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REVIEW

Rational use of mesenchymal stem cells in the treatment of autism spectrum disorders

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Abstract

Autism and autism spectrum disorders (ASD) refer to a range of conditions characterized by impaired social and communication skills and repetitive behaviors caused by different combinations of genetic and environmental influences. Although the pathophysiology underlying ASD is still unclear, recent evidence suggests that immune dysregulation and neuroinflammation play a role in the etiology of ASD. In particular, there is direct evidence supporting a role for maternal immune activation during prenatal life in neurodevelopmental conditions. Currently, the available options of behavioral therapies and pharmacological and supportive nutritional treatments in ASD are only symptomatic. Given the disturbing rise in the incidence of ASD, and the fact that there is no effective pharmacological therapy for ASD, there is an urgent need for new therapeutic options. Mesenchymal stem cells (MSCs) possess immunomodulatory properties that make them relevant to several diseases associated with inflammation and tissue damage. The paracrine regenerative mechanisms of MSCs are also suggested to be therapeutically beneficial for ASD. Thus the underlying pathology in ASD, including immune system dysregulation and inflammation, represent potential targets for MSC therapy. This review will

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focus on immune dysfunction in the pathogenesis of ASD and will further discuss the therapeutic potential for MSCs in mediating ASD-related immunological disorders.

Key words: Autism spectrum disorders; Mesenchymal stem cells; Major histocompatibility complex; Inflammation; Maternal immune activation; Cell therapy

Core tip: Autism spectrum disorder (ASD) is a complex, behaviorally defined disorder characterized by severe impairments in social communication and repetitive behavior. Because of an incomplete understanding of the pathology of ASD, available treatment options in ASD are only symptomatic. We discuss the role of immune dysfunction in the etiology of ASD and function of mesenchymal stem cells. We summarize the pre-clinical and clinical evidence for mesenchymal stem cell therapy in ASD and suggest that more basic experiments are needed to better understand the therapeutic mechanisms of mesenchymal stem cells in ASD.

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INTRODUCTION

Autism spectrum disorder (ASD) is a complex, behaviorally defined disorder characterized by severe and pervasive impairments in social communication and repetitive behavior. According to the 5th edition of the diagnostic and statistical manual of mental disorders, ASD is diagnosed in individuals exhibiting three social communication and interaction deficits, at least two symptoms of restricted or repetitive behavior/interests/activities, and a variety of specific symptoms classified within each diagnostic category. ASD is one of the most common psychiatric disorders affecting 1 in 59 children aged 8 years based on the most recent estimates calculated by the United States Center of Disease Control[1]. There has recently been a steady and highly significant rise in the estimated prevalence of ASD, due both to a greater awareness of the disorder and broader diagnostic criteria[1,2]. ASD is a complex and heterogeneous psychiatric disorder, and early studies suggest a strong genetic component to autism. For example, identical twin studies estimate concordance for ASD to be between 70% and 90%[3-5]. However, growing evidence suggests that these previous studies may have overestimated the genetic component of autism because the heritability of autism and shared twin environment were similar[6]. Meanwhile, large numbers of ASD candidate genes have been uncovered by whole-genome linkage studies, gene association studies, copy number variation screening, and SNP analysis[7]. Many of the candidate genes, such as reelin (*RELN*)[8], SH3 and multiple ankyrin repeat domains 3 (*SHANK3*)[9], neuroligin 3 (*NLGN3*), *NLGN4X*[10], *MET*[11], gamma-aminobutyric acid type-A receptor beta3 subunit (*GABRB3*)[12], oxytocin receptor (*OXTR*)[13], serotonin transporter (*SLC6A4*)[14], and phosphatase and tensin homolog (*PTEN*)[15] have been demonstrated to be associated with ASD (Figure 1). Furthermore, single gene mutations cause several ASD-related syndromes, including Rett's syndrome (methyl CpG binding protein 2, *MECP2*)[16], Fragile X (fragile X mental retardation 1, *FMR1*)[17], and tuberous sclerosis (*TSC1* or *TSC2*)[18]. Proteins within the phosphoinositide-3-kinase pathway, including MET, PTEN, TSC1, and TSC2 have a major role in regulating interleukin (IL)-12 production and are involved in both innate and adaptive immunity[19]. Additionally, some of the ASD candidate genes, including the major histocompatibility complex class genes are traditionally thought to play a role exclusively in the immune system[20] (Figure 1). Even with the recent advances in identifying candidate genes involved in ASD, all identified genes account for < 20% of ASD cases[21]. Moreover, a number of these genetic risk factors are present in individuals without ASD suggesting additional risk factors are also necessary. For example, recent studies provided evidence for altered DNA

methylation in ASD[22,23]. Thus through epigenetic mechanisms, exposure to specific environmental factors may be responsible for triggering the development of ASD in some individuals (Figure 1). A variety of environmental risk factors have been identified to increase ASD risk including: maternal immune activation (MIA)[24-27]; prenatal or perinatal exposure to valproic acid (VPA)[28,29] and selective serotonin reuptake inhibitors (SSRI)[30-32]; early life exposure to stress[33,34]; advanced parental age, zinc deficiency, abnormal melatonin synthesis[35]; and environmental toxins[36] (Figure 1). MIA and maternal exposure to drugs such as SSRI and VPA are of particular interest given evidence from clinical and animal studies supporting the role for immune dysfunction and inflammation in the etiology of ASD.

