Medical Hypotheses 84 (2015) 169–177

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

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]

[a] Jerusalem, Israel
[b] Department of Medical Microbiology and Immunology, University of California Davis, USA
[c] Department of Medical Microbiology and Immunology, and the MIND Institute, University of California Davis, USA
[d] Division of Hematology, University of Toronto, Cell Therapy Program, Princess Margaret Hospital, Toronto, Canada
[e] Lautenberg Center for General and Tumor Immunology, Hebrew University, Hadassah Medical School, Jerusalem, Israel

ARTICLE INFO

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

Abbreviations: ASD, autism spectrum disorders; GVHD, graft versus host disease; HSCs, hematopoietic stem cells; MSC, multipotent stromal cells or mesenchymal stem cells; NSCs, neural stem cells.

* Corresponding author at: Migdal Eder 4, Alon Shvut, Israel. Tel.: +972 2 506 558638.

E-mail addresses: bgesund@gmail.com (B. Gesundheit), pashwood@ucdavis.edu (P. Ashwood), armand.keating@uhn.on.ca (A. Keating), davidn@ekmd.huji.ac.il (D. Naor), michalgm@gmail.com (M. Melamed), joshpros@gmail.com (J.P. Rosenzweig).

http://dx.doi.org/10.1016/j.mehy.2014.12.016
0306-9877/

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
Immunological diseases in the family history of children with ASD.

Disease [18,172–175]
• Rheumatoid arthritis
• Celiac disease
• Diabetes (Type 1)
• Ulcerative Colitis
• Psoriasis [176]
• Hypothyroidism/Hashimoto's thyroiditis: [177,178]
• Rheumatic fever
• Idiopathic Thrombocytopenic Purpura (ITP)
• Myasthenia Gravis

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

Table 2
Rose–Bona criteria for auto-immune diseases [179].

A. Direct proof	B. Indirect evidence	C. Circumstantial evidence
1. Human–Human Transfer • Disease is reproduced in normal recipient by direct transfer of autoantibody *e.g.* Idiopathic Thrombocytopenic Purpura (ITP) • Transplacental transmission of pathogenic IgG autoantibody from an afflicted mother to the fetus *e.g.* neonatal myasthenia, Graves, polychondritis • Autoantibody not recognized as pathogenic in mother produces disease in infant *e.g.* anti-Ro, Anti-TSH *2. Human–Animal Transfer* *e.g.* Pemphigus, AchR, T cell transfers to severe combined immunodeficiency (SCID) mice 3. Demonstrate pathogenicity of an antibody in *in vitro* destruction of cells with corresponding antigen *e.g.* paroxysmal cold hemoglobinuria	• Identify offending antigen • Isolate equivalent antigen in animal • Reproduce essential feature of disease by immunization	• Association with other autoimmune diseases in same individual or in his family history • Lymphocytic infiltration • Statistical association with particular MHC haplotype • Favorable response to immunosuppression

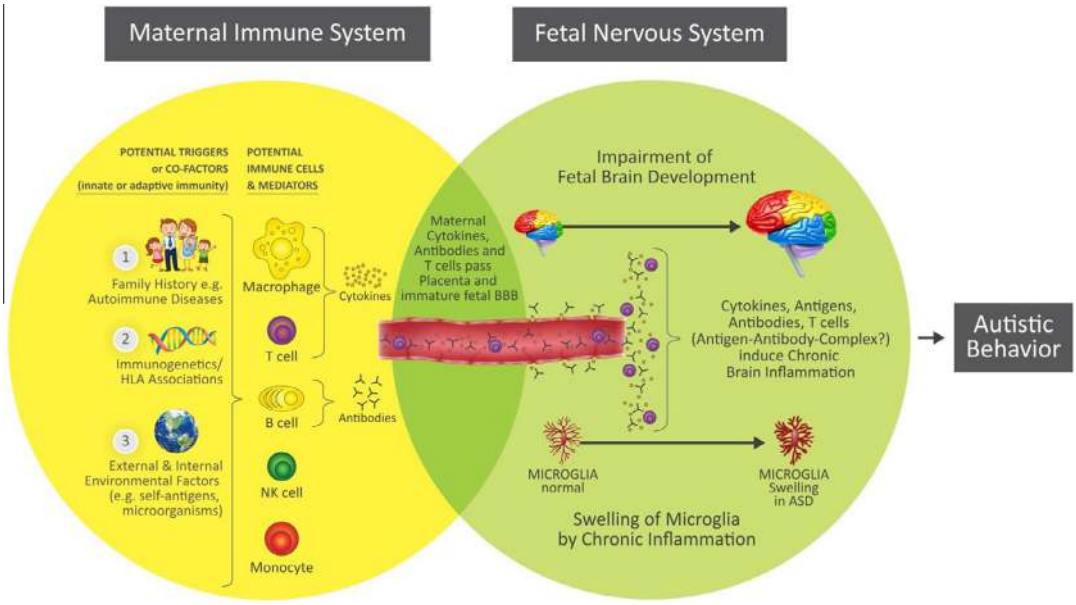

Fig. 1. Immunology in the pathogenesis of autism. *Source:* Journal of Autoimmunity.

