Autism - Open Access

ISSN: 2165-7890

Shane, et al.,, Autism Open Access 2015, 5:3
DOI: 10.4172/2165-7890.1000151

Review Article Open Access Journal

Do the Stem Cells Really Work with Autism Spectrum Disorders Associated with Neuro-Immune Interaction?

Gao Shane1*#, Wang Juan1,2#, Wu Zeyang[1],Yuan Ping[3], Gao Fengjuan[4], Zhou fei[5], Cao Limei[4], Chen Xu[4], Zhu Hongwen[6] and Xu Jun[1*]

[1]*East Hospital, Tongji University School of Medicine, Shanghai 200120, China*

[2]*Department of Biotechnology, Binzhou Medical College, Yantai, Shandong Province, 264003, China*

[3]*Tongji Hospital affiliated to Tongji University, Shanghai 200092, China*

[4]*Shanghai Eighth People's Hospital Affiliated to Jiangsu University, Shanghai 200233, China*

[5]*Shanghai ChangZheng Hospital Affiliated to the Second Military Medical School, Shanghai, 200003, China*

[6]*Tianjin Hospital, Tianjin 300211, China*

 # Authors contributed equally

[*]***Corresponding author:*** *Shane G, East Hospital, Tongji University School of Medicine, Shanghai 200120, China, Tel: 86-15801709849; E-mail: gaoshan2009@tongji.edu.cn*

Jun X, East Hospital, Tongji University School of Medicine, Shanghai 200120, China, E-mail: xunymc2000@yahoo.com

Rec date: August 13, 2015; **Acc date:** September 26, 2015; **Pub date:** October 03, 2015

Abstract

Autism spectrum disorders (ASDs), namely neurodevelopmental disorders encompassing impairments in communication, social interactions and restricted stereotypical behaviors, induces a relatively high morbidity and mortality ratio (1/166) in modern children's life. One of the serious factors accounting for ASDs is the failure of the appropriate neuro-immune interaction. Although a relationship between altered immune responses and ASDs was firstly recognized nearly 40 years ago, only recently has new evidence started to shed light on the complex multifaceted communication between neuro-immune dysfunction and behavior in ASDs. Extensive alterations in immune function have now been described in both children and adults with ASDs, including ongoing inflammation in brain specimens, elevated pro-inflammatory cytokine profiles in the Cerebro-Spinal Fluid (CSF) and blood, increased presence of brain-specific auto-antibodies and altered immune cell function. Accumulated data both from clinical and lab research proposed the essential role of neuro-immune interaction during the pathogenesis of ASDs. Stem cells, which account for normal turnover and injury repair, might do great favors on ASDs due to their ability to give rise to new functional cells as a cell replacement source, paracrine secretion as trophic and cytokine contributor, immune modulator to balance the pro-inflammation and anti-inflammation as well as the inhibitor of chronic inflammation in ASDs brain, etc. Here in this review, we focus on the current development of stem cell administration in ASDs especially on mesenchymal stem cells (MSCs), which proved to be the most plastic and efficient to interfere with ASDs neuro-immune interaction, moreover summarize the propbable mechanism and efficient therapeutic methods to treat ASDs withMSCs.

Keywords: Stem cells; Mesenchymal stem cells (Mscs); Autism spectrum disorders (Asds); Neuro-immune interaction

Introduction

Autism spectrum disorders (ASDs) are a series of pervasive development disorders including autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's syndrome or pervasive developmental disorder not otherwise specified (PDD-NOS). ASDs incidence is reaching epidemic proportions, afflicting approximately 1 in 166 children [1]. It is currently characterized in several areas of development: reciprocal social interaction skills, communication skills, or the presence of stereotyped behavior, interests and activities (APA, 2000) [2]. ASDs are consodered complex, heterogeneous diseases caused by an interaction between genetic vulnerability and environmental factors. In an effort to better target the underlying roots of ASDs for diagnosis and treatment, efforts to identify reliable biomarkers in genetics, neuroimaging, gene expression, and measures of the body's metabolism are growing [3]. Besides the immense efforts on the genetic and transcriptome analysis, increasing evidence points to a central role for immune system and many maternal immune system-related risk factors-including autoimmunity, infection and fetal reactive antibodies-which are closely associated with ASDs [2]. Moreover, there is close correlation between ongoing immune dysregulation and ASDs either in individuals or animal models [4]. Recently, several molecular signalling pathways-including those downstream of cytokines, the receptor MET, major histocompatibility complex class I molecules, microglia and complement factors have been identified as the links mediating immune activation to ASDs phenotypes [5-7]. Together, these findings indicate that the immune system is a point of convergence for multiple ASDs-related genetic and environmental risk factors [8-10]. Simone Gupta's group revealed dysregulation of innate immune response genes and neuronal activity-dependent genes between region-matched autism and control brains by transcriptome analysis [11]. These accumulated data from epidemiology, clinician observers and neurological scientists led to a point that brain immune dysfunction mediate the genetic factors to the environmental ones and the ultimate ASDs. In this way, one of the most probable efficient ASDs treatments is to perform immune modulation. Modern science witnessed the revolution of stem cell

research which has brought new insights into the intervention of traditional intractable diseases such as ASDs, Amyotrophic Lateral Sclerosis (ALS), Rett Syndrome, Spinal Muscular Atrophy (SMA) etc. due to stem cells's intrinsic properties of regeneration against degeneration, immune regulation resisting the immune dysfunction, neurotrophic ability to reverse the insufficient neurotrophic capacity of these diseases. Stem cells have undoutedly become one of the most promising and effective treatment methods for most of the Central Nerve System (CNS) diseases.

