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Originally published by the Stem Cell Network November 2013

Autism

Research is a dynamic activity that creates new ideas. It provides a forum for generating observations and testing why they occur. Because people and their diseases are so diverse, clinical trials are the ONLY WAY it is possible to test whether new ideas about how to diagnose or treat human disease will work. But the process of taking research from bench to bedside is a lengthy one and demands not only vision but also years of teamwork and dedication on the part of scientists, physicians and patients. This document presents basic information about autism and frames the context for the discussion that follows about how stem cells could be used to better understand and eventually treat autism spectrum disorders. Readers may also wish to peruse additional web resources or speak with their physicians for more information about autism.

About Autism and Autism Spectrum Disorders

Autism describes a spectrum of neurodevelopmental disorders negatively affecting brain development and causing life-long deficits in communication, social and behavioural skills. Children with autism appear normal at birth but symptoms typically start to appear within the first 36 months, with boys being four times more susceptible than girls. Because there is no cure for autism, the burden to the individual, caregivers and health care system is enormous. Early identification is very important and screening from birth to 36 months is highly recommended because interventions and services administered at this early age can help mitigate ongoing symptoms.

Diagnosis

There is no single test to detect autism. Parents often embark on a 'diagnostic odyssey' while health professionals utilize a gamut of tests such as physical examinations, personal histories, clinical assessment tools, and genetic testing, if warranted, to make a positive diagnosis. This is no simple task, however, because tremendous variation has been a consistent theme among patients even from the earliest description of autism, attributed to American psychiatrist Leo Kanner in 1943. In his 10-year observational study, Kanner described 'autistic disturbances' in 11 children (eight boys and three girls). Although the children shared "essential common characteristics" in terms of their "inability to relate to themselves", their preference for "autistic aloneness" and "their insistence on sameness", there was considerable variation from child to child in terms of the severity of the problem and how it developed over time.

Since Kanner's day, innumerable professionals have studied autistic children and contributed towards honing the criteria for making a diagnosis. But because the continuum of symptoms and level of functioning continue to vary so widely, it has been challenging for health professionals across different centres to make a consistent diagnosis for different autism-related disorders. Today, clinicians use the Diagnostic and Statistical Manual of Mental Disorders (DSM) to guide clinical decisions, and the newest version, the DSM-5 (updated from the DSM-IV) creates a unified autism spectrum disorder (ASD) designation under which four related disorders apply: autistic disorder (also known as classical autism), its milder form called Asperger's disorder, childhood disintegrative disorder (CDD, also known as Heller's disease) and pervasive developmental disorder not otherwise specified (PDD-NOS). The prior classification of Rett syndrome as an ASD was changed to account for the fact that it may or may not be present with ASD.

Based on the DSM-5, a positive diagnosis of ASD requires patients to demonstrate a core number of symptoms involving types of social/communication and restrictive and repetitive behaviours. Autism Canada organizes the myriad symptoms of ASD under the headings of impaired communication, lack of awareness, abnormal seeking of comfort when distressed, impaired imitation skills, abnormal toy play, inability to form friendships, dependence on routine, abnormal responses to sensory stimulation, behavioural problems, variability of intellectual functioning, uneven development profile, difficulties in sleeping, immune irregularities and gastrointestinal problems. Despite the many weak-

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nesses exhibited by individuals with ASD, they may also possess unusual skills for their age in categories of reasoning, reading, movement, drawing, computers, memory, visual/spatial cognition and music.

As the new DSM-5 guidelines are integrated across the medical community, there will be ongoing evaluation to study whether they can meet the intended goal of improving diagnostic accuracy and consistency of diagnoses across medical, educational and social communities without compromising either services to autistic patients or the ability to combine data from previous clinical trials.