The first part of this review discusses immune-related genetic and environmental risk factors for ASD, from both human and animal studies, and the role of immune activation in the etiology of ASD-related behavioral and neuropathological abnormalities. Understanding how immune abnormalities are involved in the etiology of ASD will provide a valuable starting point for further work towards potential stem cell therapies for ASD. There is great potential for the use of stem cells in the future of molecular and regenerative medicine. Amongst the various stem cell subtypes, mesenchymal stem cells (MSCs) are the most promising clinical candidate for the treatment of several diseases related with inflammation, tissue damage, and subsequent regeneration and repair[37]. Therefore, the second part of this review will focus on underlying treatment mechanism of MSCs in ASD.

EVIDENCE FOR IMMUNE ABNORMALITIES IN ASD

Immune-related genetic risk factors for ASD

Major histocompatibility complex molecules: Major histocompatibility complex (MHC) occurs on the short arm of chromosome 6 and is divided into three regions; MHC class I, II, and III (MHC-I, MHC-II, and MHC-III). The human leukocyte antigen refers to the MHC locus in humans, which contains a large number of genes involved in integrating the innate and adaptive immune system. MHC-I molecules are found on all nucleated cells, and present epitopes to T-cell receptor proteins on cytotoxic CD8+ T lymphocytes[38]. As a result of MHC-I presentation, cytotoxic CD8+ T lymphocytes become activated and play an important role in the clearance of bacterial and viral infections. While MHC-I molecules have long been known for their primary role in adaptive immunity, they also bind to inhibitory receptors on natural killer (NK) cells, which are part of the innate immune system[39,40]. Interestingly, some recent studies have demonstrated novel roles of MHC-I molecules in regulating synaptic function, plasticity of the cerebral cortex, and cortical glutamatergic connectivity[41-43]. Several lines of evidence have indicated that abnormalities in the balance between excitatory (glutamate-mediated) and inhibitory (gamma-Aminobutyric acid-mediated) neurotransmission may be a key pathological mechanism in autism[44-46]. MHC may also function in social communication and the formation of social memories[47,48]. Moreover, the class one allele of human leukocyte antigen-A2, an important MHC-I antigen presenting molecule, is linked to higher incidence of autism[49]. Thus, it is interesting to speculate that human leukocyte antigen polymorphisms might contribute to the abnormal social communication in ASD by altering excitatory/inhibitory balance in the brain.

Unlike MHC-I, MHC-II molecules are expressed exclusively by the antigen presenting cells, including B cells, dendritic cells, and macrophages, in response to inflammation signals[50]. In general, helper CD4+ T lymphocytes can recognize exogenous antigen presented on MHC-II through T cell receptors. Once activated, helper CD4+ T lymphocytes promote B cell differentiation and antibody production and secrete many cytokines and chemokines. MHC-II alleles are associated with autoimmune disease[51], and interestingly, many studies report that a family history of autoimmune disease is a significant risk factor for ASD[52]. Moreover, in the developing and adult brain, MHC-II molecules are expressed mainly on microglia, astrocytes, and perivascular monocytes[53-55]. *In vitro* experiments suggest that the expression of MHC-II differs in astrocytes and microglia. For example, glutamate, an excitatory neurotransmitter abundantly present in the central nervous system (CNS), inhibits expression of MHC-II induced by interferon-gamma (IFN-γ) on astrocytes, but not on microglia cells[54]. Hellendall and Ting[56] reported that cytokine (IFN-γ) induced expression of MHC-II on astrocytes is mediated through a cAMP and protein kinase C-dependent pathway. Whilst a mitogen-activated protein kinase (MAPK) signal pathway including extracellular signal-regulated kinases 1/2, c-Jun N-terminal kinase, and p38 MAPK and cyclic AMP responding element binding protein, may be involved in lipopolysaccharide (LPS)-activated microglia[57]. Altered microglial