What kind of stem cells rank as the best appropriate for treating ASDs?

Stem cells are group of cells that can keep self-renewal and at the same time give rise to terminal functional adult cells. Among them, mesenchymal stem cells (MSCs) exist in most of the mesenchymal tissues such as bone marrow, adipose tissue, umbilical cord, etc. at relatively high ratio and are easy to be isolated and expanded in vitro. MSCs are firstly isolated by Friedenstein and coworkers, identified as a nonphagocytic cell population with fibroblast-like appearance, able to originate discrete fibroblastic colonies in vitro [12,13]. In 1991, They were defined as mesenchymal stem cells (MSCs) by Caplan and regarded as new therapeutic tools for tissue repair, due to their capacity of differentiation and commitment to unique tissue types (e.g., cartilage and bone) [14]. Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) determined that multipotent mesenchymal stromal cells (with the acronym MSCs) were the more appropriate term to be used. In addition, this committee proposes that these cells must be defined by three minimal criteria. First, they must be plastic-adherent when maintained under standard culture conditions. Second, they must present CD105, CD73, and CD90 expression (≥95%) and lack expression of CD45, CD34, CD14, or CD11b, CD79alpha or CD19 and HLA-DR (≤2% positive). Third, they must be able to differentiate into osteoblasts, adipocytes, and chondroblasts when cultured under standard in vitro differentiating conditions [15]. Given the disturbing rise in incidence rates for ASDs, and the fact that no pharmacological therapy for ASDs 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 MSCs for other immunological and neurological conditions has shown promising results in preclinical and even clinical studies [16]. MSCs have demonstrated the ability to suppress the immune system and to promote neurogenesis with a anticipated safety profile. These characteristics may be attributed to the fact that MSCs are intrinsically derived from perivascular cells, pericytes, liberated from their basement membrane tethers surrounding blood vessels upon injury or inflammation. Many experiments have accumulated related data on the treatment of ASDs using MSCs with high plasticity. Actually, MSCs are in late phases of clinical trials for treatment of two immune dysregulation conditions of graft versus host disease (GVHD) and Crohn's Disease. Cord blood CD34+ cells are known to be potent angiogenic stimulators, having demonstrated positive effects in not only peripheral ischemia, but also in models of cerebral ischemia. Additionally, anecdotal clinical cases have reported responses in autistic children receiving cord blood CD34+ cells. Therefore, Ichim TE et al proposed that combined use of MSC and cord blood CD34+cells may be useful in the treatment of autism [1]. Lv Y T et al provides us a clinical evidence by a non-randomized, open-label, single center phase I/II trial investigating the safety and efficacy of combined transplantation of human cord blood mononuclear cells (CBMNCs) and umbilical cord-derived mesenchymal stem cells (UCMSCs) in treating children with autism [17]. They concluded that transplantation of CBMNCs demonstrated efficacy compared to the control group; however, the combination of CBMNCs and UCMSCs showed larger therapeutic effects than the using CBMNC alone. There were no safety issues noted during infusion and the whole monitoring period. Simberlund J et al suggested that MSC transplantation for the treatment of autism spectrum disorders is a novel approach that deserves further investigation, however substantial methodological and theoretical challenges and pitfalls remain before this can be considered a viable therapeutic option [18]. If MSCs can be fluently translated into clinical usage, the mechanism by which MSC modulate immune system should be firstly explored and clarified. Siniscalco D et al proposed the following MSC mechanism: stimulation of repair in the damaged tissue, e.g., inflammatory bowel disease; synthesizing and releasing anti-inflammatory cytokines and survival-promoting growth factors; integrating into existing neural and synaptic network, and restoring plasticity [19,20].

How does failure of neuro-immune dysfunction induce ASDs?

McDougle et al reviewed the evidence and the research results of immune mediated subtype of ASDs [21]. A role for immunological involvement in ASDs has long been hypothesized. Although Kanner (1943) did not specifically address this in his initial description of the syndrome, a detailed review of the original 11 patient cases reveals some potentially important and pertinent observations and comments. In 10 of the 11 case descriptions, clinical information was provided that could represent, in part, immune dysregulation. This is the earliest indication of correlation between immune and ASDs. The most important factor which mediates immune dysfunction to ASDs is microglia in the brain. Microglia are the tissue macrophages of the CNS and provide immune surveillance [22]. When neuronal injury occurs, microglia changes their morphology and turns into macrophage-like cells and mediate inflammation [23,24]. However, the multiple roles of microglia in maintaining brain health have been under appreciated until current research focusing on microglia appeared. Microglia have been wisely called 'the constant gardeners' of the brain for their roles in synaptic pruning [25]. Once considered as passive custodians until activated by foreign signals, a immense body of literature has emerged over the past years pointing to the critical roles of microglia in removing weak, damaged or dysfunctional synaptic connections to maintain healthy brain function. Since faulty synaptic pruning has been associated with ASDs, it was logical for investigators to begin to study the role of microglia in the neuronal pathobiology of ASDs [26-28]. Paul Patterson's laboratory first demonstrated that a maternal immune response induces autism-like behaviors in mouse offspring using maternal respiratory infection with influenza virus [29]. For safe and easy to use, preclinical models have utilized antigen mimics that effectively induce an innate immune response without infection. A well-established maternal immune activation (MIA) procedure involves administration of the viral mimic Poly I:C to pregnant mice during a critical period of fetal brain development. Poly I:C is a synthetic double-stranded RNA with high affinity for the pattern recognition receptor Toll-like Receptor 3 (TLR3), which induces an acute-phase immune response and closely resembles the systemic symptoms seen with acute viral infections [30]. MIA induces long-lasting and region-specific changes in brain cytokines in offspring, including alterations during peak periods of synaptogenesis and plasticity. Poly I:C enhances the production and release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α