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].

Table 3
Allogeneic versus autologous.

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

(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].

Table 4
MSCs and neurological diseases.

Disease	Current state of research
• Multiple sclerosis (MS) [180]	Clinical Trials-ongoing
• Spinal cord injury [181]	Clinical Trials-ongoing
• Stroke [182]	Clinical Trials-ongoing
• Amyotrophic lateral sclerosis (ALS) [183]	Clinical Trials-ongoing
• Huntington's disease (HD) [184]	Preclinical
• Parkinson's disease (PD) [185]	Clinical Trials-ongoing

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].

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 (PGE_2) and TNF-stimulated gene 6 protein (TSG-6) [103,110,122,143,144]. PGE_2 is known to inhibit T cell proliferation, to affect apoptosis of T cells in either direction depending on the maturation and activation state of the cell [144], and influence the production of cytokines by T cells [144]. PGE_2 is also known to induce and suppress B cells depending on the maturity of the B cells. In addition, PGE_2 can modulate the function of antigen presenting cells such as dendritic cells [145] and macrophages. In fact, PGE_2 released by MSC can reprogram macrophages to produce more IL-10, inhibit dendritic cell maturation, and shift the balance between T_H1 and T_H2 [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 PGE_2, 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].

Table 5
MSCs and immunological/autoimmune diseases.

Disease	Current state of research
• Graft versus host disease (GVHD) [84,158]	Approved by Canada Health in pediatric population
• Multiple sclerosis (MS) [180]	Clinical Trials-ongoing
• Rheumatoid arthritis (RA) [162]	Preclinical
• Type I diabetes [157]	Clinical Trials-ongoing

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 (CBMNCs) 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 empiric 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 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.

David Naor: Dr. Naor 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

[1] Kim YS, Leventhal BL, Koh YJ, et al. Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry 2011;168:904–12.
[2] Cidav Z, Marcus SC, Mandell DS. Implications of childhood autism for parental employment and earnings. Pediatrics 2012;129:617–23.
[3] Gesundheit B, Rosenzweig JP, Naor D, et al. Immunological and autoimmune considerations of autism spectrum disorders. J Autoimmun 2013;44:1–7.
[4] Chopp M, Li Y. Treatment of neural injury with marrow stromal cells. Lancet Neurol 2002;1:92–100.
[5] Prockop DJ, Brenner M, Fibbe WE, et al. Defining the risks of mesenchymal stromal cell therapy. Cytotherapy 2010;12:576–8.
[6] Schumann CM, Nordahl CW. Bridging the gap between MRI and postmortem research in autism. Brain Res 2011;1380:175–86.
[7] Courchesne E, Pierce K, Schumann CM, et al. Mapping early brain development in autism. Neuron 2007;56:399–413.
[8] Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. Trends Neurosci 2008;31:137–45.
[9] Courchesne E, Mouton PR, Calhoun ME, et al. Neuron number and size in prefrontal cortex of children with autism. JAMA 2011;306:2001–10.
[10] Hutsler JJ, Zhang H. Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. Brain Res 2010;1309:83–94.
[11] Morgan JT, Chana G, Abramson I, Semendeferi K, Courchesne E, Everall IP. Abnormal microglial-neuronal spatial organization in the dorsolateral prefrontal cortex in autism. Brain Res 2012;1456:72–81.
[12] Suzuki K, Sugihara G, Ouchi Y, et al. Microglial activation in young adults with autism spectrum disorder. JAMA Psychiatry 2013;70:49–58.
[13] Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 2005;57:67–81.

