Therapeutic properties of mesenchymal stem cells for autism spectrum disorders

Benjamin Gesundheit a,⇑, Paul Ashwood b, c, Armand Keating d, David Naor e, Michal Melamed e, Joshua P. Rosenzweig a

Article history:
Received 6 November 2014
Accepted 22 December 2014

Abstract

Recent studies of autism spectrum disorders (ASD) highlight hyperactivity of the immune system, irregular neuronal growth and increased size and number of microglia. Though the small sample size in many of these studies limits extrapolation to all individuals with ASD, there is mounting evidence of both immune and nervous system related pathogenesis in at least a subset of patients with ASD. Given the disturbing rise in incidence rates for ASD, and the fact that no pharmacological therapy for ASD has been approved by the Food and Drug Administration (FDA), there is an urgent need for new therapeutic options. Research in the therapeutic effects of mesenchymal stem cells (MSC) for other immunological and neurological conditions has shown promising results in preclinical and even clinical studies. MSC have demonstrated the ability to suppress the immune system and to promote neurogenesis with a promising safety profile. The working hypothesis of this paper is that the potentially synergistic ability of MSC to modulate a hyperactive immune system and its ability to promote neurogenesis make it an attractive potential therapeutic option specifically for ASD. Theoretical mechanisms of action will be suggested, but further research is necessary to support these hypothetical pathways. The choice of tissue source, type of cell, and most appropriate ages for therapeutic intervention remain open questions for further consideration. Concern over poor regulatory control of stem cell studies or treatment, and the unique ethical challenges that each child with ASD presents, demands that future research be conducted with particular caution before widespread use of the proposed therapeutic intervention is implemented.

Introduction/background

ASD are a group of heterogeneous neurodevelopmental disorders presenting in early childhood with a prevalence of 0.7–2.6% [1]. The diagnosis is based on a clinical triad of repetitive behavior, impaired social interactions and communication skills. ASD persists for life with major implications for the individual, the family and the entire health care system [2]. While the etiology remains unknown, various indications suggest an association with immune dysfunction [3]. There are currently no FDA approved therapies for ASD but only for symptoms such as aggression/tantrums associated with ASD. There is therefore an urgent need to explore the pathogenesis of ASD in order to inform and develop effective therapeutic opportunities.

Recent preclinical and clinical research on the therapeutic role of mesenchymal stem cells (MSC) also known as multi-potent stromal/stem cells for neurological and autoimmune diseases, has shown promising results. The known immune-modulating properties of MSC support our hypothesis that there may be a potential effect on at least a subset of children with ASD that display immune dysfunction. Furthermore, the ability of MSCs to promote neurogenesis in neuro-degenerative conditions [4] supports the hypothesis of a potential therapeutic effect in neuro-developmental impairments such as ASD. MSC have been studied in many...
clinical settings [5], leading to their first regulatory approval for treatment of graft versus host disease in the pediatric population.

In this article, we will describe the immune modulatory properties of MSC, the effects of MSC on the nervous system, the immune characteristics of ASD, and the neurological attributes of ASD in an effort to present a rationale for their use in ASD. Ongoing clinical success with MSC in related conditions, including safety profiles, will help inform the strategy for such use in ASD, and identify further areas for research in the field.

Only some of the neuropathological and immunological findings in ASD that are at present deemed germane to mechanism of action of potential MSC therapy are presented.

Evidence supporting the hypothesis of neurological and immunological components of ASD

The nervous system and ASD

Post-mortem studies and magnetic resonance imaging (MRI) indicate an atypical pattern of early overgrowth in total brain volume during the toddler years in some infants with ASD [6], followed by a slowing down of growth during childhood and adulthood [7,8]. Explanations for this early growth pattern, and attempts at localizing specifically affected areas of the brain have proven controversial. Increase in the number of neurons [9], increase in neuronal dendritic volume and synapses [10], and increase in the number and size of microglial cells [11] are three posited explanations for the unusual growth pattern in ASD. In addition, important findings of increased numbers and size of microglia and excessive microglial activation has been shown in wide age range of individuals with ASD [12–14]. Genetic findings linking ASD to a number of pathways associated with neuronal synaptic function including the SHANK3 gene and mutations of other synaptic cell adhesion molecules, suggest that ASD may result, at least partially, from disruption of synapse formation or elimination [15,16].