and type I interferons IFN-alpha and IFN-beta [31-33]. Accordingly, a single maternal injection of the cytokine IL-6 causes some of the deficits observed in Poly I:C MIA offspring, while co-administration of an anti-IL-6 antibody with Poly I:C prevents these deficits [34], suggesting that IL-6 is critical in mediating some of the behavioral changes observed in Poly I:C MIA offspring. An extensive study of 23 cytokines in the blood and three brain regions (frontal cortex, cingulate cortex, and hippocampus) of Poly I:C MIA offspring demonstrated significant alterations in various pro-inflammatory, anti-inflammatory, and regulatory cytokines, as well as chemokines [35]. Taken together, these findings support the hypothesis that disruptions of cytokine signaling influence the behavioral and physiological abnormalities observed in MIA offspring. Therefore, effective intervention of immune dysfunctional ASDs should return to the immune modulation or anti-inflammation drugs or live cells, for example stem cells or in vitro adaptive immune cells.

The general mechanism through which MSCs interfere with ASDs

Site-activated MSCs produce a curtain of immuno-modulation behind which slow and specific tissue regeneration takes place. In addition, MSCs sense the tissue microenvironment and adjusts the curtain and regenerative activity accordingly. This includes the production of antibiotic proteins like LL37 that both kills intruding bacteria on contact, but calls forth macrophage and other members of the hematopoietic system to further medicate the injury site. Thus, MSCs appear to be local managers of the tissues' innate regenerative potential. In this way, MSC should denote "Medicinal Signaling Cells" since they serve as "drug stores" for sites of injury or inflammation [36]. Moreover MSCs 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 [37]. At the same time, MSC possess unique immunological properties including expression of major histocompatibility complex (MHC) class I molecules but not MHC class II molecules [38-41]. Therefore, they normally do not act as antigen presenting cells [42,43], 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 [44]. MSC have demonstrated complex immunomodulatory effects [45-48] on both humoral and cell mediated immune responses [49-53]. In the cell-mediated immune response [52,53] 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 [54-60]. MSC have also been found to inhibit natural killer (NK) cell proliferation, NK cell cytokine production and NK cell-mediated cytotoxicity through various mechanisms [60] still under investigation. In the humoral response, MSC inhibit B cell proliferation, maturation, migration, and immunoglobulin and antibody production [61,62]. 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 [63-65]. Furthermore, MSC have been found to block recruitment of neutrophils, likely protect neutrophils from apoptosis, and block production of TNF-a from activated macrophages [66,67]. 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 C57/BL6 (H2b) mice [68]. When MSC enter injured tissues, inflammatory triggers such as cytokines stimulate the release of many growth factors by MSC [37] including: epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-b), 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) [69-71]. These factors produced by MSCs can maintain endothelial integrity and regulate endothelial cell proliferation [37]. Inconsistently to the above reports about the MSC anti-inflammation function, Lee S H, et al demonstrated that MSCs combined with enzyme chondroitinase ABC (chABC) introduction into the spinal cord of chronic spinal cord injury dog models did not resulted in anti-inflammatory effects because of improved expression of pro-inflammatory cytokine factors such as COX2 and TNF-α [72]. This result may attribute to the degradation of chondroitin sulfate proteoglycans (CSPGs) by chABC, which may incur a second larger inflammation following the administration of MSCs and chABC beyond the inflammation modulation ability of MSCs.

The molecular mechanism in which MSCs affect ASD neuro-immune interaction for rescuing ASDs?