Causes

The precise cause of ASD remains somewhat of a mystery but mounting evidence points to both genetic and environmental components. The role for genetics is indisputable: more than 50% of identified mutations are de novo (meaning that they are present in a family member for the first time) but there is also a high risk of inheriting ASD (37 – 90%). Various chromosomal abnormalities have been identified, and a number of single gene disorders (e.g. Rett syndrome and fragile X) share symptoms with ASD. In addition, scientists have identified hundreds of ASD-linked genes that they predict confer susceptibility to ASD.

Researchers are striving to understand how ASD-linked genes might work. Some are known to produce proteins that are part of the machinery at neural synapses, contributing to the development of normal synaptic networks in the brain during embryonic development. Others are known to play critical roles in the function of the immune system signaling, activation and regulation. One theory as to what might go awry in ASD is that when such genes are over-active at the wrong time and place during embryonic development, the forming neural circuitry is compromised, contributing to abnormal brain development. As researchers continue to identify the functional effect of these genes, one of the greatest challenges is to understand how they give rise to such a broad spectrum of symptoms in different individuals. To answer some of these questions, scientists are drawing on newer technologies such as comprehensive space/time maps of gene expression, microarrays and next generation sequencing.

Despite all the evidence for a genetic contribution to ASD, genetic abnormalities cannot be attributed to all cases, leaving many individuals bereft of a specific cause for developing ASD. To make matters more complex, none of the single genetic defects identified to date appears to contribute to more than 1% of ASD, and no single gene is associated only with ASD and not also with other intellectual disabilities and developmental conditions. Recent twin studies have shown that environmental factors are also important and researchers are investigating the role of toxins, infectious agents, imbalances in the immune system via activation, autoimmunity, neuroinflammation, allergy, and deregulation of the blood brain barrier. Untangling the complex web of genetic and environmental interactions that predispose individuals to ASD is a far from a simple task but one that the research community continues to actively explore.

Treatment

Treatments for autism fall under the category of behavioural, nutritional and pharmacological. Behavioural interventions and social skill training appear to provide the most benefit but they are not able to correct all the symptoms experienced by patients with ASD. As yet, there are no effective drugs but physicians prescribe stimulants, anticonvulsants, antipsychotics, or antidepressants in an attempt to address the symptoms. As the number of potential alternative therapies grows (herbal remedies, vitamins, minerals, diet, dietary supplements, acupuncture, sensory training), the medical system is seeking to evaluate and understand their usefulness. Because effective therapies are clearly lacking, some researchers have decided to focus on stem cells to ask if they are able to contribute in any way.

How can stem cells help with understanding ASD?

The use of stem cells as a therapy for autism is still many years away. At present, the focus of research is on understanding the disease; primarily on developing stem cell based models of ASD and autism-related disorders as drug screening platforms. Scientists are also investigating how the immune system and inflammation are involved in the development of ASD, and assessing whether stem cells could help play an anti-inflammatory role by modulating the immune system in patients.

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Research and clinical directions

Modeling disease using stem cells

The possibility of modeling autism in a dish is exciting because to date there are no good human models of the disease. Mouse models for autism-related disorders have some benefits, but they are still not able to capture all the complexities of human biology. In addition, interspecies differences have been proven to exist such that genetic conditions that are known to contribute to autism in humans do not have the same effect in mice. Creating good human models of autism is clearly a priority for the field, but finding a source of neurons for in vitro models has been difficult as it is not possible to remove neurons from a living person with autism and neurons in post-mortem tissue are not viable.

With the advent of induced pluripotent stem cells, researchers now have a potential approach that can address these challenges. The creation of induced pluripotent stem cells in 2006 was nothing short of revolutionary: its discoverer, Dr. Shinya Yamanaka was awarded the Nobel Prize in Medicine or Physiology (along with Dr. John Gurdon) in 2012. Yamanaka managed to turn back the clock on adult skin cells and reprogram them to a younger, embryonic-like state. The cells are called 'pluripotent' because they are no longer locked into making only one cell type but instead can produce a variety of different cell types. (In Latin, 'pluripotent' means 'very many' and 'having power'.) In the seven short years since the technology was first developed, scientists now have methods in place for differentiating iPS cells in the laboratory from skin into a variety of variety of specialized cells, including brain, heart and blood cells.