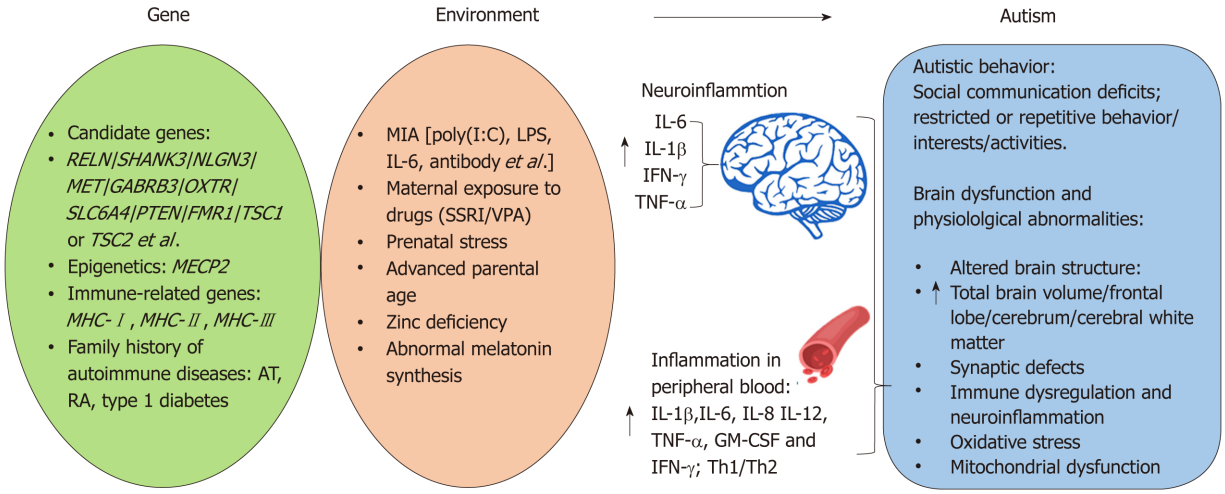

Figure 1 Genetic and environmental risk factors for autism spectrum disorders. Genetic risk factors for autism spectrum disorder (ASD) including: important candidate genes, immune-related genes (such as *MHC*), epigenetics, and family history of autoimmune disease. Prenatal infection, maternal exposure to drugs, prenatal stress, advanced parental age, zinc deficiency, and abnormal melatonin synthesis are important environmental risk factors for ASD. ASD children exhibit social communication deficits and repetitive behavior. Brain dysfunction and physiological abnormalities are observed in ASD patients and animal models. RELN: Reelin; GABRB3: Gamma-aminobutyric acid type-A receptor beta3 subunit; OXTR: Oxytocin receptor; SLC6A: PTEN: Phosphatase and tensin homolog; FMR1: Fragile X mental retardation 1; TSC1/2: Tuberous sclerosis 1/2; MECP2: Methyl CpG binding protein 2; MHC: Major histocompatibility complex; AT: Autoimmune thyroiditis; RA: Rheumatoid arthritis; MIA: Maternal immune activation; LPS: Lipopolysaccharide; SSRI: Selective serotonin reuptake inhibitors; VPA: Valproic acid.

activation in the brain is accompanied by the behavioral phenotype of autism (*e.g.*, anxiety, abnormal social interaction, and learning impairment) in MIA animal models[58,59]. Meanwhile, an increased average microglia somal volume in white matter and microglial density in grey matter has been reported in post-mortem studies of ASD[60,61]. Furthermore, several studies have reported that the *DRβ1*04* allele of the MHC-II region is associated with ASD[62-64].

The MHC-III region encodes a cluster of proteins with immune functions including complement proteins (C2 and C4), tumor necrosis factor (TNF)-α, and heat shock proteins. The CB4 null allele of MHC-III has been implicated in ASD[65]. In addition, strong evidence has demonstrated that MHC-III molecules play an important role in brain development and function. For example, TNF-α enhances dendrite growth and synaptic connectivity, balances neuronal excitation and inhibition, and alters synaptic plasticity[66-68].

Clearly, the MHC molecules play a vital role in the formation, refinement, maintenance, and plasticity of the brain. Thus, disruptions in the expression of MHC molecules in the developing brain induced by mutations and/or immune dysregulation might contribute to the altered brain function and endophenotypes of ASD.

Environmental risk factors in ASD

MIA and ASD: Epidemiological studies indicate that generalized activation of the maternal immune system caused by maternal infection during prenatal life is a strong risk factor for ASD[69-72]. Consistent with these reports, our research group and others have demonstrated non-specific induction of MIA using viral analogues such as the double stranded RNA poly(I:C), and this is sufficient to bring about neuropathologic, neuroimaging, and behavioral phenotypic changes in the offspring, which are analogous to those observed in human ASD[22,24-26,73,74]. In addition, MIA can be induced in both rodent and non-human primate models with influenza[75], IL-6[76], maternal anti-fetal brain antibody[77], and LPS[78]. Altogether, these large epidemiological findings and animal experiments point to a primary role for MIA in the etiology of ASD.

It is now well understood that shortly after maternal injection with poly(I:C), pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α are elevated in the maternal bloodstream, placenta, and fetal brain[59,79]. IL-6 in particular may be a crucial immunological mediator of the link between maternal immune activation and altered adult brain functions. This is because, unlike IL-1β and TNF-α, IL-6 may cross the placenta and enter the fetal brain after MIA[80,81]. Indeed, maternal IL-6 injection is sufficient to precipitate offspring prepulse inhibition and latent inhibition deficits usually consequent on poly(I:C) exposure[76]. Simultaneous injection of an anti-IL-6 antibody can prevent behavioral maldevelopment and gene expression changes

caused by MIA[76]. More convincingly, IL-6 knock-out mice are resistant to the effects of prenatal poly(I:C) exposure[76]. There is also evidence that maternal IL-6 dependent activation of the Janus kinase/signal transducer and activator of transcription 3 pathway in the placenta demonstrates a direct transfer of the MIA response from maternal to fetal cells[79]. Interestingly, pathways downstream of the Janus kinase/signal transducer and activator of transcription 3 signaling including the MAPK cascade that contains Ras/Raf, mitogen-activated protein kinase kinase 1, and phosphorylated extracellular signal-regulated kinases, have been demonstrated to contribute to the fetal brain dysfunction observed in the MIA mice model[82]. Moreover, several recent studies from our group and others report that MIA induces epigenetic alterations in the brain, suggesting that stable DNA methylation is a plausible mechanism underlying the disruption of gene transcription, brain development, and behavioral functions in response to immune challenge *in utero*[22,83-85].