The immune system and ASD

In 1971 Money et al. first reported an association between family history of immune system dysfunction and ASD [17]. Since that time, research on whether there is or is not immune dysfunction in ASD, has been divided into three major categories:

- Epidemiological studies demonstrating an association between family history of autoimmune diseases (Table 1) and ASD [18].
- Immune biological markers or signatures in the blood of children with ASD [19] and in postmortem brain specimens [20].
- Immunogenetics, aiming to identify Human Leukocyte Antigen (HLA) associations or other gene products associated with ASD [21–24].

Table 1

<table>
<thead>
<tr>
<th>Immunological diseases in the family history of children with ASD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease [18,172–175]</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Diabetes (Type 1)</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
</tr>
<tr>
<td>Psoriasis [176]</td>
</tr>
<tr>
<td>Hypothyroidism/Hashimoto’s thyroiditis’ [177,178]</td>
</tr>
<tr>
<td>Idiopathic Thromocytopenic Purpura (ITP)</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Suggest neurological and immunological properties and mechanisms of MSC</th>
</tr>
</thead>
</table>

Work on immune profiles in ASD [25] has demonstrated that a state of immune dysfunction exists in at least a subset of children with ASD, as reflected by deviations in levels of cytokines [26] or other immune factors [27,28]. With many of these studies showing that as immune activation increases there is a correlation to more impaired behavior [29,30]. Similarly, a few studies have focused on the role of autoantibodies in autism and their relationship with behavior [31–33]. In particular, several studies point to increased autoimmunity in children with ASD. Recently we reviewed the various autoimmune components of ASD [3] in light of the Rose–Bona criteria for autoimmune diseases (Table 2, Fig. 1).

While the focus of this proposal is to highlight immune features in children with ASD that can potentially serve as targets for MSC therapy, a brief discussion of the immune status of mothers of children with ASD is in order, due to the interesting findings supporting the overall theory of an immune etiology in a subset of children with ASD. One study demonstrated a correlation between maternal antibody status and behavior of children with ASD [34]. Maternal antibodies from the human mother of a child with ASD were injected into a pregnant mouse and the offspring of the mouse demonstrated behavioral changes, despite the fact that the pregnant mouse did not exhibit any abnormalities [35–37]. Similar studies were performed on rhesus monkeys with similar results [38,39]. Additionally, recent research of maternal immune activation models suggests lasting changes in macrophage function [40]. Though these results strongly suggest that the immune aberrations detected during pregnancy and in infants with ASD are connected to behavioral changes that occur in individuals with ASD, caution must be exercised regarding over-interpretation of such connections until such studies are repeated and expanded. Nevertheless, the methodology presents an exciting opportunity to assess the inter-relationship between ASD and the immune system.

Now that the immune aspects of at least a subset of children with ASD have been identified, the literature on MSC therapy with a particular focus on the effect of MSCs on the immune system will be reviewed in order to support the hypothesis that MSC therapy is particularly suited for ASD.

Suggested neurological and immunological properties and mechanisms of MSC

Recent research suggests several possible properties of MSC, that have therapeutic potential for what some previously regarded as untreatable conditions [41]. These include: the ability to differentiate in vitro into a variety of cell types including bone, cartilage, muscle, and nerve; their “immune privileged” status (or ability to avoid immunological allorecognition), and their ability to cause immunosuppression. MSC also secrete a multitude of growth factors which impact endogenous regeneration and tissue repair. In choosing stem cells for any clinical indication, several basic questions must be addressed.

