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Review Article

Autism Spectrum Disorders: Is Mesenchymal Stem Cell Personalized Therapy the Future?

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Autism and autism spectrum disorders (ASDs) are heterogeneous neurodevelopmental disorders. They are enigmatic conditions that have their origins in the interaction of genes and environmental factors. ASDs are characterized by dysfunctions in social interaction and communication skills, in addition to repetitive and stereotypic verbal and nonverbal behaviours. Immune dysfunction has been confirmed with autistic children. There are no defined mechanisms of pathogenesis or curative therapy presently available. Indeed, ASDs are still untreatable. Available treatments for autism can be divided into behavioural, nutritional, and medical approaches, although no defined standard approach exists. Nowadays, stem cell therapy represents the great promise for the future of molecular medicine. Among the stem cell population, mesenchymal stem cells (MSCs) show probably best potential good results in medical research. Due to the particular immune and neural dysregulation observed in ASDs, mesenchymal stem cell transplantation could offer a unique tool to provide better resolution for this disease.

1. Autism Spectrum Disorders

Autism and autism spectrum disorders (ASDs) are heterogeneous neurodevelopmental disorders [1]. They are enigmatic conditions that have their origins in the interaction of genes and environmental factors. ASDs are characterized by dysfunctions in social interaction and communication skills, in addition to repetitive and stereotypic verbal and nonverbal behaviours [2, 3]. Several biochemical events are associated with ASDs: oxidative stress; endoplasmic reticulum stress; decreased methylation capacity; limited production of glutathione; mitochondrial dysfunction; intestinal dysbiosis; increased toxic metal burden; immune dysregulation; immune activation of neuroglial cells [4]. The exact aetiology of ASDs is unknown, likely it results from a complex combination of genetic, environmental, and immunological factors [5, 6]. This heritable disorder derives from genetic variations in multiple genes [7], making its treatment particularly difficult. Environment (i.e., air pollution, organophosphates, and heavy metals) also contributes to the incidence of ASDs [8].

Frequency of these disorders is increasing: 56% reported increase in paediatric prevalence between 1991 and 1997 [9] until present rates of about 60 cases per 10,000 children, according to Center for Disease Control [10, 11]. ASDs are increasingly being recognized as a public health problem [12]. Pathophysiology and defined mechanisms of pathogenesis of autism remain still unclear. There are no

drugs effective for treatment of core symptoms of ASDs [10]. Indeed, ASDs are still untreatable. Current available treatments for autism can be divided into behavioural, nutritional, and pharmacological options, in addition to individual and family psychotherapy and other nonpharmacologic interventions [13]. However, no defined standard approach exists [14]. Pharmacological approaches are direct towards neuropsychiatric disorders coassociated with ASDs. Psycho-stimulants, alpha-2 agonists, beta blockers, lithium, anticonvulsant mood stabilizers, atypical antipsychotics, traditional antipsychotics, selective serotonin reuptake inhibitors, antidepressants, and antipsychotics, are drugs commonly prescribed [14–16]. Catatonia is treated with lorazepam and bilateral electroconvulsive therapy [17]. Selective serotonin reuptake inhibitors are prescribed for the treatment of depression, anxiety, and obsessive-compulsive ASD-associated behaviours [2].

Other nonpsychotropic drugs which are supported by at least 1 or 2 prospective randomized controlled trials or 1 systematic review include melatonin, acetylcholinesterase inhibitors, naltrexone, carnitine, tetrahydrobiopterin, vitamin C, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory treatments, oxytocin, and even music therapy and vision therapy [18].

Alternative and complementary treatments, not sufficiently supported by medical literature, include herbal remedies, vitamin and mineral therapies, piracetam, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, special dietary supplements, acupuncture, neurofeedback, and sensory integration training [14, 19, 20]. On the other hand, behavioural treatment could represent the effective intervention strategy for autism [21–23]. A plethora of behavioural strategies and social skill trainings have been used [24–26]. However, it has been demonstrated that no definitive behavioural intervention completely improves all symptoms for all ASD patients [27, 28].