Maternal exposure to SSRI and ASD: Depression during pregnancy is not uncommon; the prevalence is reported to be around 7%-12%[86,87]. SSRIs are the most frequently prescribed antidepressants during pregnancy because they are thought to be relatively safe for the fetus compared to other antidepressants. However, recent meta-analyses have suggested that SSRI exposure during pregnancy increases the risk for preterm birth and low birth weight[88], congenital malformation[89], and unfavorable effects on language or behavioral development in children[90]. SSRIs can cross the placenta and are able to reach the fetal brain, which might have long-term neurobehavioral and neurodevelopmental consequences in the offspring[91]. An imbalance of serotonin (5-HT) in prenatal life may be a risk factor for ASD. Experimental investigations have demonstrated that SSRIs have the potential to cause changes in brain circuitry and maladaptive behaviors, due to elevated levels of 5-HT[92]. *In utero*, exposure to an SSRI during a key developmental window lead to dysfunctional 5-HT signaling, loss of 5-HT terminals, and behavioral abnormalities in animals[92]. 5-HT levels are reported to be decreased in ASD patients[93]. Additionally, several clinical studies have reported that the use of SSRIs during pregnancy increases the risk of ASD in children[30,94-96]. Although several reviews and meta-analyses have recently been published addressing this issue, there are conflicting conclusions when controlling for maternal psychiatric disease and other confounding factors, such as genetic syndromes and congenital anomalies that are associated with ASD-like behavior[97-99]. To answer this question more accurately further investigation is warranted, in particular focusing on maternal psychiatric conditions and/or SSRI treated and untreated siblings.

Given that 5-HT plays a role as an immunomodulator, it is possible that prenatal SSRI exposure may contribute to the pathophysiology of ASD through interactions between an altered serotonergic system and the immune system. 5-HT modulates the function of a wide range of immune cells, including macrophages, NK cells, dendritic cells, T-cells, and B-cells through binding to 5-HT receptors during the immune response[100]. In addition, there is an association between serum 5-HT levels and the presence of certain MHC genes in ASD children[101]. It is possible that abnormal synaptic or extracellular levels of 5-HT may affect the immune system, triggering abnormalities as seen in ASD. However, a direct experimental investigation is needed to verify the 5-HT-mediated neuro-immune crosstalk in ASD.

Valproic acid and ASD: VPA has been used for the treatment of seizures and mood swings for more than 30 years. Several lines of clinical evidence have suggested that maternal exposure to VPA is associated with increased risk of ASD[102-104]. Our research group and others have shown that rodents exposed to VPA prenatally develop behavioral traits and neurochemical alterations that may be relevant to ASD[28,105]. Interestingly, prenatal exposure to VPA on gestation day 9 before neural tube closure disrupts the maturation of serotonergic neurons thereby interrupting early development of the serotonergic system[106]. In addition, prenatal exposure to VPA on gestation day 9 results in an elevated level of 5-HT in the hippocampus and hyperserotonemia in blood[107]. Furthermore, Dufour-Rainfray *et al*[108] reported that decreased 5-HT levels in the hippocampus of rats exposed to VPA at gestation day 9 may be associated with behavioral impairments. Therefore, these results suggest prenatal VPA exposure may play a role in the development of ASD through disruption of the normal development of the serotonin system. However, further research is required to elucidate the mechanisms by which this occurs. Clinical use of VPA is often associated with hepatotoxicity and the pathology of VPA-induced hepatotoxicity has been studied extensively. Oxidative stress and hepatic inflammation are apparent; elevated levels of nuclear NF-κB in the liver is accompanied by the induction of IL-1β, IL-6, and TNF-α, and these play important

roles in the pathology of VPA-induced hepatotoxicity[109]. Moreover, moderate or high doses of prenatal exposure to VPA can also induce toxicity and even death in the offspring in animals[28]. However, the underlying mechanism of VPA-induced toxicity in the CNS is not clear yet. We suspect that oxidative stress and/or neuroinflammation may also play an important role in the altered brain function observed in prenatal exposure to VPA. Further study is required to improve understanding of the mechanisms by which prenatal VPA exposure may induce ASD, through investigation of the serotoninergic system and immune responses in the fetal brain.

Inflammation in ASD

A consistent body of data has suggested that there is active inflammation in the CNS in ASD patients. Increased activation of astroglia and microglia has been found in the postmortem brain and cerebrospinal fluid samples in ASD patients[61]. In addition, elevated macrophage chemoattractant protein-1 and tumor growth factor-β1 derived from neuroglia are the most prominent cytokines in the brain samples of ASD patients; marked expression of a prominent inflammatory cytokine profile, macrophage chemoattractant protein-1, IL-6, IL-8, and IFN-γ is shown in the cerebrospinal fluid of ASD patients[61]. Another study further demonstrates that pro-inflammatory cytokines including TNF-α, IL-6, IL-8, granulocyte macrophage-colony stimulating factor, and IFN-γ (Th1 cytokines) are significantly increased in the brains of ASD patients[110]. However, there is no increase in IL-4 or IL-5 (Th2 cytokines), thus Th1/Th2 ratio is significantly raised in ASD patients, suggesting that the Th1 pathway is activated in ASD[110].