Type of stem cell

Embryonic stem cells (ESC) contain the complete set of genes of the body. They are capable of dividing indefinitely and developing into any cell type of the body (pluripotency), but due to potentially uncontrolled proliferation there is controversy and legal limitations upon their research and clinical use.

Adult stem cells (or tissue-specific cells) are capable of renewal and trans-differentiation and replenish cells of the body as needed. Their ability to develop into other cell types is genetically regulated to shut off as the specialization process goes on. They are more limited in their ability to differentiate into different organ-specific lineage than
the more versatile ESC. The bone marrow contains two major types of stem cells, hematopoietic stem cells (HSC) and MSC. HSC have been used successfully over decades for autologous and allogeneic HSC-transplantations. The MSC are defined by their biological capacity to differentiate in vitro into various organ-specific cells such as adipocytes, osteocytes, connective tissues and chondrocytes. MSC can be harvested from umbilical cord tissue and blood, dental pulp, amniotic fluid, adipose tissue, and other sources. MSC have been proven to possess immune-modulatory properties (see “Effect of MSC on the immune system” below).

Neural stem cells (NSC) are self-renewing, multipotent cells that differentiate into neurons, astrocytes, and oligodendrocytes. NSC are found throughout the fetal central nervous system (CNS) and in the adult forebrain. Upon transplantation, NSC have been found to be neuro-protective [42] through either cell replacement, immunomodulatory effects [43], or endogenous repair. The complex role of Toll-like receptors and microglia [43] in neurogenesis and on NSC [44] is potentially of interest in ASD.

The choice between MSC and NSC for ASD demands further research and might depend on the underlying pathology of ASD, among other considerations. Due to more extensive experience with MSC, we will limit our discussion to MSC.

Tissue source

Four main tissue sources are typically harvested for stem cells. These include bone marrow (BM-MSC), adipose (AT-MSC), placental (hp-MSC), umbilical cord (UC-MSC). In assessing the differences between the various tissue sources, studies have compared the following categories: immunogenicity, immunomodulatory effect, availability, proliferative potential, migratory potential, expression of activation markers, indoleamine 2,3-dioxygenase (IDO) activation, and ability to differentiate into various cell types in vitro. Further head to head research comparing these tissue sources specifically in the context of immunogenicity and immune modulation would elucidate which might be more appropriate for potential ASD treatment.

Effect of MSC on the nervous system

Potential mechanisms of action of MSC on the nervous system

The mechanisms of action of MSC on the nervous system remain largely unknown, but are an intense area of research. Some of the suggested mechanisms of action include: (A) neuroprotection [45,46], (B) neurogenesis [47], and (C) synaptogenesis [48].

(A) The potential utility of MSC for the protection of neural tissue from degeneration and apoptosis [49] via autocrine and paracrine mechanisms has been demonstrated by the release of neurotrophins [50,51], inhibition of neuron apoptosis [52], inhibition of microglia activation [53], induction of microglia phenotype switch [54], inhibition of astrocyte proliferation [55], and inhibition of oxidative stress molecules [56].
(B) To date there is some evidence that MSC induce endogenous neurogenesis [57,58], and there is mounting evidence that MSC differentiate into functional neurons in vitro [59–61].

(C) One proposal for the mechanism by which MSC improve neurological function is that MSC supply bioactive agents that stimulate the action of intrinsic neural progenitor cells to regenerate functional neurological pathways including via synaptogenesis [62]. Some researchers have suggested that MSC transplantation increases synaptic plasticity of existing and newly formed neurons [63]. One mechanism for sustaining synaptic plasticity might be via stimulation of tissue plasminogen activator (tPA) production and increasing synaptophysin expression [64]. Reduction of synaptic detachment mediated via brain-derived neurotrophic factor (BDNF) release or astroglia has also been proposed as an effect of MSC [48]. Exogenous BDNF has been found to repair synaptic circuitry [65]. Glial cells have been suggested to be involved in controlling synapse number [66]. Two groups found increased expression of the synaptogenesis marker synaptophysin after administration of MSC [67,68]. Others have suggested that MSC upregulate neurotransmitter receptors contributing to synapse formation through cell fusion-like processes [69]. Further research is necessary to understand the precise mechanisms for the effect of MSC on synaptogenesis.