The growing body of literature suggests that the immune system might be dysregulated in individuals affected by autism spectrum disorder (ASDs) or their unaffected family members [73,74]. Studies of biological markers of immune function in individuals with ASDs have found neuro-inflammation in brain tissues [75-77], immunoglobulin imbalances, including increased levels of plasma IgG4 [78], reduced levels of IgG and IgM [79,80] or of total IgG [81]; imbalances in cytokine/chemokine levels [8,82-84], abnormal ratios of CD4+ to CD8+ T-cells or increased blood levels of nitric oxide metabolites [74]. Most importantly, various studies demonstrated a specific effect of MSC on microglia [85], which play a crucial role in ASDs. In experimental ALS, the number of microglia cells was significantly decreased in the spinal cord after administration of MSC [86]. Similar results were reported in a rat focal ischemia model of transient middle cerebral artery occlusion [87] and neonatal hypoxic-ischemic brain injury, where MSC reduced expansion of microglia and favoring the formation of new neurons. Consistently, our lab used human adipose derived stem cells (hADSCs), one type of mesenchymal stem cell isolated from adipose tissue, to treat C57/BL6 mouse middle of cerebral artery occlusion (MCAO) and Spinal Cord Injury (SCI) models, decreased ionized calcium-binding adapter molecule 1 (Iba1) positive and glial fibrillary acidic protein (GFAP) was observed indicating suppression the reactivation of microglia cells and astrocytes induced by inflammation [88-90]. In experimental Parkinson's disease, hMSC treatment significantly decreased lipopolysaccharide (LPS)-induced microglial activation [91,92]. One controversy still exists whether the immunosuppressive effect of MSC is a direct effect or requires activation via some specific cytokines or pathways [42, 43, 93, 94]. 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 systemMSC mediate the suppression of T cell proliferation via an indoleamine 2,3-dioxygenase (IDO) immunosuppressive pathway [57,95]MSC bring in two negative feedback loops in the very early phase of inflammation by secretion of prostaglandin (PGE2) and TNF-stimulated gene 6 protein (TSG-6) [53,60,96-98]. PGE2 is known to inhibit T cell proliferation, to affect apoptosis of T cells in either direction depending on the cell maturation and activation state [98], and influence the production of cytokines by T cells [98]. PGE2 is also known to induce and suppress B

cells depending on the maturity of the B cells. In addition, PGE2 can modulate the function of antigen presenting cells such as dendritic cells and macrophages [99]. In fact, PGE2 released by MSC can reprogram macrophages to produce more IL-10, inhibit dendritic cell maturation, and shift the balance between TH1 and TH2 [37,53,65,100]. TSG-6 is expressed at sites of inflammation and has been shown to reduce inflammatory damage through inhibiting neutrophil trans-endothelial migration induced by CXCL8- [101-104]. It is known that at the presence of PGE2, the effects of IDO in MSC-mediated immunoregulation of T-cell proliferation and NK cell activation can also be enhanced [60,94]. What should be pointed out is that, the above mechanisms might be species-specific [105]. The underlying mechanism of the immune modulation of MSC intervention with many diseases especially CNS ones has been broadly and deeply explored. The concise flow chart to explain the mechanism is drawn as below in Figure1.

Administration timing, dosage and delivery route of MSC affect the treatment effects of ASDs

Previous research on MSC intervention of ASDs seems efficient, attracts enomous pre-clinical and clinical trials and derserves deeper exploration. However, the pivotal factors that affect the outcomes are the window timing for cell delivery, the celll dosage, the method of cell delivery and the objective effect detection. MSC treating ASDs is an extremely complicated course in which MSCs interact with various endogenous cells such as T cells, B cells, macrophages, microglia cells, astrocytes, neurons, oligodendrocytes, etc. This process is automatic and time consuming. Thus, the time to detect the effects becomes ambiguous since there is absence of good parameters and experiences. In addition, different MSC delivery methods may incur totally different treatment effects. Basically, clinical trials adopt their cell delivery as intravenous injection. This method theoretically cans not recruite sufficient MSCs onto the damaged or affected region, leading to unsatisfied clinical outcomes. In situ injection seems harder to handle than intravenous delivery, however, it can make sure enough amounts of cells possibly localized in the affected region, which thus results in better clinical efficacy.

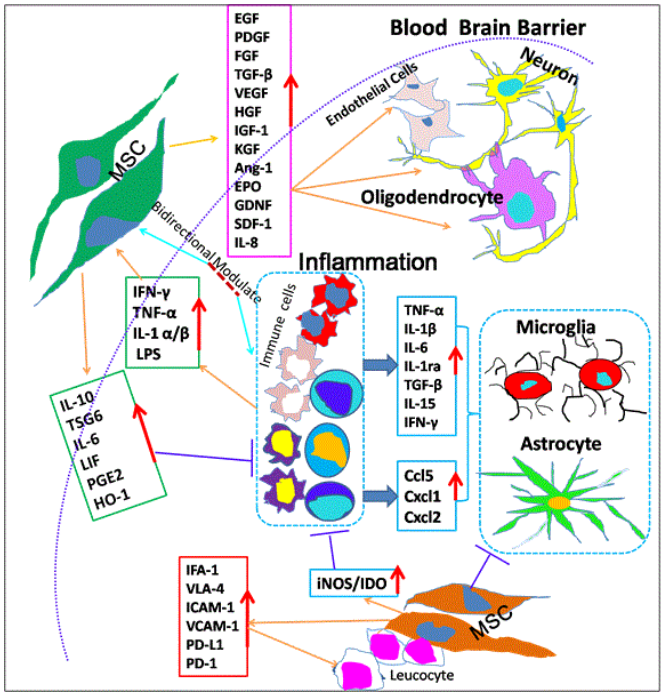

Figure 1: The network crosstalk by which MSC interfere with the host nerve immune system: (1) MSCs can supress the over reactivity of glia cells such as microglia and astrocytes through, cytokine secretion; (2) MSCs can directly manipulate the cytokine secretion profile of immune cells such as B cells, T cells, Neutrophil, Dendritic cells, leukocytes, etc.. At the same time, the cytokine secreted by the immune cells can modulate the function of MSCs; (3) MSCs can secrete some trophic factors to support the endogenous cells such as neurons, oligodendrocytes and endothelial cells recovery from injury shock. → means promote the downstream events, ⊣ means suppress the downstream events, ↑ means secretion upregulated, ↔ means bidirectional modulation.