A number of studies have shown that IL-1β, IL-12, TNF-α, and IFN-γ are increased in the peripheral blood of autistic patients[111]. Two recent large case-control studies comparing ASD and typically developing children have further confirmed increased levels of plasma cytokines including the Th1-like IL-12p40 and pro-inflammatory cytokines IL-1β, IL-6, IL-8, and granulocyte macrophage-colony stimulating factor[112], and chemokines, including MCP-1, regulated on activation normal T cell expressed and secreted, and eotaxin[113]. These elevated levels of cytokines and chemokines are associated with behavioral and cognitive impairments[112,113].

POTENTIAL FOR MSCS IN THE TREATMENT OF ASD

MSCs

MSCs are a population of progenitor cells of mesodermal origin found principally in the bone marrow, which possess the capacity of self-renewal and also exhibit multilineage differentiation[114,115]. In addition to bone marrow, MSC populations can also be obtained readily from adipose tissue[116], placenta[117], skin[118], umbilical cord blood[119], umbilical cord perivascular cells[120], umbilical cord Wharton's jelly[121], amniotic fluid[122], synovial membrane[123], breast milk[124], alveolar epithelium[125], myocardium[126], menstrual blood[127], and endometrium[128] (Table 1). MSCs are relatively easy to isolate and expand in culture and capable of self-renewal and differentiation, making them a promising treatment option for a variety of clinical conditions. Although the multipotency of MSCs is demonstrated *in vitro*[129], this is still not definite *in vivo*. Until now, it is also still unclear whether MSCs isolated from different tissue sources have similar therapeutic potentials[130]. Furthermore, it is uncertain whether systematic delivery (*i.e.*, intravenous) of MSCs is sufficient to reach the brain as compared to direct implantation of MSCs[131,132]. Though intranasal application of cells provides an alternative, non-invasive method to deliver MSCs directly into the CNS[133]. At present, neither intravenous nor direct injection of MSCs have been able to yield consistent clinical results because infused cells exhibit limited survival and transient functionality in host tissues[134-136].

As well as the ability to self-renew and differentiate, MSCs can also secrete immunomodulatory, anti-apoptotic, anti-inflammatory, pro-angiogenic, pro-mitogenic, and antibacterial molecules that contribute to immunomodulatory and trophic effects[137]. Thus recent recognition of the immunomodulatory functions of MSCs may result in the exploration and development of new therapies for ASD.

Effects of MSCs on the nervous system in health and ASD

Although the mechanism of action of MSCs on the nervous system remains largely unknown, recent research suggests that neuroprotection, neurogenesis, and synaptogenesis may be involved[138]. Genetic findings linking ASD to synapse-associated genes, such as SH3 and multiple ankyrin repeat domains 3 (SHANK3) and mutations of other synaptic cell adhesion molecules, suggest that ASD may result, at

Table 1 Tissue sources of mesenchymal stem cells

Tissue sources	MSCs	Ref.
Bone marrow	BM-MSCs	[115]
Adipose	Ad-MSCs	[116]
Placenta	Pl-MSCs	[117]
Skin	S-MSCs	[118]
Umbilical cord blood	UCB-MSCs	[119]
Umbilical cord perivascular cells	UCPVC-MSCs	[120]
Umbilical cord Wharton's jelly	WJ-MSCs	[121]
Amniotic fluid	AF-MSCs	[122]
Synovial membrane	SM-MSCs	[123]
Breast milk	M-MSCs	[124]
Alveolar epithelium (lung)	AE-MSCs	[125]
Myocardium (heart)	Myo-MSCs	[126]
Menstrual blood	Men-MSCs	[127]
Endometrium	En-MSCs	[128]

MSCs: Mesenchymal stem cells; BM-MSCs: Bone marrow MSCs; Ad-MSCs: Adipose MSCs; UCB-MSCs: Umbilical cord blood MSCs.

least partially, from disruption of synapse function and plasticity[139]. MSCs act through several possible mechanisms to regulate synaptic function and plasticity, that is, secreting survival-promoting growth factors (*e.g.*, brain-derived neurotrophic factor; nerve growth factor), sustaining synaptic plasticity, restoring synaptic transmitter release by providing local re-innervations, integrating into existing synaptic networks, and re-establishing functional afferent and efferent connections[138,140,141].

Effects of MSCs on the immune system and autoimmune diseases in health and ASD

There is a considerable body of literature documenting the effects of MSCs on the immune system. MSCs act on both the adaptive and innate immune system by suppressing pro-inflammatory activities, inhibiting dendritic cell maturation, polarizing macrophages towards anti-inflammatory M2-like state, promoting the generation of regulatory T cells *via* IL-10, suppressing proliferation and cytotoxicity of NK cells, and reducing B cell activation and proliferation. These functions of MSCs on the immune system have been covered extensively in several reviews[142-146]. As discussed above in this review, ASD patients show an imbalance between Th1 and Th2, as well as NK cells, overproduction of pro-inflammation, and reduction of anti-inflammation. MSCs immunoregulatory effects have the potential to restore this immune imbalance, inhibit TNF-α, IL-1β and IFN-γ production, and increase IL-10 and IL-4 levels[147].

