Rett Syndrome

Exciting new treatment strategies for Rett Syndrome: What we are learning from mouse models.

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Rett Syndrome is a neurodevelopmental disorder, almost exclusively affecting females, and results from mutations in an X-linked gene (found on the X-chromosome), methyl CpG-binding protein 2 (*MECP2; Xq28*)[1]. Rett syndrome is thought to originate from *de novo* mutations, meaning that neither parent carry the mutation, and occurs in approximately 1/10,000 female births[2].

First described in the 1960s and with discovery of the genetic cause in 2001, sadly few treatment options are available. Moreover, those that are currently available only focus on ameliorating the symptoms, which include growth defects, stereotypic hand wringing, gastrointestinal disorders, seizures and bone defects (scoliosis), among many others. Wheelchair bound, and most often non-verbal, Rett Syndrome patients require round-the-clock care, causing significant burden to both their families, and the health care system.

Fortunately, work by a number of researchers, predominantly using specialised mouse models, is beginning to uncover new and exciting treatment possibilities for this debilitating syndrome.

In 2007, researchers made the exciting discovery that replacing the mutated gene in adulthood ablated many of the symptoms of Rett Syndrome[3]. In the first study of its type, researchers used a specialised mouse model to explore the effect of switching the gene back on, effectively making a Rett Syndrome mouse "normal" again. To their surprise, they were able to show a reversal of the neurological defects seen in the mouse, and restored health. This particularly exciting rectification provided renewed hope for Rett Syndrome sufferers and their families, that symptom reversal was a real possibility for in these patients. Whilst the complex mouse genetics used to achieve this reversal is not possible in humans, the proof-of-concept that the syndrome could be reversed was exciting for the field.

Perhaps more-excitingly, in 2012 a group from University of Virginia (USA) demonstrated that a bone marrow transplant (similar to that used in humans with leukaemia) was able to treat symptoms in mice including improving breathing, walking (gait) and growth[4]. Transplantation of bone marrow from a healthy mouse into a mouse with Rett Syndrome resulted in healthy cells migrating into the brain, taking on a "microglial phenotype" (behaving like normal brain-derived white blood cells) which arrested the development of the disease. While it is necessary to explore the underlying mechanism behind the success of the bone-marrow transfer, this type of treatment proposes a very exciting possibility for future treatment strategies.

Most recently, a team at Baylor College of Medicine (USA) have identified a simple and effective treatment for Rett Syndrome, in mice using Statin drugs, the same drugs used to treat high cholesterol in millions of people world-wide[5]. Using yet another complex mouse genetic model, researchers were able to identify that there was a defect in the production of cholesterol in Rett Syndrome, a novel finding. Using genetics to manipulate the levels of cholesterol production, researchers were able to reduce the severity of the disease in mice, including motor function (walking; gait), and significantly increase lifespan. Building on this finding, researchers used the

statin class of cholesterol-lowering drugs, to reduce cholesterol, significantly improve symptoms and extend the lifespan of mice with Rett Syndrome. While the underlying cause of high-cholesterol in Rett Syndrome remains elusive, a therapy as simple as a drug currently approved for treatment of high cholesterol, poses perhaps the most exciting finding yet in the Rett field.

While we are not able to genetically modify humans to treat Rett Syndrome, and the effectiveness, efficacy and ethical responsibilities all need to be considered before translating any of these treatments into patients with Rett Syndrome, it would appear that the future remains bright. Exciting research lead by exceptional teams of researchers are leading the way for the treatment of the underlying causes of Rett Syndrome, rather than management of the symptoms, which will likely be able to be translated throughout the field of neurodegenerative research.

NB: Work by Buckovecky et al (2013) is currently under embargo pending publication in Nature Genetics. CI Brown is a co-author on the publication. Publication of this manuscript is expected to be complete by August 2013.

References

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