In light of the above mentioned known effects of MSCs on the nervous system, a variety of studies have begun investigating the utility of MSCs in neurological diseases.

**Experience with MSC in neurological diseases**

In recent years MSC have been studied in a variety of preclinical models and applied clinically. We will focus on the current experience in neurological diseases relevant for to our hypothesis of treating ASD with MSC.

MSC are a unique subset of stem cells endowed with multiple capabilities relevant to neurological diseases (Table 4) [41,70,71]. These capabilities include ability of MSC to induce neurogenesis [58,72,73], neuroprotection [47,56,74–76], neural regeneration [4,77], remyelination [78–80], and angiogenesis [81,82]. Preclinical and clinical studies with MSC significantly improved the clinical course of neurological diseases [83]. These include induction of neuronal plasticity and remodeling of the brain in multiple sclerosis (MS) [84–86] and tissue regeneration e.g. in spinal cord injury [84,87]. Similar improvement by MSC treatment was detected in animal models of stroke [88], Amyotrophic lateral sclerosis (ALS) [89], Huntington’s disease [90] and Parkinson’s disease [91,92]. Furthermore, preclinical data suggest potential benefits of MSC for neuropsychiatric disorders [93].

**Effect of MSC on the immune system**

**Potential mechanisms of action of MSC on the immune system**

MSC have the ability to communicate with damaged tissues, where they can trigger immunosuppression or immune enhancement depending on the milieu, and engraft at sites of inflammation or injury [94]. MSC possess unique immunological properties including expression of major histocompatibility complex (MHC) class I molecules but not MHC class II molecules [95–98]. Therefore, they normally do not act as antigen presenting cells [99,100], a feature that becomes important in their clinical use and they demonstrate a so-called ‘stealth’ ability to go undetected by a host immune system [101]. MSC have demonstrated complex immunomodulatory effects [102–104,100,105,106] on both humoral and cell mediated immune responses [107–111]. In the cell-mediated immune response [109–111] MSC inhibit T cell proliferation, decrease pro-inflammatory cytokine production like tumor necrosis factor-alpha (TNF-α), interferon gamma (IFN-γ) and decrease cell-mediated cytotoxicity [110,112–121]. MSC have also been found to inhibit natural killer (NK) cell proliferation, NK cell cytokine production and NK cell-mediated cytotoxicity through various mechanisms [122–124] still under investigation as discussed below (section “Experience with MSC in immunological and autoimmune diseases”). In the humoral response, MSC inhibit B cell proliferation, maturation, migration, and immunoglobulin and antibody production [125,126]. Beyond the effect of MSC on T cells and B cells, MSC also exert an inhibitory effect on dendritic cell maturation, activation, and antigen presentation [127–129]. Furthermore, MSC have been found to block recruitment of neutrophils, likely protect neutrophils from apoptosis, and block production of TNF-α from activated macrophages [130,131]. It is not clear that the protective effect against neutrophil apoptosis is beneficial, as neutrophils are supposed to die off quickly. MSC can also suppress the delayed type hypersensitivity response in C57BL/6 (H2b) mice [132].

When MSC enter injured tissues, inflammatory triggers such as cytokines stimulate the release of many growth factors by MSC [94] including: epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin growth factor-1 (IGF-1), angiopoietin-1 (Ang-1), keratinocyte growth factor (KGF) and stromal cell-derived factor-1 (SDF-1) [133–136]. In addition, MSCs produce various factors, such as Ang-1, VEGF, HGF, EGF, PDGF, FGF, KGF and TGF-β, which maintain endothelial integrity and regulate endothelial cell proliferation [94].