[14] Morgan JT, Chana G, Pardo CA, et al. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. Biol Psychiatry 2010;68:368–76.
[15] Bourgeron T. A synaptic trek to autism. Curr Opin Neurobiol 2009;19:231–4.
[16] Ebert DH, Greenberg ME. Activity-dependent neuronal signalling and autism spectrum disorder. Nature 2013;493:327–37.
[17] Money J, Bobrow NA, Clarke FC. Autism and autoimmune disease: a family study. J Autism Child Schizophr 1971;1:146–60.
[18] Atladóttir HO, Pedersen MG, Thorsen P, et al. Association of family history of autoimmune diseases and autism spectrum disorders. Pediatrics 2009;124(2):687–94.
[19] Stigler K, Sweeten T, Posey D, McDougle C. Autism and immune factors: a comprehensive review. Res Autism Spectr Disord 2009;3:840–60.
[20] Enstrom AM, Van de Water JA, Ashwood P. Autoimmunity in autism. Curr Opin Investig Drugs 2009;10:463–73.
[21] Torres AR, Maciulis A, Stubbs EG, Cutler A, Odell D. The transmission disequilibrium test suggests that HLA-DR4 and DR13 are linked to autism spectrum disorder. Hum Immunol 2002;63:311–6.
[22] Torres AR, Sweeten TL, Cutler A, et al. The association and linkage of the HLA-A2 class I allele with autism. Hum Immunol 2006;67:346–51.
[23] Torres AR, Westover JB, Gibbons C, Johnson RC, Ward DC. Activating killer-cell immunoglobulin-like receptors (KIR) and their cognate HLA ligands are significantly increased in autism. Brain Behav Immun 2012;26:1122–7.
[24] Torres AR, Westover JB, Rosenspire AJ. HLA immune function genes in autism. Autism Res Treat 2012;2012:959073.
[25] Buehler MR. A proposed mechanism for autism: an aberrant neuroimmune response manifested as a psychiatric disorder. Med Hypotheses 2011;76:863–70.
[26] Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, Van de Water J. Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain Behav Immun 2011;25:40–5.
[27] Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah IN, Van de Water J. Altered T cell responses in children with autism. Brain Behav Immun 2011;25:840–9.
[28] Rose S, Melnyk S, Trusty TA, et al. Intracellular and extracellular redox status and free radical generation in primary immune cells from children with autism. Autism Res Treat 2012;2012:986519.
[29] Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun 2012;26:383–92.
[30] Napolioni V, Ober-Reynolds B, Szelinger S, et al. Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder. J Neuroinflammation 2013;10:38.
[31] Goines P, Haapanen L, Boyce R, et al. Autoantibodies to cerebellum in children with autism associate with behavior. Brain Behav Immun 2011;25:514–23.
[32] Rossi CC, Van de Water J, Rogers SJ, Amaral DG. Detection of plasma autoantibodies to brain tissue in young children with and without autism spectrum disorders. Brain Behav Immun 2011.
[33] Piras IS, Haapanen L, Napolioni V, Sacco R, Van de Water J, Persico AM. Anti-brain antibodies are associated with more severe cognitive and behavioral profiles in Italian children with autism spectrum disorder. Brain Behav Immun 2014;38:91–9.
[34] Braunschweig D, Duncanson P, Boyce R, et al. Behavioral correlates of maternal antibody status among children with autism. J Autism Dev Disord 2011.
[35] Dalton P, Deacon R, Blamire A, et al. Maternal neuronal antibodies associated with autism and a language disorder. Ann Neurol 2003;53:533–7.
[36] Singer HS, Morris C, Gause C, Pollard M, Zimmerman AW, Pletnikov M. Prenatal exposure to antibodies from mothers of children with autism produces neurobehavioral alterations: a pregnant dam mouse model. J Neuroimmunol 2009;211:39–48.
[37] Braunschweig D, Golub MS, Koenig CM, et al. Maternal autism-associated IgG antibodies delay development and produce anxiety in a mouse gestational transfer model. J Neuroimmunol 2012;252:56–65.
[38] Bauman MD, Iosif AM, Ashwood P, et al. Maternal antibodies from mothers of children with autism alter brain growth and social behavior development in the rhesus monkey. Transl Psychiatry 2013;3:e278.
[39] Martin LA, Ashwood P, Braunschweig D, Cabanlit M, Van de Water J, Amaral DG. Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism. Brain Behav Immun 2008;22:806–16.
[40] Onore CE, Schwartzer JJ, Careaga M, Berman RF, Ashwood P. Maternal immune activation leads to activated inflammatory macrophages in offspring. Brain Behav Immun 2014;38:220–6.
[41] Keating A. Mesenchymal stromal cells: new directions. Cell Stem Cell 2012;10:709–16.
[42] De Feo D, Merlini A, Laterza C, Martino G. Neural stem cell transplantation in central nervous system disorders: from cell replacement to neuroprotection. Curr Opin Neurol 2012;25:322–33.
[43] Kokaia Z, Martino G, Schwartz M, Lindvall O. Cross-talk between neural stem cells and immune cells: the key to better brain repair? Nat Neurosci 2012;15:1078–87.
[44] Rolls A, Shechter R, London A, et al. Toll-like receptors modulate adult hippocampal neurogenesis. Nat Cell Biol 2007;9:1081–8.
[45] Li Y, Chen J, Zhang CL, et al. Gliosis and brain remodeling after treatment of stroke in rats with marrow stromal cells. Glia 2005;49:407–17.
[46] Shen LH, Li Y, Chen J, et al. Therapeutic benefit of bone marrow stromal cells administered 1 month after stroke. J Cereb Blood Flow Metab 2007;27:6–13.