Summarizing, all these therapies indicate that further research is needed to better address treatment of several medical conditions experienced by ASD patients [29].

2. Mesenchymal Stem Cells

Nowadays, stem cell therapy represents the great promise for the future of molecular medicine. The progression of several diseases can be slowed or even blocked by stem cell transplantation [30].

Among the stem cell population, mesenchymal stem cells (MSCs) show probably best potential good results in medical research [31–33]. These cells are nonhematopoietic stem cells having a multilineage potential, as they have the capacity of differentiating into both mesenchymal and nonmesenchymal lineages. MSCs are a population of progenitor cells of mesodermal origin found principally in the bone marrow of adults, giving rise to skeletal muscle cells, blood, fat, vascular, and urogenital systems, and to connective tissues throughout the body [34–36]. According to the International Society of Cellular Therapy, MSCs are defined by the following minimal set of criteria: (1) grown in adherence to plastic surface of dishes when maintained in standard culture conditions; (2) express cytospecific cell surface markers, that is, CD105, CD90, and CD73, to be negative for other cell surface markers, that is, CD45, CD34, CD14, and CD11b; (3) possess the capacity to differentiate into mesenchymal lineages, under appropriate *in vitro* conditions [37]. MSCs can be isolated from different tissues other than bone marrow: adipose tissue, liver, tendons, synovial membrane, amniotic fluid, placenta, umbilical cord, and teeth. MSCs show a high expansion potential, genetic stability, stable phenotype, high proliferation rate as adherent cells, and self-renew capacity and can be easily collected and shipped from the laboratory to the bedside and are compatible with different delivery methods and formulations [38, 39]. In addition, MSCs have two other extraordinary properties: they are able to migrate to sites of tissue injury, where they are able to inhibit the release of proinflammatory cytokines and have strong immunosuppressive activity that renders them a useful tool for successful autologous, as well as heterologous, transplantations without requiring pharmacological immunosuppression [40–43]. Besides, MSCs are easily isolated from a small aspirate of bone marrow and expanded with high efficiency [44]. Given that MSCs are multipotent cells with a number of potential therapeutic applications, and they represent a future powerful tool in regenerative medicine, including ASDs. Mesenchymal stem cells could be transplanted directly without genetic modification or pretreatments. They simply eventually differentiate according to cues from the surrounding tissues and do not give uncontrollable growth or tumours. In clinical application, there is no problem with immune rejection because of their *in vivo* immunosuppressive properties [45, 46]. In addition, MSCs can readily be isolated from the patients requiring transplant or from their parents. There is also no tumour formation on transplantation [47]. No moral objection or ethical controversies are involved [48].

In principle, mesenchymal stem cells can act through several possible mechanisms, that is, stimulating the plastic response in the host damaged tissue, secreting survival-promoting growth factors, restoring synaptic transmitter release by providing local reinnervations, integrating into existing neural and synaptic network, and reestablishing functional afferent and efferent connections [49]. Since MSCs have the capability to produce a large array of trophic and growth factors both *in vivo* and *in vitro.* (MSCs constitutively secrete interleukins (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 [50]). A more reasonable explanation for the functional benefit derived from MSC transplantation is their paracrine activity, by which these cells are able to produce factors that activate endogenous restorative mechanisms within injured tissues contributing to recovery of function lost as a result of lesions [49, 51].

3. Autism, Personalized Therapy through Mesenchymal Stem Cells

MSCs have a strong long-lasting immunosuppressive capacity [52]. This extraordinary property is mediated via soluble