The direct clinical application of neurons made from iPS technology is still many years away but in the meantime scientists are putting this technology to good use by creating banks of disease-specific iPS cell lines (from mice and humans) to study the phenotypic changes of disease and as drug screening platforms. As yet there are few published accounts of iPS cell lines made from ASD patients. One research team accomplished this by using skin cells from the hair shaft of patients with a specific mutation (SHANK3) associated with ASD. Another group made ASD-specific iPS cells derived from lymphocytes collected in the peripheral blood of patients with ASD – and then went on to grow them into neurons that could produce the important neurotransmitter called GABA (gamma amino butyric acid). As the number of ASD-specific iPS lines grow, researchers will be working out the conditions to differentiate them into various populations of neurons so that they can study changes at the neuronal level that describe ASD.

Scientists are also learning about ASD by making iPS lines derived from people who display autistic characteristics, as is the case for Rett syndrome, Fragile X, and Timothy syndrome. Screening candidate drugs against these lines is underway and has already yielded some interesting results. For example, in the case of Rett syndrome, where the mutated MeCP2 gene causes neurological impairment and synaptic deficiencies in the majority of patients, the defect in iPS derived neurons (specifically, small neuron size and reduced number of synaptic protrusions) could be corrected with the addition of a growth factor called IGF-1. The results from one small clinical trial testing the safety of administering IGF-1 in six girls with Rett syndrome have shown that IGF-1 is well tolerated, with no major or permanent adverse effects. Although three of the six girls reported benefits in motor abilities, larger, more stratified trials will be needed to judge the safety and effectiveness of this therapy.

There are many challenges yet to overcome in using iPS technology to model ASD, not least of which will be the arduous process of characterizing ASD phenotypes in disease specific lines given the tremendous heterogeneity among patients. Although studying disease in dish precludes the ability to study behavioural complexities, the iPS technology nevertheless provides scientists with a powerful new tool to study genetic and biological underpinnings of ASD, and to dissect the altered pathways and cellular characteristics that are unique to autism-related disorders.

Modulating inflammation using stem cells

Various immunological disorders are known to be associated with autism, including immune deficiencies, autoimmunity, allergy, and over-activation of certain immune cell populations such as mast cells, T cells and macrophages.

However, the precise mechanism of immune involvement in the development of autism is not clear. One theory is that early inflammation, possibly even starting in the womb, might be an important contributing factor.

There are ongoing efforts to assess whether stem cells could play a role in mitigating inflammation in people with ASD. Because there is clear evidence that hematopoietic stem cells and cord blood stem cells can do this in other diseases and because the extent of debilitation shouldered by patients with ASD is so high, it is tempting to rush forward

with clinical trials, piggybacking on the reputation of these stem cells to modulate the immune system and treat various blood disorders and cancers. However, researchers and clinicians are proceeding with caution and agree that the most important next steps should be to better understand the mechanisms underlying the function of stem cells and the biology of ASD, and to mine that information to create better models in which to test various stem cells and drug therapies for benefits prior to translating the information into safe clinical trials.

Web Resources

Readers may wish to peruse the recommended sites or review the selected reading list below for more information about the application of stem cells to treat autism.

- Autism Fact Sheets: http://www.ninds.nih.gov/disorders/autism/detail_autism.htm
- Autism Canada: http://www.autismcanada.org/
- Autism Ontario: http://www.autismontario.com/
- Autism Speaks Canada: http://www.autismspeaks.ca/

Selected Reading List

- Autism Spectrum Disorder, 2013 American Psychiatric Association http://www.dsm5.org/Documents/Autism%20Spectrum%20Disorder%20Fact%20Sheet.pdf.
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