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Review

MeCP2 Mutation and Rett Syndrome

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ABSTRACT

Methyl-CpG-binding protein 2 (MeCP2) is a gene important for brain function and is one of the most common causes in RTT (Rett syndrome) cases to encode a protein with the same name. This condition, which is more common in females and rare in men, is caused by the X chromosome and manifests itself as mental retardation. RTT develops normally in girls during their first 6 to 18 months of infancy, but the disease's symptoms spread over time. After a period, most RTT patients lose their mobility and are more prone to acquire Parkinson's disease (PD) as they age. RTT does not have a cure, although its symptoms can be controlled. The link of RTT with the MeCP2 gene as a significant neurological condition, as well as numerous treatment techniques explored, were discussed in this article.

Keywords: Methyl-CpG-binding protein2, MeCP2E1, MeCP2E2, nervous system, Rett syndrome.

MeCP2 (MeTHYL-CPG-BINDING PROTEIN 2)

Methyl CpG binding protein 2 is a gene important for brain functions. MeCP2, a protein with the same name that is prevalent in neurons but expressed in different amounts in human tissue, is encoded by this gene.[1,2] This protein is a chromosomal protein that can bind methylated DNA via a methyl binding domain (MBD).[3-6] It has been found in the brain that the distribution and levels of MeCP2 are different. Recent studies have shown the distribution of MeCP2 in different regions of the mouse brain, particularly in the olfactory bulb, cortex, striatum, hippocampus, thalamus, cerebellum, and brain stem. The highest expression of MeCP2 was observed in the cortex and cerebellum with the analysis of all cell samples taken from these regions. Analysis of core extracts from the same brain regions also showed relatively equal levels of MeCP2E1 and different levels of MeCP2E2.[7,8] The expression of MeCP2, except for neurons, was also found in astrocytes, oligodendrocytes, and microglia.[7-12] Methyl-CpG-binding protein 2 has been found to be sensitive to substances like cocaine, ethanol, and methamphetamine.[13-16]

Methyl-CpG-binding protein2 expression is linked to central nervous system (CNS) postnatal maturation and neuronal differentiation, and it is thought to play a role in CNS maintenance and function.[17] Methyl-CpG-binding protein 2 contains a lot of basic amino acids such lysine, arginine, proline, and serine. Methyl-CpG-binding protein 2 is a proximal gene silencer with two functional domains: a methyl DNA binding domain (MBD) and a transcription repression domain (TRD), according to its description. Deacetylation of core histones is caused by interactions between this transcription repressor complex and chromatin-bound MeCP2, resulting in transcription suppression.[18,19]

MeTHYL-CPG-BINDING PROTEIN 2 PHOSPHORYLATION IN THE BRAIN

This gene can be present in all vertebrates, but not in fruit flies or earthworms, which are invertebrate

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genetic model animals. To better understand the onset and severity of clinical symptoms, mouse models were used.[20,21] The researchers discovered a unique area on the MeCP2 protein termed serine-421 (S421) that acts as a trigger to activate MeCP2 during its regular function in mice trials. In response to neuronal activity, MeCP2 is activated by a process known as phosphorylation. Because MeCP2 selectively phosphorylates exclusively in the S421 region of the brain, mutations in the brain that impact the S421 region target brain development.[22]

THE IMPACT OF METHYL-CPG-BINDING PROTEIN 2 ON OTHER GENES AND ITS RELATIONSHIP TO RETT SYNDROME (RTT)

Researchers previously believed that the RTT gene was a "shut down" switch or a suppressor for other genes, however it has recently been shown that it is an "open" key for a startling number of genes. When the copy number of the MeCP2 gene is changed in mice, it influences the expression of many other genes, inhibiting some but activating many.[23] The MeCP2 gene regulates downstream too many genes, mutations or copying in this gene cause a change in the expression of genes in this downward direction. When the extra copy of MeCP2 is deleted, these gene expression differences are likewise normalized.[3]