The possible side-effects and ethical problems of MSC intervention with ASDs

Though previous enormous lab and clinical evidence has pointed to an important conclusion that MSC could be an alternative stem cell therapy source with bright future application especially in their positive immune modulation, there are still many uncertainties including the specific underlying mechanism, the side-effects, the delivery methods and window timing of MSC intervention, etc. One of the mostly concerned side-effect and biological safety problems is their

possible tumor formation ability of MSCs in vivo. To date, there is no tumor transformation ex vivo under proper expansion or tumorigenic potential in vivo published [106,107]. In our long-term (10 months) animal experimental observation, no tumor formation was found with hADSCs administration in NOD/SCID mice. The mice behaviors were significantly improved with no apparent toxicity side-effects. The Canadian Critical Care Trials Group has published a meta-analysis of randomized, non-randomized, controlled and uncontrolled, phase I and phase II clinical trials [108], besides, no correlation between autologous or allogeneic MSCs administration and tumor formation was previously reported in the 36 studies reviewed by them. Nonetheless, longer follow-up is required to draw a final conclusion regarding human MSCs' tumorigenic potential. One of the advantages of MSCs compared with other stem cells is their ethical previlege due to their autologous transplantation and possible allogeneic transplantation because of their low immunogenecity.

Conclusions and Future Research Directions

Taken together, dysfunction of neuro-immune interaction make up large percentage of ASDs. Active interference with chronic inflammation and immune modulation may be a good choice for ASDs treatment. MSCs can act as a perfect cell source candidate due to their allogeniec transplantation possibility, easy isolation and expansion, abundance in various mesenchymal tissues, multi-potential differentiation capacity, low immunogenicity and superior immune modulation. The mechanism of MSC rescuing ASDs has been excellently unravelled as mainly through close crosstalk with the host immune system such as suppression of reactive glia cells, manipulate the cytokine secretion profile by negative feedback loops, and secrete trophic factors to protect the endogenous cells from injured damages. The most important job to do in the future research is to evaluate the clinical safety, efficiency, correlation between cell dosage administrated and efficacy output as well as the deeper mechanism of MSCs for ASDs treatment and translate MSCs into treating various clinical immune related diseases or degenerative diseases.

References

1. Ichim TE, Solano F, Glenn E, Morales F, Smith L, et al. (2007) Stem cell therapy for autism. J Transl Med 5: 30.
2. Estes ML, McAllister AK (2015) Immune mediators in the brain and peripheral tissues in autism spectrum disorder. Nat Rev Neurosci 16: 469-486.
3. Goldani AA, Downs SR, Widjaja F, Lawton B, Hendren RL (2014) Biomarkers in autism. Front Psychiatry 5: 100.
4. Kipnis J, Gadani S, Derecki NC (2012) Pro-cognitive properties of T cells. Nat Rev Immunol 12: 663-669.
5. Walsh JT, Watson N, Kipnis J (2014) T cells in the central nervous system: Messengers of destruction or purveyors of protection? Immunology 141: 340-344.
6. Walsh JT, Hendrix S, Boato F, Smirnov I, Zheng J, et al. (2015) MHCII-independent CD4+ T cells protect injured CNS neurons via IL-4. J Clin Invest 125: 2547.
7. Walsh JT, Zheng J, Smirnov I, Lorenz U, Tung K, et al. (2014) Regulatory T cells in central nervous system injury: a double-edged sword. J Immunol 193: 5013-5022.
8. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah IN, et al. (2011) Altered T cell responses in children with autism. Brain Behav Immun 25: 840-849.
9. Ashwood P, Corbett BA, Kantor A, Schulman H, Van de Water J, et al. (2011) In search of cellular immunophenotypes in the blood of children with autism. PLoS One 6: e19299.
10. Ashwood P, Van de Water J (2004) A review of autism and the immune response. Clin Dev Immunol 11: 165-174.
11. Gupta S, Ellis SE, Ashar FN, Moes A, Bader JS, et al. (2014) Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. Nat Commun 5: 5748.
12. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP (1968) Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation 6: 230-247.
13. Friedenstein AJ, Chailakhjan RK, Lalykina KS (1970) The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet 3: 393-403.
14. Caplan AI (1991) Mesenchymal stem cells. J Orthop Res 9: 641-650.
15. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, et al. (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8: 315-317.
16. Gesundheit B, Ashwood P, Keating A, Naor D, Melamed M, et al. (2015) Therapeutic properties of mesenchymal stem cells for autism spectrum disorders. Med Hypotheses 84: 169-177.
17. Lv YT, Zhang Y, Liu M, Qiuwaxi JN, Ashwood P, et al. (2013) Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. J Transl Med 11: 196.
18. Simberlund J, Ferretti CJ, Hollander E (2015) Mesenchymal stem cells in autism spectrum and neurodevelopmental disorders: Pitfalls and potential promises. World J Biol Psychiatry .
19. Siniscalco D, Bradstreet JJ, Sych N, Antonucci N (2014) Mesenchymal stem cells in treating autism: Novel insights. World J Stem Cells 6: 173-178.
20. Siniscalco D, Sapone A, Cirillo A, Giordano C, Maione S, et al. (2012) Autism spectrum disorders: Is mesenchymal stem cell personalized therapy the future? J Biomed Biotechnol 2012: 480289.
21. McDougle CJ, Landino SM, Vahabzadeh A, O'Rourke J, Zurcher NR, et al. (2015) Toward an immune-mediated subtype of autism spectrum disorder. Brain Res 1617: 72-92.
22. Aguzzi A, Barres BA, Bennett ML (2013) Microglia: scapegoat, saboteur, or something else? Science 339: 156-161.
23. Banati RB (2002) Visualising microglial activation in vivo. Glia 40: 206-217.
24. Banati RB (2003) Neuropathological imaging: in vivo detection of glial activation as a measure of disease and adaptive change in the brain. Br Med Bull 65: 121-131.
25. Hughes V (2012) Microglia: The constant gardeners. Nature 485: 570-572.
26. Kettenmann H, Kirchhoff F, Verkhratsky A (2013) Microglia: new roles for the synaptic stripper. Neuron 77: 10-18.
27. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, et al. (2012) Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74: 691-705.
28. Rodriguez JI, Kern JK (2011) Evidence of microglial activation in autism and its possible role in brain under connectivity. Neuron Glia Biol 7: 205-213.
29. Shi L, Smith SE, Malkova N, Tse D, Su Y, et al. (2009) Activation of the maternal immune system alters cerebellar development in the offspring. Brain Behav Immun 23: 116-123.
30. Traynor TR, Majde JA, Bohnet SG, Krueger JM (2004) Intratracheal double-stranded RNA plus interferon-gamma: A model for analysis of the acute phase response to respiratory viral infections. Life Sci 74: 2563-2576.
31. Kimura M, Toth LA, Agostini H, Cady AB, Majde JA, et al. (1994) Comparison of acute phase responses induced in rabbits by lipopolysaccharide and double-stranded RNA. Am J Physiol 267: R1596-1605.
32. Meyer U, Nyffeler M, Engler A, Urwyler A, Schedlowski M, et al. (2006) The time of prenatal immune challenge determines the specificity of