In addition, MSCs are capable of crossing the blood-brain-barrier and migrating to sites of tissue injury and inflammation[148,149]. MSCs act through Toll-like receptor (TLR) signaling to initiate the clearance of pathogens and promote the repair of injured tissue. These TLRs respond to so-called "danger signals" from microbial invasion, such as double-stranded RNA (dsRNA), LPS, and heat shock proteins, triggering intracellular signaling pathways. This results in the induction of inflammatory cytokines, type I IFNs, and upregulation of co-stimulatory molecules leading to the activation of the adaptive immune response[150]. As mentioned above, prenatal exposure to poly(I:C), a synthetic analog of dsRNA, elicits a plethora of intracellular signaling pathways through binding to TLR3 in a MIA model of ASD[151], whilst LPS elicits distinct molecular profiles through binding to TLR4[152]. In TLR3- and TLR4-mediated signaling pathways, toll–IL-1 receptor domain-containing adaptor inducing IFN-β (TRIF) leads to activation of the transcription factors interferon regulatory factor 3 (IRF3), which are responsible for induction of IFN-β[153] (Figure 2A). TRIF-dependent signaling pathway, both downstream of TLR-3 and TLR-4, also leads to activation of MAPKs and production of cytokines, such as IL-6 and TNF-α[153,154]. Interestingly, TLRs may polarize MSCs toward pro-inflammatory (MSC1) or anti-inflammatory (MSC2) phenotypes. For example, TLR4 (LPS) priming results in production of pro-inflammatory cytokines such as IL-6 or IL-8 (MSC1), while TLR3 (dsRNA, ployI:C) priming induces secretion of anti-inflammatory

molecules such as IL-10, IL-4, indoleamine 2,3-dioxygenase, or prostaglandin (MSC2)[155,156] (Figure 2B). These polarizing effects of TLR priming depend on the ligand concentration, timing, and kinetics of activation. This may also explain the contradictory results obtained so far regarding the effects of TLRs on immunomodulation by MSCs[155,156]. However, in contradiction to the reported LPS polarizing process (MSC1 phenotype) observed *in vitro*, several studies have reported beneficial effects of MSC treatment in animal models of LPS-induced tissue injury[157-159]. Therefore, the *in vivo* modulation of MSCs by TLR ligands deserves further investigation and clarification. In particular, the MIA model of prenatal exposure to poly(I:C) represents a good animal model in which to explore the underlying mechanism of MSC treatment in ASD.

Numerous autoimmune conditions have been associated with ASD, including autoimmune thyroiditis, rheumatoid arthritis, ulcerative colitis, celiac disease, and type 1 diabetes[160] (Table 2). The potential use of MSC therapy has been investigated in many of these conditions. Preclinical experiments and clinical trials have demonstrated the safety and efficacy of MSC therapy in rheumatoid arthritis animal models and patients[161]. In addition, MSC therapy has been reported to increase regulatory T cells, restore Th1/Th2 balance in blood and induce apoptosis of infiltrated leukocytes in pancreatic islet cells in mice with type 1 diabetes[162]. However, in order to translate this finding from bench to bedside, further in-depth mechanistic studies of the therapeutic effects of MSCs on type 1 diabetes are warranted. Recent pre-clinical research has shown the restorative effect of MSCs in mice with autoimmune thyroiditis through the MAPK signaling pathway[163]. Furthermore, graft-versus-host-disease and multiple sclerosis have been targeted for MSC treatment in both animal experiments and clinical trials[164-167] (Table 2). However, the use of MSCs in the treatment of graft-versus-host-disease has failed to give consistent results in animal experiments[167].

Pre-clinical and clinical evidence for MSC therapy in ASD

To date, only a few pre-clinical studies have demonstrated the therapeutic potential of MSC treatment in animal models of ASD. Ha *et al*[168] reported that adipose MSCs are transplanted intraventricularly into the brains of neonatal fetal pups at a very early stage. This early intervention reduces repetitive behavior and anxiety, and improves social deficits in mice prenatally exposed to VPA through the rescue of decreased IL-10 and vascular endothelial growth factor levels together with upregulation of reduced PTEN proteins in the brain. In addition, it has been demonstrated that by promoting the maturation of newly formed neurons in the granular cell layer of the dentate gyrus, MSC transplantation restores post-developmental hippocampal neurogenesis in VPA-exposed mice[169]. This is associated with improvements in cognitive and social behavior 2 wk after transplantation of the MSCs and thus may be related to the modulation of hippocampal neurogenesis[169].

A widely accepted mouse model of ASD is the BTBR T+, tf/J (Black and Tan Brachyury, BTBR) inbred mouse strain, which display autistic-like behavior and neuroanatomical abnormalities, including absence of corpus callosum and reduced hippocampal commissure, analogous to the core endophenotype of autism[170-172]. It has been shown that intracerebroventricular transplant of human MSCs into BTBR mice results in a reduction of stereotypical behaviors and cognitive rigidity and an improvement in social behavior[173]. Furthermore, elevated brain-derived neurotrophic factor levels and hippocampal neurogenesis were detected in the MSCs-transplanted BTBR mice[173]. This finding then promoted an investigation of the behavioral effects of transplanted MSCs, which were induced to secrete a higher amount of neurotrophic factors (NurOwn®) in BTBR mice[174]. This study demonstrated NurOwn®[175] are superior to MSCs without induced neurotrophic factors in several aspects. In particular, NurOwn® contains 2 and 5 fold levels of brain-derived neurotrophic factor and glial cell-derived neurotrophic factor, respectively, compared to MSCs from the same donor[176]. Moreover, NurOwn® transplantation increases male-female social interaction, decreases repetitive behavior (changes which can be sustained for 6 mo after treatment), and improves cognitive flexibility in BTBR mice[174]. Exosomes derived from MSCs serve as the main mediators of the therapeutic effect of MSC, with an involvement in repairing damaged tissues, suppressing inflammatory responses, and modulating the immune system[177,178]. Their potential as a surrogate of therapeutic MSCs has been widely explored. Recently, it has been shown that BTBR mice treated with exosomes derived from MSCs via intranasal administration present with significant behavioral improvements in social interaction and ultrasonic communication and reduced repetitive behavior. Interestingly, BTBR mothers that were treated with exosomes derived from MSCs showed improvements in maternal behaviors such as pup retrieval behavior[179].