**Table 3**

Allogeneic versus autologous.

<table>
<thead>
<tr>
<th>Autologous source of MSC</th>
<th>Allogeneic source of MSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s own cells (might be affected by disease)</td>
<td>From healthy &amp; young individuals</td>
</tr>
<tr>
<td>No immune reactions</td>
<td>Potential immune reaction</td>
</tr>
<tr>
<td>Bone marrow aspiration &amp; sedation required</td>
<td>No need for procedure and laboratory work (for commercial MSCs)</td>
</tr>
<tr>
<td>Laboratory work necessary for each patient</td>
<td>Cellular treatment is clinically ready to go</td>
</tr>
<tr>
<td>Procedure dependent treatment</td>
<td>Opportunity for patentability</td>
</tr>
<tr>
<td>Expensive and time consuming</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4**

MSCs and neurological diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Current state of research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis (MS) [180]</td>
<td>Clinical Trials-ongoing</td>
</tr>
<tr>
<td>Spinal cord injury [181]</td>
<td>Clinical Trials-ongoing</td>
</tr>
<tr>
<td>Stroke [182]</td>
<td>Clinical Trials-ongoing</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS) [183]</td>
<td>Clinical Trials-ongoing</td>
</tr>
<tr>
<td>Huntington’s disease (HD) [184]</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Parkinson’s disease (PD) [185]</td>
<td>Clinical Trials-ongoing</td>
</tr>
</tbody>
</table>
Most importantly, various studies demonstrated a specific effect of MSC on microglia [54], which play a crucial role in ASD (as discussed above in section “The nervous system and ASD”). In experimental ALS, the number of microglia cells was significantly decreased in the spinal cord after administration of MSC [137]. Similar results were reported in a rat focal ischemia model of transient middle cerebral artery occlusion [138] and neonatal hypoxic-ischemic brain injury, where MSC reduced expansion of microglia and favoring the formation of new neurons. [63] In experimental Parkinson’s disease, hMSC treatment significantly decreased lipopolysaccharide (LPS)-induced microglial activation [139]. Controversy exists whether the immunosuppressive effect of MSC is a direct effect or requires activation via cytokines [99,100,117,140]. While further investigation is needed, the majority of the evidence points to an inhibitory role of MSC on immune function.

Various theories try to elucidate the possible mechanisms of action of MSC on the immune system with two possible mechanisms discussed most in the literature to date being:

1. MSC induce the inhibition of T cells via an indoleamine 2,3-dioxygenase (IDO) immunosuppressive pathway [115,141,142].
2. MSC introduce two negative feedback loops in the very early phase of inflammation by secretion of prostaglandin (PGE2) and TNF-stimulated gene 6 protein (TSG-6) [103,110,122,143,144]. PGE2 is known to inhibit T cell proliferation, to affect apoptosis of T cells in either direction depending on the maturity and activation state of the cell [144], and influence the production of cytokines by T cells [144]. PGE2 is also known to induce and suppress B cells depending on the maturity of the B cells. In addition, PGE2 can modulate the function of antigen presenting cells such as dendritic cells [145] and macrophages. In fact, PGE2 released by MSC can reprogram macrophages to produce more IL-10, inhibit dendritic cell maturation, and shift the balance between Th1 and Th2 [94,110,129,146].

TSG-6 is expressed at sites of inflammation and has been shown to reduce inflammatory damage through inhibiting CXCL8-induced transendothelial migration of human neutrophils [147–150].

It would go beyond the scope of this hypothesis paper, to fully discuss the interaction and synergisms of the mechanisms above [122]. However, it is known that in the presence of PGE2, the effects of IDO in MSC-mediated immunoregulation of T-cell proliferation and NK cell activation can also be enhanced [122]. Furthermore, these mechanisms might be species-specific [151,152].