inflammation-mediated brain and behavioral pathology. J Neurosci 26: 4752-4762.

33. Meyer U, Murray PJ, Urwyler A, Yee BK, Schedlowski M, et al. (2008) Adult behavioral and pharmacological dysfunctions following disruption of the fetal brain balance between pro-inflammatory and IL-10-mediated anti-inflammatory signaling. Mol Psychiatry 13: 208-221.
34. Smith SE, Li J, Garbett K, Mirnics K, Patterson PH (2007) Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 27: 10695-10702.
35. Garay PA, Hsiao EY, Patterson PH, McAllister AK (2013) Maternal immune activation causes age- and region-specific changes in brain cytokines in offspring throughout development. Brain Behav Immun 31: 54-68.
36. Caplan AI, Sorrell JM (2015) The MSC curtain that stops the immune system. Immunol Lett.
37. Ma S, Xie N, Li W, Yuan B, Shi Y, et al. (2014) Immunobiology of mesenchymal stem cells. Cell Death Differ 21: 216-225.
38. Fu X, Li H (2009) Mesenchymal stem cells and skin wound repair and regeneration: Possibilities and questions. Cell Tissue Res 335: 317-321.
39. Ilancheran S, Moodley Y, Manuelpillai U (2009) Human fetal membranes: a source of stem cells for tissue regeneration and repair? Placenta 30:2-10.
40. Trivedi P, Hematti P (2008) Derivation and immunological characterization of mesenchymal stromal cells from human embryonic stem cells. Exp Hematol 36: 350-359.
41. Zhang W (2008) Mesenchymal stem cells in cancer: friends or foes. Cancer Biol Ther 7: 252-254.
42. Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC (2003) Suppression of allogeneic T-cell proliferation by human marrow stromal cells: Implications in transplantation. Transplantation 75: 389-397.
43. Krampera M, Glennie S, Dyson J, Scott D, Laylor R, et al. (2003) Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood 101: 3722-3729.
44. Murphy MB, Moncivais K, Caplan AI (2013) Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 45: e54.
45. Fibbe WE, Nauta AJ, Roelofs H (2007) Modulation of immune responses by mesenchymal stem cells. Ann N Y Acad Sci 1106: 272-278.
46. Zhao S, Wehner R, Bornhäuser M, Wassmuth R, Bachmann M, et al. (2010) Immunomodulatory properties of mesenchymal stromal cells and their therapeutic consequences for immune-mediated disorders. Stem Cells Dev 19: 607-614.
47. Le Blanc K, Tammik L, Sundberg B, Haynesworth SE, Ringden O (2003) Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand J Immunol 57: 11-20.
48. Maccario R, Podesta M, Moretta A, Cometa A, Comoli P, et al. (2005) 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 90: 516-525.
49. Tyndall A, Walker UA, Cope A, Dazzi F, De Bari C, et al. (2007) 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 9: 301.
50. Deng W, Han Q, Liao L, You S, Deng H, et al. (2005) Effects of allogeneic bone marrow-derived mesenchymal stem cells on T and B lymphocytes from BXSB mice. DNA Cell Biol 24: 458-463.
51. Beyth S, Borovsky Z, Mevorach D, Liebergall M, Gazit Z, et al. (2005) Human mesenchymal stem cells alter antigen-presenting cell maturation and induce T-cell unresponsiveness. Blood 105: 2214-2219.
52. Augello A, Tasso R, Negrini SM, Amateis A, Indiveri F, et al. (2005) Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway. Eur J Immunol 35: 1482-1490.
53. Aggarwal S, Pittenger MF (2005) Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 105: 1815-1822.
54. Nasef A, Chapel A, Mazurier C, Bouchet S, Lopez M, et al. (2007) 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 13: 217-226.
55. English K, Barry FP, Field-Corbett CP, Mahon BP (2007) IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells. Immunol Lett 110: 91-100.
56. Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, et al. (2007) Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood 109: 228-234.
57. Meisel R, Zibert A, Laryea M, Gobel U, Daubener W, et al. (2004) Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation. Blood 103: 4619-4621.
58. Du J, Zhou L, Chen X, Yan S, Ke M, et al. (2012) IFN-gamma-primed human bone marrow mesenchymal stem cells induce tumor cell apoptosis in vitro via tumor necrosis factor-related apoptosis-inducing ligand. Int J Biochem Cell Biol 44: 1305-1314.
59. Plumas J, Chaperot L, Richard MJ, Molens JP, Bensa JC, et al. (2005) Mesenchymal stem cells induce apoptosis of activated T cells. Leukemia 19: 1597-1604.
60. Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, et al. (2008) Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: Role of indoleamine 2,3-dioxygenase and prostaglandin E2. Blood 111: 1327-1333.
61. Asari S, Itakura S, Ferreri K, Liu CP, Kuroda Y, et al. (2009) Mesenchymal stem cells suppress B-cell terminal differentiation. Exp Hematol 37: 604-615.
62. Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, et al. (2006) Human mesenchymal stem cells modulate B-cell functions. Blood 107: 367-372.
63. Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, et al. (2007) Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation 83: 71-76.
64. Djouad F, Charbonnier LM, Bouffi C, Louis-Plence P, Bony C, et al. (2007) Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism. Stem Cells 25: 2025-2032.
65. Spaggiari GM, Abdelrazik H, Becchetti F, Moretta L (2009) 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 113: 6576-6583.
66. Ortiz LA, Dutreil M, Fattman C, Pandey AC, Torres G, et al. (2007) Interleukin 1 receptor antagonist mediates the anti-inflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. Proc Natl Acad Sci USA 104: 11002-11007.
67. Raffaghello L, Bianchi G, Bertolotto M, Montecucco F, Busca A, et al. (2008) Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche. Stem Cells 26: 151-162.
68. Lim JH, Kim JS, Yoon IH, Shin JS, Nam HY, et al. (2010) Immunomodulation of delayed-type hypersensitivity responses by mesenchymal stem cells is associated with bystander T cell apoptosis in the draining lymph node. J Immunol 185: 4022-4029.
69. Shi Y, Su J, Roberts AI, Shou P, Rabson AB, et al. (2012) How mesenchymal stem cells interact with tissue immune responses. Trends Immunol 33: 136-143.
70. Shi Y, Hu G, Su J, Li W, Chen Q, et al. (2010) Mesenchymal stem cells: a new strategy for immunosuppression and tissue repair. Cell Res 20: 510-518.

