing cell trials, while creating very stringent regulations on cell culture conditions, diseases to be treated, and patient safety. However, in some other countries (*e.g.*, Ukraine, China, Dominican Republic, Panama, and Mexico) the access to cell therapy is more readily available.

CONCLUSION

The rapidly increasing prevalence of ASDs worldwide is creating an urgent need for effective restorative therapies. The lack of safe and effective psychopharmaceuticals and other definitive medical therapies, together with the limited understanding of the pathophysiology, has created an urgency to identify novel and more effective therapies^[47]. MSCs appear to offer a greater potential in regenerative medicine for complex disorder like autism than existing pharmaceutical protocols. Promising and impressive early results have been achieved from a few clinical studies, although the exact restorative mechanisms of action of MSCs in ASDs are still largely unknown.

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