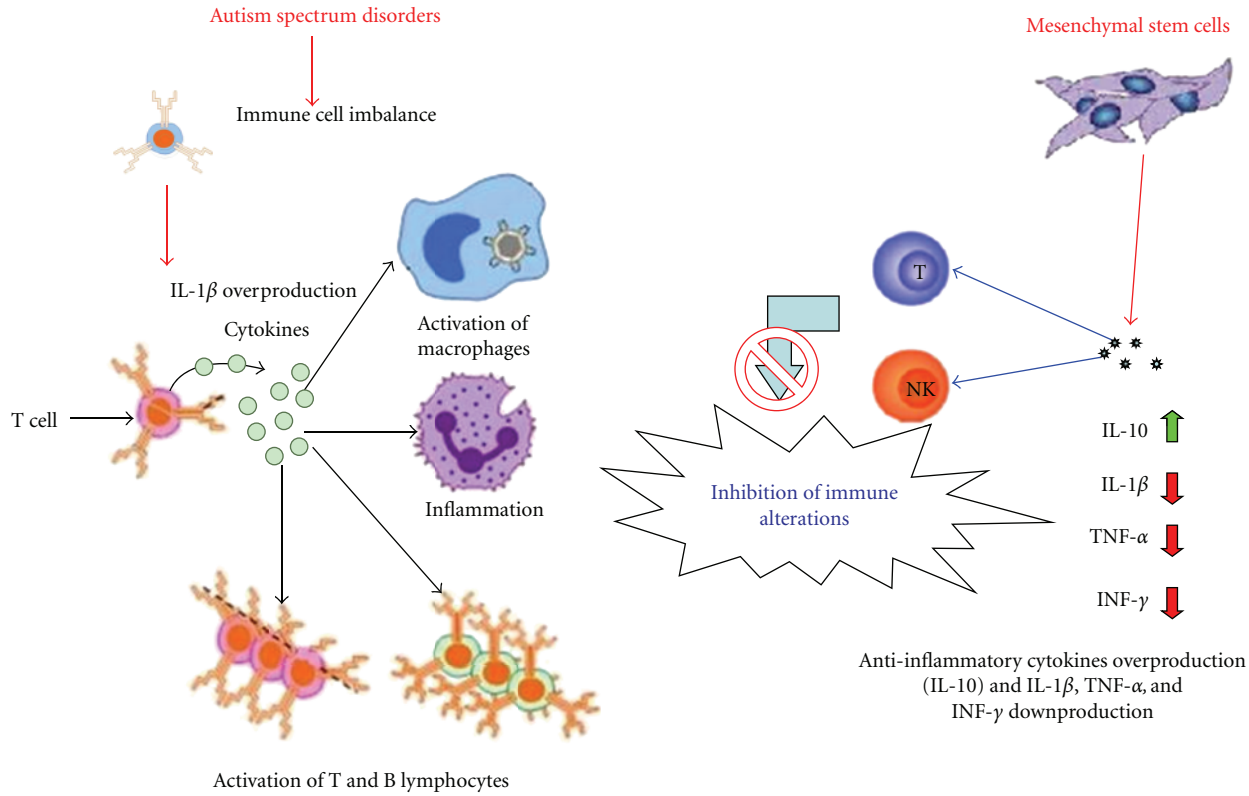

Figure 1: Paracrine and immunomodulatory effects as possible mechanisms of action of mesenchymal stem cells (MSCs) in autism spectrum disorder (ASD) treatment. In humans, ASDs are associated with immune alterations and pro-inflammatory cytokines (i.e., IL-1β) overproduction. These cytokines are able to trigger pro-inflammatory cellular events. Data from *in vitro* models show that MSCs are able to affect not only T cells, but also other cells of the immune system (i.e., NK cells). Immunoregulatory properties of MSCs are through secretion of large amounts of several bioactive molecules (paracrine activity), that is, PGE-2, IL-10. These molecules cause the inhibition or the unresponsiveness of T-cell mediated responses.