71. Ma XL, Liu KD, Li FC, Jiang XM, Jiang L, et al. (2013) Human mesenchymal stem cells increases expression of Î±-tubulin and angiopoietin 1 and 2 in focal cerebral ischemia and reperfusion. Curr Neurovasc Res 10: 103-111.
72. Lee SH1, Kim Y1, Rhew D1, Kuk M1, Kim M1, et al. (2015) Effect of the combination of mesenchymal stromal cells and chondroitinase ABC on chronic spinal cord injury. See comment in PubMed Commons below Cytotherapy 17: 1374-1383.
73. Goines PE, Ashwood P (2013) Cytokine dysregulation in autism spectrum disorders (ASD): Possible role of the environment. Neurotoxicol Teratol 36: 67-81.
74. Krause I, He XS, Gershwin ME, Shoenfeld Y (2002) Brief report: immune factors in autism: a critical review. J Autism Dev Disord 32: 337-345.
75. Li X, Chauhan A, Sheikh AM, Patil S, Chauhan V, et al. (2009) Elevated immune response in the brain of autistic patients. J Neuroimmunol 207: 111-116.
76. Pardo CA, Vargas DL, Zimmerman AW (2005) Immunity, neuroglia and neuroinflammation in autism. Int Rev Psychiatry 17: 485-495.
77. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 57: 67-81.
78. Enstrom AM, Lit L, Onore CE, Gregg JP, Hansen RL (2009) Altered gene expression and function of peripheral blood natural killer cells in children with autism. Brain Behav Immun 2009 23: 124-133.
79. Heuer L, Ashwood P, Schauer J, Goines P, Krakowiak P, et al. (2008) Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Res 1: 275-283.
80. Heuer LS, Rose M, Ashwood P, Van de Water J (2012) Decreased levels of total immunoglobulin in children with autism are not a result of B cell dysfunction. J Neuroimmunol 251: 94-102.
81. Grether JK, Croen LA, Anderson MC, Nelson KB, Yolken RH (2010) Neonatally measured immunoglobulins and risk of autism. Autism Res 3: 323-332.
82. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, et al. (2011) Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain Behav Immun 25: 40-45.
83. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah IN, et al. (2011) Associations of impaired behaviors with elevated plasma chemokines in autism spectrum disorders. J Neuroimmunol 232: 196-199.
84. Suzuki K, Matsuzaki H, Iwata K, Kameno Y, Shimmura C, et al. (2011) Plasma cytokine profiles in subjects with high-functioning autism spectrum disorders. PLoS One 6: e20470.
85. Giunti D, Parodi B, Usai C, Vergani L, Casazza S, et al. (2012) Mesenchymal stem cells shape microglia effector functions through the release of CX3CL1. Stem Cells 30: 2044-2053.
86. Uccelli A, Milanese M, Principato MC, Morando S, Bonifacino T, et al. (2012) Intravenous mesenchymal stem cells improve survival and motor function in experimental amyotrophic lateral sclerosis. Mol Med 18: 794-804.
87. Sheikh AM, Nagai A, Wakabayashi K, Narantuya D, Kobayashi S, et al. (2011) Mesenchymal stem cell transplantation modulates neuroinflammation in focal cerebral ischemia: contribution of fractalkine and IL-5. Neurobiol Dis 41: 717-724.
88. Zhou F, Gao S, Wang L, Sun C, Chen L, et al. (2015) Human adipose-derived stem cells partially rescue the stroke syndromes by promoting spatial learning and memory in mouse middle cerebral artery occlusion model. Stem Cell Res Ther 6: 92.
89. Zhou F, Gao S, Sun C, Cao L, Ren H, et al. (2014) Adipose-derived stem cells in stroke treatment: translational possibility and mechanism. Chin Med J (Engl) 127: 3657-3663.