Experience with MSC in immunological and autoimmune diseases

Attempts at capitalizing on the unique immune regulatory properties of MSC (see section “Potential mechanisms of action of MSC on the immune system” above) for the prevention and treatment of autoimmune diseases have produced conflicting results both at the preclinical and clinical levels (Table 5). Some of the conditions that have been targeted for MSC treatment include graft-versus-host-disease (GVHD) [153], MS [154], rheumatoid arthritis [155,156] and type I diabetes [157]. In GVHD, at the clinical level, Le Blanc et al. found that more than half of the patients with steroid-refractory acute GVHD responded to treatment with MSC and their survival rate was better than in patients not treated with MSC [153]. Recently, MSC treatment for GVHD became the first pediatric indication to be approved by Health Canada [158].

For MS, at the preclinical level, in the experimental autoimmune encephalomyelitis (EAE) model, disease onset improved after administration of MSC [120]. In clinical phase I trials, MSC administered intravenously or intrathecally are well tolerated, with some preliminary evidence of efficacy [84,159].

In type I diabetes, at the preclinical level, the administration of bone marrow cells (BMC) and MSC to a model of murine Streptozotocin (STZ)-induced diabetes resulted in blood glucose and serum insulin levels returning to normal levels [160]. Research at the clinical level is currently ongoing.

In Collagen Induced Arthritis (CIA – a mouse analogue of RA), cell therapy using allogeneic bone marrow derived MSC prevents tissue damage [161]. Similarly, administration of human adipose-derived MSC prior to CIA disease onset markedly decreased the incidence of arthritis, ameliorated clinical signs, hindered damage to the joints, and administration of AT-MSC after disease had entered an irreversible clinical course, displayed a true therapeutic effect for CIA [162].

Hypothesis-the neuroimmune properties of MSC are well suited to address neuroimmune dysregulation in ASD

In assessing the therapeutic value of MSC therapy in ASD, the various suggested mechanisms of action for the effect of MSC must be discussed along with any potential synergistic effect among them. Though the immunological and neurological investigations of ASD might represent separate phenomena, integrating them suggests that both immune dysfunction and unusual patterns of neurological growth at a very young age might be the underlying pathology in at least a subset of children with ASD. Genetic research linking ASD to synapse-associated genes such as SHANK3, combined with an understanding of the interplay of microglia with synapses [163], and an appreciation of the pathological microglial findings in ASD, suggest that this is a fertile area for further research that might have clinical applications.

Based on the known beneficial effects of MSC for various neurological and immunological conditions and their encouraging safety profile, MSC offer a logical and promising treatment option for ASD. The ability of MSC to suppress the immune response and potential for neuroprotection, neurogenesis, and synaptogenesis suggest a potential synergistic effect that matches the suggested underlying pathology of a subset of ASD individuals. Clinical studies must still determine the preferred age, source, dosages and administration for the treatment of children with ASD using MSC and ethical concerns must be addressed.

Clinical strategies

Many critical open questions regarding the most effective protocol for treating ASD with MSC exist, including whether the cells should be autologous or allogeneic (Table 3), the preferred route of administration (IV, IM, Intraventricular), the ideal age, disease status, and the proper dosage. The discussion of these questions is beyond the scope of this paper and need to be addressed in future research. Studies with MSC derived from cord blood are currently ongoing [164]. Initial results demonstrate statistically significant improvement in Childhood Autism Rating Scale (CARS), Aberrant
Behavior Checklist (ABC) scores and Clinical Global Impression (CGI) evaluation in groups treated with human cord blood mononuclear cells (CBMCs) and umbilical cord-derived mesenchymal stem cells (UCMSCs) compared to the control at 24 weeks post-treatment ($p < 0.05$). No safety issues were noted during or the monitoring period. Some of the limitations of this study include small sample size ($n = 37$), the fact that it was non-blinded, non-randomized, and that Autism Diagnostic Observation Schedule (ADOS), the current gold standard for ASD diagnosis was not used.