factors. MSCs are able to inhibit the proliferation of $CD8^+$ and $CD4^+$ T lymphocytes and natural killer (NK) cells, to suppress the immunoglobulin production by plasma cells, to inhibit the maturation of dendritic cells (DCs) and the proliferation of regulatory T cells [53]. It has been demonstrated that MSCs are also able to inhibit T lymphocyte pro-inflammatory cytokine production *in vitro* [54, 55], as well as *in vivo* [56]. Their ability to modulate the immune system opens a wide range of cell-mediated applications, not only for autoimmune diseases and graft-versus-host disease. Due to the particular immune system dysregulation observed in ASDs [57, 58], mesenchymal stem cell transplantation could offer a unique tool to provide better resolution for this disease. Indeed, in ASDs pathogenesis, innate and adaptive immunity changes have been reported [59]. ASD patients show an imbalance in $CD3^+$, $CD4^+$, and $CD8^+$ T cells, as well as in NK cells. In addition, peripheral blood mononuclear cells (PBMCs) extracted from ASD patients are able to overproduce IL-1β resulting in long-term immune alterations [60]. MSC-mediated immune suppressive activity could restore this immune imbalance (Figure 1). Indeed, MSC immunoregulatory effects strongly inhibit T-cell recognition and expansion by inhibiting TNF-α and INF-γ production and increasing IL-10 levels [51].

It has been demonstrated that in postmortem brains from ASD patients there is evidence of abnormal functioning and cerebellum alterations [61–63]. Indeed, ASD subjects show a decreased number of Purkinje cells in the cerebellum [64]. These changes could reflect defective cortical organization in ASDs development. In addition, autism is associated with dysregulation in the maturation and plasticity of dendritic spine morphology [65]. Restoring injured brain functioning could be achieved by stem-cell-based cell replacement [66]. Indeed, transplanted MSCs are able to promote synaptic plasticity and functional recovery and rescue cerebellar Purkinje cells [67, 68]. Challenging newest study from Deng et al. suggests that granulocyte colony-stimulating factor (G-CSF) is able to mobilize MSCs into peripheral blood. These mobilized MSCs are incorporated and integrate into damaged brain in craniocerebral injured mice, ameliorating the effect of trauma [69]. It is noteworthy that MSC ability to migrate to the sites of injury and participate in the repair process is a key issue in tissue repair [70]. Also by this way, MSC therapy could restore the altered brain organization seen in autistic subjects (Table 1).

A key dilemma in stem-cell-based therapy for autism treatment is whether endogenous or exogenous MSC administration is the best way of stem cell delivery. Endogenous

Table 1: Potential ameliorative effects mediated by MSCs in ASD treatment.

ASD-induced changes in human brain	Potential MSC ameliorative roles seen in preclinical models
Abnormal functioning	Improving functional recovery
Cerebellum alterations	Integrating in altered brain and restoring damaged functions
Decreased number of Purkinje cells (PCs)	Restoring cerebellar PCs
Defective cortical organization	Reinforcing cortical plasticity
Altered plasticity of dendritic spine morphology	Promoting synaptic plasticity

strategy could be limited by the availability of MSCs. Exogenous MSCs could show low rate of engraftment to provide cellular replacement. It is unclear if differentiated cells are able to develop functional interconnections with the intrinsic cells of the recipient host [49]. Controversy, few exogenous MSCs are able to exert paracrine activity. Indeed, exogenously applied MSCs have been shown to home to injured tissues and repair them by producing chemokines, or by cell or nuclear fusion with host cells [71]. On the other hand, exogenous culture-expanded MSCs could address endogenous MSCs in order to activate them and guide intrinsic repair [72]. In addition, exogenous delivery bypasses surgical intervention on the autistic child.

Cellular therapy could represent a new frontier in the treatment of several diseases. Despite the fact that MSCs have been enrolled in several clinical trials, long-term safety of MSC-based therapies is not yet well established; this fact could be one major limitation to clinical translation [73]. At the present, there are no preclinical studies on the use of MSCs in ASD models. There is just one clinical trial (NCT01343511 http://www.clinicaltrial.gov/) concerning the safety and efficacy of human umbilical cord mesenchymal stem cells (hUC-MSCs) and human cord blood mononuclear cells (hCB-MNCs) transplantation in patients with autism by Shenzhen Beike Bio-Technology Co., China. Results are not yet posted.

However, personalized stem cell therapy will be the most effective treatment for a specific autistic child, opening a new era in autism management in the next future.

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