[47] Ziv Y, Finkelstein A, Geffen Y, et al. A novel immune-based therapy for stroke induces neuroprotection and supports neurogenesis. Stroke 2007;38:774–82.
[48] Spejo AB, Carvalho JL, Goes AM, Oliveira AL. Neuroprotective effects of mesenchymal stem cells on spinal motoneurons following ventral root axotomy: synapse stability and axonal regeneration. Neuroscience 2013.
[49] Bai LH, Lennon DP, Eaton V, et al. Human bone marrow-derived mesenchymal stem cells induce Th2-polarized immune response and promote endogenous repair in animal models of multiple sclerosis. Glia 2009;57:1192–203.
[50] Crigler L, Robey RC, Asawachaicharn A, Gaupp D, Phinney DG. Human mesenchymal stem cell subpopulations express a variety of neuro-regulatory molecules and promote neuronal cell survival and neuritogenesis. Exp Neurol 2006;198:54–64.
[51] Nicaise C, Mitrecic D, Pochet R. Brain and spinal cord affected by amyotrophic lateral sclerosis induce differential growth factors expression in rat mesenchymal and neural stem cells. Neuropathol Appl Neurobiol 2011;37:179–88.
[52] Wang SP, Wang ZH, Peng DY, Li SM, Wang H, Wang XH. Therapeutic effect of mesenchymal stem cells in rats with intracerebral hemorrhage: reduced apoptosis and enhanced neuroprotection. Mol Med Rep 2012;6:848–54.
[53] Zhou C, Zhang C, Chi S, et al. Effects of human marrow stromal cells on activation of microglial cells and production of inflammatory factors induced by lipopolysaccharide. Brain Res 2009;1269:23–30.
[54] Giunti D, Parodi B, Usai C, et al. Mesenchymal stem cells shape microglia effector functions through the release of CX3CL1. Stem Cells 2012;30:2044–53.
[55] Bai L, Caplan A, Lennon D, Miller RH. Human mesenchymal stem cells signals regulate neural stem cell fate. Neurochem Res 2007;32:353–62.
[56] Lanza C, Morando S, Voci A, et al. Neuroprotective mesenchymal stem cells are endowed with a potent antioxidant effect in vivo. J Neurochem 2009;110:1674–84.
[57] Mahmood A, Lu D, Chopp M. Marrow stromal cell transplantation after traumatic brain injury promotes cellular proliferation within the brain. Neurosurgery 2004;55:1185–93.
[58] Kan I, Barhum Y, Melamed E, Offen D. Mesenchymal stem cells stimulate endogenous neurogenesis in the subventricular zone of adult mice. Stem Cell Rev 2011;7:404–12.
[59] Woodbury D, Schwarz EJ, Prockop DJ, Black IB. Adult rat and human bone marrow stromal cells differentiate into neurons. J Neurosci Res 2000;61:364–70.
[60] Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurol 2002;174:11–20.
[61] Bae KS, Park JB, Kim HS, Kim DS, Park DJ, Kang SJ. Neuron-like differentiation of bone marrow-derived mesenchymal stem cells. Yonsei Med J 2011;52:401–12.
[62] Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem 2006;98:1076–84.
[63] van Velthoven CT, Kavelaars A, van Bel F, Heijnen CJ. Mesenchymal stem cell treatment after neonatal hypoxic-ischemic brain injury improves behavioral outcome and induces neuronal and oligodendrocyte regeneration. Brain Behav Immun 2010;24:387–93.
[64] Xin H, Li Y, Shen LH, et al. Increasing tPA activity in astrocytes induced by multipotent mesenchymal stromal cells facilitate neurite outgrowth after stroke in the mouse. PLoS One 2010;5:e9027.
[65] Novikov LN, Novikova LN, Holmberg P, Kellerth J. Exogenous brain-derived neurotrophic factor regulates the synaptic composition of axonally lesioned and normal adult rat motoneurons. Neuroscience 2000;100:171–81.
[66] Ullian EM, Sapperstein SK, Christopherson KS, Barres BA. Control of synapse number by glia. Science 2001;291:657–61.
[67] Gutiérrez-Fernández M, Rodríguez-Frutos B, Ramos-Cejudo J, et al. Effects of intravenous administration of allogenic bone marrow- and adipose tissue-derived mesenchymal stem cells on functional recovery and brain repair markers in experimental ischemic stroke. Stem Cell Res Ther 2013;4:11.
[68] Shen LH, Li Y, Chen J, et al. One-year follow-up after bone marrow stromal cell treatment in middle-aged female rats with stroke. Stroke 2007;38:2150–6.
[69] Bae JS, Han HS, Youn DH, et al. Bone marrow-derived mesenchymal stem cells promote neuronal networks with functional synaptic transmission after transplantation into mice with neurodegeneration. Stem Cells 2007;25:1307–16.
[70] Huang H, Chen L, Sanberg P. Cell therapy from bench to bedside translation in CNS neurorestoratology era. Cell Med 2010;1:15–46.
[71] Tolar J, Le Blanc K, Keating A, Blazar BR. Concise review: hitting the right spot with mesenchymal stromal cells. Stem Cells 2010;28:1446–55.
[72] Yoo SW, Kim SS, Lee SY, et al. Mesenchymal stem cells promote proliferation of endogenous neural stem cells and survival of newborn cells in a rat stroke model. Exp Mol Med 2008;40:387–97.
[73] Munoz JR, Stoutenger BR, Robinson AP, Spees JL, Prockop DJ. Human stem/progenitor cells from bone marrow promote neurogenesis of endogenous neural stem cells in the hippocampus of mice. Proc Natl Acad Sci USA 2005;102:18171–6.
[74] Johnson TV, Bull ND, Hunt DP, Marina N, Tomarev SI, Martin KR. Neuroprotective effects of intravitreal mesenchymal stem cell

