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# Therapeutic properties of mesenchymal stem cells for autism spectrum disorders

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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.

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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