Although there have been few pre-clinical studies of MSC therapy for ASD, several

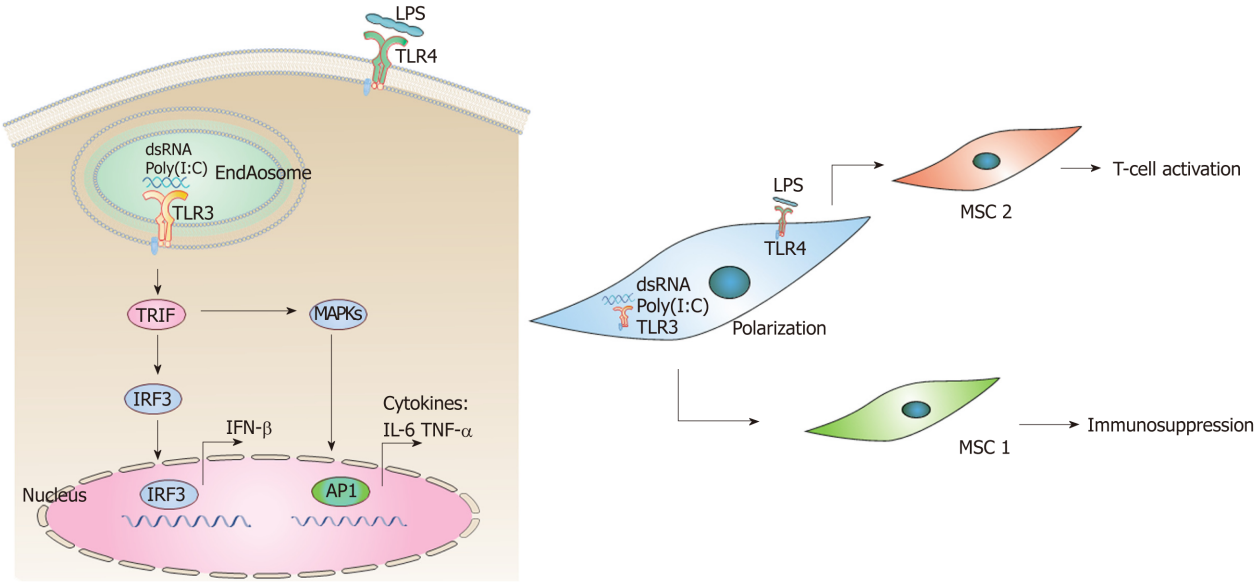

Figure 2 Poly(I:C)-toll-like receptor 3 signaling pathway and polarization of mesenchymal stem cells. A: Poly(I:C)-induced toll-like receptor 3(TLR3) signaling pathway. TLR3 recognizes dsRNA analog poly(I:C) in the endosomes and initiates signaling by TRIF, leading to activation of IRF3 and induction of IFN-β. TRIF-dependent signaling pathway also induces activation of MAPKs and AP-1, and culminates in the production of inflammatory cytokines, such as IL-6 and TNF-α; B: Polarization of MSCs into MSC1 (M1 type with a proinflammatory response) and MSC2 cells (M2 type with an anti-inflammatory response) as a result of activation of TLR3 and TLR4 respectively. Poly(I:C): polyinosinic–polycytidylic acid; dsRNA: Double-stranded RNA; TLR3: Toll-like receptor 3; TLR4: Toll-like receptor 4; TRIF: Toll–IL-1 receptor domain-containing adaptor inducing IFN-β; IRF3: Interferon regulatory factor 3; MAPKs: Mitogen-activated protein kinases; AP1: Activator protein 1; IFN-β: Interferon β; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor α; LPS: Lipopolysaccharide.

clinical trials on human have been conducted. Lv *et al*[180] performed a non-randomized, open-label, controlled, proof-of-concept clinical trial to exam the treatment, safety and efficacy of umbilical cord blood MSCs and/or cord blood mononuclear cells in children with autism. At 24 wk post-treatment, significant reductions in symptom severity are observed with the greatest improvement in the combined group (umbilical cord blood-MSCs + cord blood mononuclear cells), suggesting a synergic effect of dual therapy[180]. There is no significant safety issue related to the treatment and no observed severe adverse effects.