transplantation in experimental glaucoma. Invest Ophthalmol Vis Sci 2010;51:2051–9.
[75] Uccelli A, Benvenuto F, Laroni A, Giunti D. Neuroprotective features of mesenchymal stem cells. Best Pract Res Clin Haematol 2011;24:59–64.
[76] Kassis I, Vaknin-Dembinsky A, Karussis D. Bone marrow mesenchymal stem cells: agents of immunomodulation and neuroprotection. Curr Stem Cell Res Ther 2011;6:63–8.
[77] Tohill M, Mantovani C, Wiberg M, Terenghi G. Rat bone marrow mesenchymal stem cells express glial markers and stimulate nerve regeneration. Neurosci Lett 2004;362:200–3.
[78] Akiyama Y, Radtke C, Honmou O, Kocsis JD. Remyelination of the spinal cord following intravenous delivery of bone marrow cells. Glia 2002;39:229–36.
[79] Miller RH, Bai L. Cellular approaches for stimulating CNS remyelination. Regen Med 2007;2:817–29.
[80] Satake K, Lou J, Lenke LG. Migration of mesenchymal stem cells through cerebrospinal fluid into injured spinal cord tissue. Spine (Phila Pa 1976) 2004;29:1971–9.
[81] Zacharek A, Chen J, Cui X, et al. Angiopoietin1/Tie2 and VEGF/Flk1 induced by MSC treatment amplifies angiogenesis and vascular stabilization after stroke. J Cereb Blood Flow Metab 2007;27:1684–91.
[82] Iwase T, Nagaya N, Fujii T, et al. Comparison of angiogenic potency between mesenchymal stem cells and mononuclear cells in a rat model of hindlimb ischemia. Cardiovasc Res 2005;66:543–51.
[83] Bao X, Wei J, Feng M, et al. Transplantation of human bone marrow-derived mesenchymal stem cells promotes behavioral recovery and endogenous neurogenesis after cerebral ischemia in rats. Brain Res 2011;1367:103–13.
[84] Freedman MS, Bar-Or A, Atkins HL, et al. The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group. Mult Scler 2010;16(4):503–10.
[85] Uccelli A, Mancardi G. Stem cell transplantation in multiple sclerosis. Curr Opin Neurol 2010;23:218–25.
[86] Chopp M, Li Y, Zhang J. Plasticity and remodeling of brain. J Neurol Sci 2008;265:97–101.
[87] Wright KT, El Masri W, Osman A, Chowdhury J, Johnson WE. Bone marrow for the treatment of spinal cord injury: mechanisms and clinical application. Stem Cells 2010.
[88] Sokolova IB, Fedotova OR, Zin'kova NN, Kruglyakov PV, Polyntsev DG. Effect of mesenchymal stem cell transplantation on cognitive functions in rats with ischemic stroke. Bull Exp Biol Med 2006;142:511–4.
[89] Mazzini L, Mareschi K, Ferrero I, et al. Stem cell treatment in amyotrophic lateral sclerosis. J Neurol Sci 2008;265:78–83.
[90] Rossignol J, Boyer C, Lévèque X, et al. Mesenchymal stem cell transplantation and DMEM administration in a 3NP rat model of Huntington's disease: morphological and behavioral outcomes. Behav Brain Res 2011;217:369–78.
[91] Wolff EF, Gao XB, Yao KV, et al. Endometrial stem cell transplantation restores dopamine production in a Parkinson's disease model. J Cell Mol Med 2011;15:747–55.
[92] Laguna Goya R, Kuan WL, Barker RA. The future of cell therapies in the treatment of Parkinson's disease. Expert Opin Biol Ther 2007;7:1487–98.
[93] Barzilay R, Ganz J, Sadan O, et al. Mesenchymal stem cells protect from sub-chronic phencyclidine insult in vivo and counteract changes in astrocyte gene expression in vitro. Eur Neuropsychopharmacol 2013;23:1115–23.
[94] Ma S, Xie N, Li W, Yuan B, Shi Y, Wang Y. Immunobiology of mesenchymal stem cells. Cell Death Differ 2014;21:216–25.
[95] Fu X, Li H. Mesenchymal stem cells and skin wound repair and regeneration: possibilities and questions. Cell Tissue Res 2009;335:317–21.
[96] Ilancheran S, Moodley Y, Manuelpillai U. Human fetal membranes: a source of stem cells for tissue regeneration and repair? Placenta 2009;30:2–10.
[97] Trivedi P, Hematti P. Derivation and immunological characterization of mesenchymal stromal cells from human embryonic stem cells. Exp Hematol 2008;36:350–9.
[98] Zhang W. Mesenchymal stem cells in cancer: friends or foes. Cancer Biol Ther 2008;7:252–4.
[99] Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. Transplantation 2003;75:389–97.
[100] Krampera M, Glennie S, Dyson J, et al. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood 2003;101:3722–9.
[101] Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 2013;45:e54.
[102] Fibbe WE, Nauta AJ, Roelofs H. Modulation of immune responses by mesenchymal stem cells. Ann N Y Acad Sci 2007;1106:272–8.
[103] Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood 2007;110:3499–506.
