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Stem Cell Research 2018-A Review of the Placenta and Trophoblast Induced Pluripotent Stem Cells in Autism Spectrum Disorder Research- Sona Jasani- Rutgers Robert Wood Johnson Medical School

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Abstract

Autism Spectrum Disorder (ASD) imposes a huge health burden with psychological, social and economic implications. The biology of ASD is complex involving genetic, molecular, hormonal and immunological factors, but the point of convergence of these different factors has not yet been identified. Limited evidence exists to suggest that the placenta may play such a leading role in the manifestation of ASD. The placenta is a neuroendocrine modulator by participating in the hypothalamic axis hypothalamic gonadal pituitary gland (HPG) and also regulates the intrauterine environment attenuating fetal exposure to damaging factors to modulate the response to fetal stress. Placental dysfunction has been associated with developmental abnormalities and neuropsychiatric pathology adding to the biological plausibility of the guiding role that the placenta can play in the development of ASD. Using current technology such as Induced Pluripotent Stem Cells (iPSC), a practical model system can be created to study ASD, providing an alternative method for further research on the placenta in the development of ASD.

Introduction

Autism Spectrum Disorder (ASD) is a huge health burden and a huge research effort into the etiology has been done. Although a large body of research has identified candidate genes, gene networks and possible molecular pathways, the underlying regulation of these steps is currently unknown. The expansion of research on ASD to include environmental exposures and perinatal factors has not identified a point of convergence for these different actors. Neurobiological results suggest that the pathophysiology of ASD may arise during fetal development. Given these data, a plausible focal point appears to be the placenta, which is known to regulate good fetal development in utero. The placenta could therefore be considered as the last common path in the development of ASD fusing the relevant genetic, structural and environmental factors that have an impact on the development of the fetal brain. Targeting the placenta and trophoblast to understand the complex biology of ASD may therefore be a more effective strategy to guide basic, translational and clinical scientific research. A challenge that exists in the pursuit of ASD research is the lack of a standard model system for studying the etiology of the disorder. Most autism research is based on retrospective studies, biological samples taken from autistic adults or post-mortem brain autopsies. Although useful for identifying biomarkers in autistic individuals, it is difficult to prove causation rather than simple correlation. These methods have been found to have limitations that reduce their effectiveness in developing a complete model of ASD. Induced pluripotent stem cell (iPSC) technology can advance current research on ASD by providing a way around the limitations associated with traditional research paradigms. Recreation of placental tissue from individuals diagnosed with ASD can be achieved by converting cryopreserved peripheral blood cells to iPSC and then inducing differentiation into the types of hormone-secreting trophoblastic cells. The cellular characteristics of autistic patients can be reflected in such experimental systems, the technology provides a solution to tissue availability and prolonged cryopreservation of placental tissue. The use of iPSCs can identify cellular and genetic pathways related to ASD and can elucidate the epigenetic and synergistic effects of the environment and the stress on these pathways in the placenta. A tissue culture model is capable of measuring the cellular response to various stimuli, including pro-inflammatory

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cytokines, infectious agents, pesticides and oxidative stress, all of which can be administered in the trophoblastic culture system. The iPSC-trophoblast model is therefore ideal for research by creating precursor placental stem cells to examine the role of trophoblasts and placenta in the integration of genetic, hormonal, environmental and perinatal contributors to autism. This article summarizes the limited existing data supporting the placental convergence hypothesis. We review the biology and pathophysiology of the placenta with regard to neuropsychiatric findings highlighting the development and function of trophoblasts with respect to neuromodulation and brain morphology, demonstrating the placental role in regulating the neurodevelopmental environment and explaining the differential expression of the placental genes involved in neuromodulation. We review existing data discussing the resulting pathology that occurs from placental deregulation in other organ systems to support the idea of biological plausibility of placental function in the formation of ASD. We also briefly review the clinically relevant data regarding the placental role in programming the response to fetal stress and maternal immune activation. Finally, we review the study of iPSCs in ASD research and suggest that iPSCs can also help establish causal data to support the role of the placenta in the emergence of ASDs. If iPSCs are also used to help examine differential gene expression, the model system could contribute to efforts to potentially reverse the ASD phenotype.

Conclusion

Efforts have been made to diagnose ASD as soon as possible [104], in part because the burden of the disease is extraordinary. In a cost-of-illness analysis, ASD is expected to account for up to 3.6% of GDP in 2025, exceeding the burden of stroke and hypertension [105,106]. Many research methods have been explored to meet this clinical challenge without much success. Placental contributions to neurobehavioral development disorders have been largely overlooked until recently. The placenta is a neuromodulator which influences the morphology of the brain, regulates the environment for proper development and brain function, influences the response to fetal stress and maternal immune activation. It is part of the HPG and HPA axes through its hormonal secretions and its dysfunction has been associated with clinically relevant neuropathological results. The use of iPSC technology can advance the placental origin of the theory of autism and provide new diagnostic and therapeutic markers for treatment. The re-conceptualization of ASD research involves understanding that the placental abnormality is a characteristic of ASD and that the use of iPSC technology can examine the exact genetic, biochemical and environmental factors that cause the development of ASD.

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