Meanwhile, Sharma *et al*[181] conducted another open-label proof of concept study and reported on the use of intrathecal transplantation of autologous bone marrow mononuclear cells that contain MSCs in 32 patients with ASD. This study included children as well as adults with ASD (age 3-33). Most of the patients showed improved scores in various behavioral scales after a 26 mo follow up, including improvements in social relationships and reciprocity, emotional responsiveness, speech, language, communication, behavior patterns, sensory aspects, and cognition. Only a few adverse events (including seizures and hyperactivity) were observed, and these were controlled with medications[181]. It has been reported that cerebral hypoperfusion or insufficient blood flow in the brain occurs in many brain regions in ASD[182], and interestingly, their study suggested that the cell transplantation may have had a balancing effect on the brain metabolism[181]. Comparative Positron Emission Tomography-Computed Tomography scans before and 6 mo after cell transplantation showed increased ^{18}F-fluorodeoxyglucose uptake in the areas of frontal lobe, cerebellum, amygdala, hippocampus, parahippocampus, and mesial temporal lobe[181].

Another small pilot open label study recently investigated the clinical benefits of bone marrow aspirate concentrate stem cell with intrathecal transplantation in 10 ASD children (4-12 years of age)[183]. The maximal effect of cell therapy was observed within the first 12 mo following the treatment. Interestingly they also found that improvement decreased as the age of ASD child increased[183]. However, there was no control group and the number of subjects in this study was quite small. Dawson *et al*[184] conducted an open-label phase I clinical trial of a single intravenous infusion of autologous UCB (AUCB) on 25 ASD children aged between 2 and 5 years. They found that most of the significant improvements in behavior occurred during the first 6 mo and were sustained between 6 and 12 mo post-infusion. Thus whilst a single therapy did not improve all autistic symptoms, this work has demonstrated that it is safe and feasible to perform AUCB infusions for the effective treatment of ASD in young children[184]. Dawson's research team[185] performed a secondary follow up study and reported changes in electroencephalography spectral power by 12-mo post-treatment

Table 2 Autoimmune diseases, autism spectrum disorders, and mesenchymal stem cells

Autoimmune diseases	ASD	MSCs
Autoimmune thyroiditis	+	Pre-clinical experiment
Rheumatoid arthritis	+	Pre-clinical experiment; Clinical trials on-going
GVHD	-	Pre-clinical experiment; Clinical trials
MS	-	Pre-clinical experiment; Clinical trials on-going
Type 1 diabetes	+	Pre-clinical experiment; Clinical trials on-going

ASD: Autism spectrum disorders; MSCs: Mesenchymal stem cells; GVHD: graft-versus-host-disease; MS: Multiple sclerosis; +: An association between ASD and a family history of autoimmune diseases; -: No or lack of evidence of correlation between autoimmune diseases and ASD.

of AUCB on ASD children. Baseline posterior electroencephalography beta power was positively associated with an improvement in social communication symptoms in ASD children, suggesting the electroencephalography may be a useful biomarker to predict the outcome of clinical trials for ASD.

Recently, the first randomized, double-blinded, placebo-controlled clinical trial provided further evidence that AUCB was safe, but there was minimal clinical efficacy compared to the findings of the previous open-label trial[186]. Twenty-nine ASD children 2-6 years of age were infused with either AUCB or placebo, and evaluated at baseline, 12 wk, and 24 wk[186]. This study suggested that infusion of AUCB has no serious adverse events for the treatment of ASD and potentially had an impact on socialization for children with ASD.

While the clinical trials discussed above have generally reported a good safety profile for MSC transplantation in ASD children, the follow-up checks are currently only up to 12 mo after treatment. Thus caution should still prevail as no data of long-term effects such as 5 to 20 years posttreatment are currently available.

CONCLUSION

Despite the increasing incidence of ASD, autism currently remains untreatable. The available options of behavioral, pharmacological, and nutritional therapies are only supportive treatments[84,187,188]. The underlying pathology of ASD involves immune system dysregulation, autoimmunity, and inflammation[189], and these processes are targetable with MSC therapy. MSCs can be transplanted directly without genetic modification or pretreatment, differentiated according to the cues from the surrounding tissues, and do not cause uncontrollable growth or tumors[190]. Several proof-of-concept clinical studies mentioned above and meta-analyses have shown the safety and/or efficacy of MSCs treatment in autistic patients or other clinical conditions of immune dysregulation[180,181,184,190]. Although MSCs have the potential for clinical use in ASD, a number of methodological, technical, and safety challenges still need to be considered[191]. Additionally, their response to other pharmacological interventions, tissue distribution upon administration, and their long-term safety profile are key areas in need of further investigation. Currently, it is unclear how long a single dose of MSC can sustain anti-inflammatory effects or when would be the ideal age for intervention (the early the better?). Furthermore, the most recent randomized, double-blinded, placebo-controlled clinical trial, which had a much more rigorous design than other clinical trials mentioned in this review reported lack of efficacy of AUCB for the treatment of ASD. Given that the long-term safety and efficacy of MSC treatment cannot be fully ascertained, standardized trial design needs to be considered when designing future clinical trials.

More importantly, our understanding of basic MSC biology and underlying etiology of ASD is still limited. Further basic research into endogenous functions of MSC is warranted to elucidate the mechanism by which therapeutic MSCs for the treatment of ASD mediate their action. Animal models such as the MIA and BTBR mouse models may be vital for this as they allow the simultaneous measurement of peripheral and central immune function, quantitative neuronal modification, and behavioral changes in response to MSC treatment, thus enabling a better understanding of the therapeutic mechanisms of MSCs in ASD.

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