Mutations in MeCP2 account for 90% of typical RTT cases. CDKL5 and FOXG1 genes constitute 10% of the mutations that cause RTT. Autism spectrum disorder (ASD), intellectual disability, and lupus erythematosus (SLE) have all been linked to MeCP2 mutations (butterfly disease).[24-29] This gene is linked to the X chromosome, and mutations in these genes, which are important for the proper functioning of neurons in the brain, cause RTT and affect one in 10,000 newborn girls. As a result, women with two X chromosomes are far more likely than men to develop RTT.[22,30] For this reason, it is striking that X-chromosome inactivation (XCI) is an interesting subject. XCI causes the brain to have an irregular expression of naturally type and mutant MeCP2 alleles. Although the obtained results seem complicated of the X-chromosome inactivation models (either skewed or random, whether the mutant allele is of paternal or maternal origin) was determined by these groups to be associated with RTT phenotypes.[31-33] Additional factors, such as epigenetic mechanisms and environmental modifiers, including other MeCP2-related genes, are thought to have an impact on RTT clinical severity because the association between XCI and clinical severity of RTT is unknown.[34,35] For the first six to 18 months of life, girls with RTT develop normally, but later lose motor skills and speech. By the age of four, irregular breathing and heart rhythm, as well as autistic-like symptoms, appear to be widespread.[22,30] Currently, there is no effective treatment for this disease, but its symptoms can be controlled.[36]

PROGNOSIS OF RETT SYNDROME AND BEHAVIORAL FEATURES

Most RTT phenotypes are associated with the brain and nervous system. It has been observed that the volume of specific brain regions, such as the cerebellum and cortex, is reduced in patients with RTT.[37-39]

The two main neurons in the brain are excitatory neurons that send signals to other neurons, and they are inhibitory neurons that control the activity of other neurons to control the timing and speed of information received. For the correct and controlled functioning of the brain, these neurons must behave in balance with one another; otherwise, defects may result in neurological illnesses. In an experiment in mice, it was observed that expressing MeCP2 only in inhibitory neurons extended lifespan and resolved most behavioral problems. In a second study published in this publication, it was discovered that removing MeCP2 from solely excitatory neurons in mice triggered multiple Rett-like symptoms mediated by inhibitory neurons.[40] With the onset of developmental stagnation, acquired microcephaly is accompanied by general growth retardation, weight loss, and a poor posture brought on by muscle hypotonia, the muscle's resistance to movement. Irritability, social isolation, and a loss of language become more noticeable. The expressionless face is also associated with hypersensitivity to sound, lack of eye contact, apathy for the environment, and autistic characteristics.[41] Loss of motor coordination, ataxia, and the development of gait apraxia, or gait dysfunction, accompany the onset of mental impairment. Generally, RTT girls experience shortness of respiration and discomfort with respiratory abnormalities as a result of narrowing or obstruction of the upper respiratory tract during sleep such as breathing, aerophagia and another example of apnea.[42,43] The shortening of life expectancy and the increase in sudden death rates of people with this disorder have

been associated with cardiac dysrhythmias, that is, deterioration of heart rhythm.[44] The incidence of seizures ranging from readily controlled to den intractable epilepsy is one of the most difficult aspects of RTT, and the most prevalent varieties are partial complex and tonic-clonic seizures.[43]

Seizures tend to decrease in severity after adolescence and adulthood, and problems begin to appear after the patient is forty. Despite having a normal appetite, RTT patients continue to lose weight, and as they become older, they become uncomfortable with significant spinal curvature, such as osteopenia (a loss of bone density) and scoliosis. Behavioral abnormalities at this stage include braking teeth, laughing or crying at night, seizures of scream, low moods and anxiety episodes resulting in nuisance.[45-47]

In their teenage years, the majority of RTT patients lose their mobility and become wheelchair-dependent, with an increased risk of getting PD at the same time.[48,49]

Early truncating mutations caused poor prognosis and late truncating and missense mutations caused classic RTT or preserved speech variant (PSV), and they have a later age when compared to the classic form.[50] As mention in a research, RTT has resulted in the classification of new RTT variant groups from the lower end of the phenotypic range spectrum to the more severe end. The classic and atypical RTT phenotypes differentiate in terms of onset and severity over time between different patients, even in the same patient.[50-52]