Safety profile

A recent systematic review and meta-analysis of clinical trials using MSC that included over a thousand participants concluded that MSC are safe [165]. A review of twenty-four reported clinical trials with MSC for various indications, found no reports of either acute, long-term or major adverse events including carcinogenesis, as a result of administering allogeneic MSC [166]. Furthermore, Prockop et al. analyzed over 100 registered clinical trials 2010 and found no reported significant adverse events. [5] Finally, while the clinical use of MSC was reported to be safe even for the pediatric population [158,167], caution should still prevail as no long-term data are currently available.

Ethical considerations and potential evidence against the hypothesis

Beyond the scientific extrapolations necessary for applying research from neurodegenerative diseases to a neurodevelopmental one such as ASD, there are ethical considerations to take into account: One might argue that in life-threatening conditions like ALS, MS, GVHD etc. the risk/benefit ratio justifies administration of MSC with informed consent of the patients, while ASD is not a life-threatening condition; however, it is a serious and lifelong chronic condition with no currently available effective therapies [168] and delaying clinical trials for ASD until >18 years old is not a solution since it is possible that the optimal therapeutic effect is at a young age (<5 years) due to increased neuronal plasticity in the young brain compared to older children. Since there are major difficulties in determining an optimal animal model for ASD, [169] the rationale for MSC treatment for ASD has to rely on the research of other clinical conditions, which provide empirical support to justify the administration of MSC for ASD.

Parents of children with ASD desperately search for treatments [170] but innovative therapies without properly controlled studies might not be in the best interest of these children [171]. Presenting the therapeutic rationale with the scientific community for this promising treatment option encourages international scientific and clinical collaboration for properly controlled studies for MSC in ASD. Hopefully, the results of this future research will deepen understanding of the underlying pathology of ASD and open up the potential for new treatment options.

Conclusion

A careful investigation of the ASD literature exhibits mounting evidence that at least a subset of children with ASD have either abnormalities in their immune profile, and/or abnormal neuronal and synaptic growth. In analyzing MSC literature, early preclinical and clinical experience demonstrates that MSC suppress the immune system through a variety of potential mechanisms and increase neuronal growth. Further regulated research is required to assess the hypothesis that these qualities of MSC make it a potential therapeutic option for at least a subset of children with ASD. The potential implications of successful clinical trials with MSC for ASD are particularly rewarding considering the current lack of treatment options and the rapid rise in the prevalence of ASD.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Contributor’s Statement

Benjamin Gesundheit: Dr. Gesundheit conceptualized and designed the hypothesis, revised the manuscript critically analyzed and interpreted the data, drafted the initial manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Paul Ashwood: Dr. Paul Ashwood contributed to the analysis and interpretation of data, revised the manuscript critically for important intellectual content, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Armand Keating: Dr. Keating contributed to the analysis and interpretation of data, revised the manuscript critically for important intellectual content, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Michal Melamed: Dr. Melamed contributed to the analysis and interpretation of data, revised the manuscript critically for important intellectual content, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Joshua P. Rosenzweig: Dr. Rosenzweig conceptualized and designed the hypothesis, analyzed and interpreted the data, drafted the initial manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

References


[37] Gugger ML, Rohey A, Tschopp D, Phinney DG. Human mesenchymal stem cell subpopulations express a variety of neuro-regulatory molecules and promote neuronal cell survival and neurogenesis. Exp Neurol 2006;198:54–64.


[61] Johnson TV, Bull ND, Hunt DP, Martina N, Tomarev SI, Martin KR. Neuroprotective effects of intraventricular mesenchymal stem cell


Sotropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. Stem Cells 2006;24:74–85.


Spaggiari GM, Abdulzadik H, Becchetti F, Moretta L. MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs, at an early stage of the CD14+CD1c+ DC development. Blood 2009;113:6576–83.


Prockop DJ. Two Negative Feedback Loops Place Mesenchymal/Stromal Cells (MSCs) at the Center of Early Regulators of Inflammation. Stem Cells 2013.