[104] Le Blanc K, Tammik L, Sundberg B, Haynesworth SE, Ringdén O. Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand J Immunol 2003;57:11–20.
[105] Maccario R, Podestà M, Moretta A, et al. Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune response favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype. Haematologica 2005;90:516–25.
[106] Tyndall A, Walker UA, Cope A, et al. Immunomodulatory properties of mesenchymal stem cells: a review based on an interdisciplinary meeting held at the Kennedy Institute of Rheumatology Division, London, UK, 31 October 2005. Arthritis Res Ther 2007;9.
[107] Deng W, Han Q, Liao L, You S, Deng H, Zhao RC. Effects of allogeneic bone marrow-derived mesenchymal stem cells on T and B lymphocytes from BXSB mice. DNA Cell Biol 2005;24:458–63.
[108] Beyth S, Borovsky Z, Mevorach D, et al. Human mesenchymal stem cells alter antigen-presenting cell maturation and induce T-cell unresponsiveness. Blood 2005;105:2214–9.
[109] Augello A, Tasso R, Negrini SM, et al. Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway. Eur J Immunol 2005;35:1482–90.
[110] Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105:1815–22.
[111] Krampera M, Cosmi L, Angeli R, et al. Role for interferon-gamma in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem Cells 2006;24:386–98.
[112] Nasef A, Chapel A, Mazurier C, et al. Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells. Gene Expr 2007;13:217–26.
[113] English K, Barry FP, Field-Corbett CP, Mahon BP. IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells. Immunol Lett 2007;110:91–100.
[114] Sato K, Ozaki K, Oh I, et al. Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood 2007;109:228–34.
[115] Meisel R, Zibert A, Laryea M, Göbel U, Däubener W, Dilloo D. Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation. Blood 2004;103:4619–21.
[116] Plumas J, Chaperot L, Richard MJ, Molens JP, Bensa JC, Favrot MC. Mesenchymal stem cells induce apoptosis of activated T cells. Leukemia 2005;19:1597–604.
[117] Di Nicola M, Carlo-Stella C, Magni M, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 2002;99:3838–43.
[118] Rasmusson I, Ringdén O, Sundberg B, Le Blanc K. Mesenchymal stem cells inhibit the formation of cytotoxic T lymphocytes, but not activated cytotoxic T lymphocytes or natural killer cells. Transplantation 2003;76:1208–13.
[119] Glennie S, Soeiro I, Dyson PJ, Lam EW, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood 2005;105:2821–7.
[120] Zappia E, Casazza S, Pedemonte E, et al. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. Blood 2005;106:1755–61.
[121] Kim H, Darwish I, Monroy MF, Prockop DJ, Liles WC, Kain KC. Mesenchymal stromal (stem) cells suppress pro-inflammatory cytokine production but fail to improve survival in experimental staphylococcal toxic shock syndrome. BMC Immunol 2014;15:1.
[122] Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. Blood 2008;111:1327–33.
[123] Yen BL, Chang CJ, Liu KJ, et al. Brief report – human embryonic stem cell-derived mesenchymal progenitors possess strong immunosuppressive effects toward natural killer cells as well as T lymphocytes. Stem Cells 2009;27:451–6.
[124] Sotiropoulou 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.
[125] Asari S, Itakura S, Ferreri K, et al. Mesenchymal stem cells suppress B-cell terminal differentiation. Exp Hematol 2009;37:604–15.
[126] Corcione A, Benvenuto F, Ferretti E, et al. Human mesenchymal stem cells modulate B-cell functions. Blood 2006;107:367–72.
[127] Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation 2007;83:71–6.
[128] Djouad F, Charbonnier LM, Bouffi C, et al. Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism. Stem Cells 2007;25:2025–32.
[129] Spaggiari GM, Abdelrazik H, Becchetti F, Moretta L. MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. Blood 2009;113:6576–83.
[130] Ortiz LA, Dutreil M, Fattman C, et al. Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. Proc Natl Acad Sci USA 2007;104:11002–7.
[131] Raffaghello L, Bianchi G, Bertolotto M, et al. Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche. Stem cells 2008;26:151–62.
[132] Lim JH, Kim JS, Yoon IH, et al. Immunomodulation of delayed-type hypersensitivity responses by mesenchymal stem cells is associated with bystander T cell apoptosis in the draining lymph node. J Immunol 2010;185:4022–9.