While it was once considered that RTT mainly affected women, this belief was disproved when men with classic RTT were identified.[53] In men, MeCP2 mutation was found to cause a range of neurological diseases from mental retardation to severe encephalopathy and typically caused neonatal encephalopathy and death in the first year of life.[54-57] RTT patient's emotions and behaviors undergo considerable shifts and abnormalities.[47,58,59] In these patients, an individual’s emotional state may be exacerbated by the observed physical challenges, for example, epileptic seizures, or crises, can cause an emotional increase and can lead to anxiety or tension.[59-61] They also believe that people's emotions and behaviors have evolved over time.[62] Behavioural disorders, increased stereotypes, constant shaking, itching, self-harm, or agitation can be manifested. Several studies have shown that sleep problems and emotional and behavioural disorders such as screaming in the early stages of RTT may be linked to the emergence of mental disability and diminish over time.[63-66]

TREATMENTS FOR RETT SYNDROME

There is no known cure for RTT. It has been demonstrated that certain traits can be rescued in RTT mice models, providing hope to RTT patients.[67] Because of the scarcity of patients, it is difficult to investigate such complex disorders and improve treatment.[68] It is critical to determine the associative features of RTT so that they may be measured in clinical studies. Despite the fact that no conclusions are perfect, it would be beneficial to develop better tools for RTT intervention attempts. The development of the comprehensive web-based HealthTracker™ Rett evaluation of symptoms and treatments (REST) survey is a significant step forward in this field with objective measurements, such as biometric data.[69] A strategy of gene silencing, the treatment of antisense oligonucleotide (ASO) has been taken to be tested by the Zoghbi laboratory. Using it as a DNA template to produce an RNA molecule during transcription is the first of two crucial steps in protein production, transcription and translation. Second, an RNA molecule is formed when a protein is gathered and transported to a ribosome. ASO's synthetic nucleic acids bind to the RNA molecule and prevent it from reaching a ribosome, halting translation. In a study, ASO was injected directly into the brain using tiny osmotic pumps over a period of 4 weeks. Symptoms began to fade ten weeks after treatment began, and when treatment was terminated and MeCP2 protein levels rose, symptoms reverted.[3]

Depending on the mutation, the degree of X chromosome inactivation, and the presence of regulatory genes, the MeCP2 gene could change. Because RTT affects numerous organ systems, it was suggested that patients' healing should include a therapeutic combination, which is an important point to consider. Desipramine, a norepinephrine reuptake inhibitor, alleviated respiratory abnormalities and apnea in MeCP2 mutant mice, but clinical trials in RTT patients treated with this medicine have not shown clinical development. Sarisotan, a serotonin1A agonist and dopamine D2 similar receptor, reduced respiratory apnea in MeCP2 mutant mice by 15-30% while having no effect on motor activity.[70-73]

Gene therapy can also be used to transfer a normal copy of MeCP2 to cells as a treatment for RTT. This technique offered hope for the treatment of a wide range of illnesses. For example, on mouse models of hemophilia, Hunter's syndrome, diabetes, obesity, and more, successful results have been obtained in reversing symptoms.[74] Several therapy strategies for RTT are being developed, but none of them save the entire spectrum of RTT phenotypes. The researchers discovered that putting MeCP2 into RTT mice models can help them restore their phenotypic.[74]

DISCUSSION-CONCLUSION

Rett syndrome is more prevalent in women, however it has been discovered that it can happen to men with a low risk. It has been observed that RTT patients generally increase their symptoms and discomfort as they get older. The MeCP2 gene mutation is a major factor in this illness. The expression of MeCP2 occurs in the brain, and it is of great importance in certain cell types of the brain. A notable step forward in this sector is the creation of a thorough REST survey. Rett syndrome symptoms can be regulated in mice, however there is no clear evidence on whether this will be decisive or effective in humans.

It is critical to understand that all of the treatments discussed in this study are effective for adult RTT patients. The next goal will be to turn the knowledge from animal models into human beings. Differences between mouse and human will challenge these studies and the translation of information.

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