90. Gao S, Zhao P, Lin C, Sun Y, Wang Y, et al. (2014) Differentiation of human adipose-derived stem cells into neuron-like cells which are compatible with photocurable three-dimensional scaffolds. Tissue Eng Part A 20: 1271-1284.
91. Van Velthoven CT, Kavelaars A, van Bel F, Heijnen CJ (2010) Mesenchymal stem cell treatment after neonatal hypoxic-ischemic brain injury improves behavioral outcome and induces neuronal and oligodendrocyte regeneration. Brain Behav Immun 24: 387-393.
92. Kim YJ, Park HJ, Lee G, Bang OY, Ahn YH, et al. (2009) Neuroprotective effects of human mesenchymal stem cells on dopaminergic neurons through anti-inflammatory action. Glia 57: 13-23.
93. Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, et al. (2002) Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 99: 3838-3843.
94. Ren G, Zhang L, Zhao X, Xu G, Zhang Y, et al. (2008) Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell 2: 141-150.
95. Hwu P, Du MX, Lapointe R, Do M, Taylor MW, et al. (2000) Indoleamine 2,3-dioxygenase production by human dendritic cells results in the inhibition of T cell proliferation. J Immunol 164: 3596-3599.
96. Nauta AJ, Fibbe WE (2007) Immunomodulatory properties of mesenchymal stromal cells. Blood 110: 3499-3506.
97. Prockop DJ (2013) Concise review: two negative feedback loops place mesenchymal stem/stromal cells at the center of early regulators of inflammation. Stem Cells 31: 2042-2046.
98. Harris SG, Padilla J, Koumas L, Ray D, Phipps RP (2002) Prostaglandins as modulators of immunity. Trends Immunol 23: 144-150.
99. Breece E, Paciotti B, Nordahl CW, Ozonoff S, Van de Water JA, 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 31: 69-75.
100. Nemeth K, Mezey E (2015) Bone marrow stromal cells as immunomodulators. A primer for dermatologists. J Dermatol Sci 77: 11-20.
101. Dyer DP, Thomson JM, Hermant A, Jowitt TA, Handel TM, et al. (2014) TSG-6 inhibits neutrophil migration via direct interaction with the chemokine CXCL8. J Immunol 192: 2177-2185.
102. Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, et al. (2009) 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 5: 54-63.
103. Oh JY, Roddy GW, Choi H, Lee RH, Ylöstalo JH, et al. (2010) Anti-inflammatory protein TSG-6 reduces inflammatory damage to the cornea following chemical and mechanical injury. Proc Natl Acad Sci U S A 107: 16875-16880.
104. Choi H, Lee RH, Bazhanov N, Oh JY, Prockop DJ (2011) Anti-inflammatory protein TSG-6 secreted by activated MSCs attenuates zymosan-induced mouse peritonitis by decreasing TLR2/NF-Î°B signaling in resident macrophages. Blood 118: 330-338.
105. Ren G, Su J, Zhang L, Zhao X, Ling W, et al. (2009) Species variation in the mechanisms of mesenchymal stem cell-mediated immunosuppression. Stem Cells 27: 1954-1962.
106. Arango-Rodriguez ML, Ezquer F, Ezquer M, Conget P (2015) Could cancer and infection be adverse effects of mesenchymal stromal cell therapy? World J Stem Cells 7:408-417.
107. Rubio D, Garcia S, De la Cueva T, Paz MF, Lloyd AC, et al. (2008) Human mesenchymal stem cell transformation is associated with a mesenchymal-epithelial transition. Exp Cell Res 314: 691-698.
108. Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, et al. (2012) Canadian Critical Care Trials G: Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. PLoS One 7:e47559.