[133] Shi Y, Su J, Roberts AI, Shou P, Rabson AB, Ren G. How mesenchymal stem cells interact with tissue immune responses. Trends Immunol 2012;33:136–43.
[134] Ma XL, Liu KD, Li FC, Jiang XM, Jiang L, Li HL. Human mesenchymal stem cells increases expression of α-tubulin and angiopoietin 1 and 2 in focal cerebral ischemia and reperfusion. Curr Neurovasc Res 2013;10:103–11.
[135] Aguilar S, Scotton CJ, McNulty K, et al. Bone marrow stem cells expressing keratinocyte growth factor via an inducible lentivirus protects against bleomycin-induced pulmonary fibrosis. PLoS ONE 2009;4:e8013.
[136] Hung SP, Yang MH, Tseng KF, Lee OK. Hypoxia-induced secretion of TGF-β1 in mesenchymal stem cell promotes breast cancer cell progression. Cell Transplant 2013;22:1869–82.
[137] Uccelli A, Milanese M, Principato MC, et al. Intravenous Mesenchymal Stem Cells Improve Survival and Motor Function in Experimental Amyotrophic Lateral Sclerosis. Mol Med 2012.
[138] Sheikh AM, Nagai A, Wakabayashi K, et al. Mesenchymal stem cell transplantation modulates neuroinflammation in focal cerebral ischemia: contribution of fractalkine and IL-5. Neurobiol Dis 2011;41:717–24.
[139] Kim YJ, Park HJ, Lee G, et al. Neuroprotective effects of human mesenchymal stem cells on dopaminergic neurons through anti-inflammatory action. Glia 2009;57:13–23.
[140] Ren G, Zhang L, Zhao X, et al. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell 2008;2:141–50.
[141] Keating A. Mesenchymal stromal cells. Curr Opin Hematol 2006;13:419–25.
[142] Hwu P, Du MX, Lapointe R, Do M, Taylor MW, Young HA. Indoleamine 2,3-dioxygenase production by human dendritic cells results in the inhibition of T cell proliferation. J Immunol 2000;164:3596–9.
[143] Prockop DJ. Two Negative Feedback Loops Place Mesenchymal Stem/Stromal Cells (MSCs) at the Center of Early Regulators of Inflammation. Stem Cells 2013.
[144] Harris SG, Padilla J, Koumas L, Ray D, Phipps RP. Prostaglandins as modulators of immunity. Trends Immunol 2002;23:144–50.
[145] Breece E, Paciotti B, Nordahl CW, et al. Myeloid dendritic cells frequencies are increased in children with autism spectrum disorder and associated with amygdala volume and repetitive behaviors. Brain Behav Immun 2013;31:69–75.
[146] Németh K, Leelahavanichkul A, Yuen PS, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med 2009;15:42–9.
[147] Dyer DP, Thomson JM, Hermant A, et al. TSG-6 inhibits neutrophil migration via direct interaction with the chemokine CXCL8. J Immunol 2014;192:2177–85.
[148] Lee RH, Pulin AA, Seo MJ, et al. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. Cell Stem Cell 2009;5:54–63.
[149] Oh JY, Roddy GW, Choi H, et al. Anti-inflammatory protein TSG-6 reduces inflammatory damage to the cornea following chemical and mechanical injury. Proc Natl Acad Sci USA 2010;107:16875–80.
[150] Choi H, Lee RH, Bazhanov N, Oh JY, Prockop DJ. Anti-inflammatory protein TSG-6 secreted by activated MSCs attenuates zymosan-induced mouse peritonitis by decreasing TLR2/NF-κB signaling in resident macrophages. Blood 2011;118:330–8.
[151] Ren G, Su J, Zhang L, et al. Species variation in the mechanisms of mesenchymal stem cell-mediated immunosuppression. Stem Cells 2009;27:1954–62.
[152] Matysiak M, Orlowski W, Fortak-Michalska M, Jurewicz A, Selmaj K. Immunoregulatory function of bone marrow mesenchymal stem cells in EAE depends on their differentiation state and secretion of PGE2. J Neuroimmunol 2011;233:106–11.
[153] Le Blanc K, Frassoni F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008;371:1579–86.
[154] Uccelli A, Laroni A, Freedman MS. Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological diseases. Lancet Neurol 2011;10:649–56.
[155] Jorgensen C, Djouad F, Bouffi C, Mrugala D, Noël D. Multipotent mesenchymal stromal cells in articular diseases. Best Pract Res Clin Rheumatol 2008;22:269–84.
[156] Jorgensen C. Mesenchymal stem cells in arthritis: role of bone marrow microenvironment. Arthritis Res Ther 2010;12:135.
[157] Vija L, Farge D, Gautier JF, et al. Mesenchymal stem cells: stem cell therapy perspectives for type 1 diabetes. Diabetes Metab 2009;35(2):85–93.
[158] Prasad VK, Lucas KG, Kleiner GI, et al. Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal™) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study. Biol Blood Marrow Transplant 2011;17(4):534–41.
[159] Freedman MS. Long-term follow-up of clinical trials of multiple sclerosis therapies. Neurology 2011;76:S26–34.
[160] Urbán VS, Kiss J, Kovács J, et al. Mesenchymal stem cells cooperate with bone marrow cells in therapy of diabetes. Stem Cells 2008;26:244–53.
[161] Augello A, Tasso R, Negrini SM, Cancedda R, Pennesi G. Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis. Arthritis Rheum 2007;56:1175–86.
[162] Zhou B, Yuan J, Zhou Y, et al. Administering human adipose-derived mesenchymal stem cells to prevent and treat experimental arthritis. Clin Immunol 2011;141(3):328–37.
[163] Tetreault NA, Hakeem AY, Jiang S, et al. Microglia in the cerebral cortex in autism. J Autism Dev Disord 2012.
[164] Lv YT, Zhang Y, Liu M, et al. Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. J Transl Med 2013;11:196.
[165] Lalu MM, McIntyre L, Pugliese C, et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. PLoS One 2012;7:e47559.
[166] Momin EN, Vela G, Zaidi HA, Quiñones-Hinojosa A. The oncogenic potential of mesenchymal stem cells in the treatment of cancer: directions for future research. Curr Immunol Rev 2010;6:137–48.
[167] Müller I, Kordowich S, Holzwarth C, et al. Application of multipotent mesenchymal stromal cells in pediatric patients following allogeneic stem cell transplantation. Blood Cells Mol Dis 2008;40:25–32.
[168] Z. Warren, J. Veenstra-VanderWeele, W. Stone, et al., Therapies for Children with Autism Spectrum Disorders. Comparative Effectiveness Review No. 26, Agency for Healthcare Research and Quality, Rockville, MD (2011), p. available at: <www.effectivehealthcare.ahrq.gov/reports/final.cfm>.
[169] Murcia CL, Gulden F, Herrup K. A question of balance: a proposal for new mouse models of autism. Int J Dev Neurosci 2005;23:265–75.
[170] Hanson E, Kalish LA, Bunce E, et al. Use of complementary and alternative medicine among children diagnosed with autism spectrum disorder. J Autism Dev Disord 2007;37:628–36.
[171] Bianco P. Don't market stem-cell products ahead of proof. Nature 2013;499:255.
[172] Lai MC, Lombardo MV, Baron-Cohen S. Autism Lancet 2013.
[173] Mouridsen SE, Rich B, Isager T, Nedergaard NJ. Autoimmune diseases in parents of children with infantile autism: a case-control study. Dev Med Child Neurol 2007;49(6):429–32.
[174] Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. Pediatrics 2003;112(5):e420.
[175] Keil A, Daniels JL, Forssen U, et al. Parental autoimmune diseases associated with autism spectrum disorders in offspring. Epidemiology 2010;21(6):805–8.
[176] Croen LA, Grether JK, Yoshida CK, Odouli R, Van de WJ. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch Pediatr Adolesc Med 2005;159(2):151–7.
[177] Molloy CA, Morrow AL, Meinzen-Derr J, et al. Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disorder: a CPEA Study. J Autism Dev Disord 2006;36(3):317–24.
[178] Gillberg IC, Gillberg C, Kopp S. Hypothyroidism and autism spectrum disorders. J Child Psychol Psychiatry 1992;33(3):531–42.
[179] Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol Today 1993;14(9):426–30.
[180] Uccelli A, Laroni A, Freedman MS. Mesenchymal stem cells as treatment for MS - progress to date. Mult Scler 2013;19(5):515–9.
[181] Harrop JS, Hashimoto R, Norvell D, et al. Evaluation of clinical experience using cell-based therapies in patients with spinal cord injury: a systematic review. J Neurosurg Spine 2012;17(Suppl. 1):230–46.
[182] Eckert MA, Vu Q, Xie K, et al. Evidence for high translational potential of mesenchymal stromal cell therapy to improve recovery from ischemic stroke. J Cereb Blood Flow Metab 2013;33(9):1322–34.
[183] Mazzini L, Mareschi K, Ferrero I, et al. Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study. Cytotherapy 2012;14(1):56–60.
[184] Rossignol J, Fink K, Davis K, et al. Transplants of adult mesenchymal and neural stem cells provide neuroprotection and behavioral sparing in a transgenic rat model of Huntington's disease. Stem Cells 2013.
[185] Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001;344(10):710–9.