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Mecp2: An Important Role in the Pathogenesis of RETT Syndrome

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Abstract: RETT syndrome is an X-chromosome-linked neurodevelopmental disorder mainly affecting female children, and its pathogenesis is mainly related to mutations in the Mecp2. In recent years, the role of Mecp2 in neurodevelopment and its relationship with RETT syndrome has become a hot research topic. Current research is focused on the effects of Mecp2 mutations on neuronal function and neural circuits, as well as exploring potential therapeutic approaches in animal models. Despite the results achieved, there are still gaps in the understanding of the precise molecular mechanisms of the Mecp2, gender specificity and the role of non-coding RNAs. This paper analyzed the role of Mecp2 in neurodevelopment and its relationship with Rett syndrome, and explored the molecular mechanisms and potential therapeutic strategies for Mecp2 mutations. It was found that Mecp2 mutations lead to neurological dysfunction by affecting neuronal differentiation and synaptic plasticity. In addition, this paper evaluates the current prospects for gene therapy, noting that adeno-associated viral vectors (AAV) have shown favorable therapeutic effects in animal experiments. This paper provides new insights into understanding the pathogenic mechanism of the Mecp2 in RETT syndrome and provides an important reference for future therapeutic strategies. However, the precise molecular mechanism of the Mecp2 and its gender-specific differences still need further investigation. Future studies could focus on developing safer and more effective gene therapies and exploring the role of non-coding RNAs in RETT syndrome with a view to achieving more comprehensive therapeutic strategies.

Keywords: Mecp2, RETT Syndrome, Neurodevelopmental Disorder, Epigenetics.

1. Introduction

RETT is an X-chromosomes-linked neurodevelopmental disorder that occurs predominantly in female children, with an incidence of approximately 1 in 10000 to 1 in 150001. The clinical features of typical RETT include normal growth and development between 6 and 18 months of age, followed by neurodevelopmental arrest or regression, loss of acquired manual and language skills, autistic behavior, respiratory abnormalities, and skeletal changes. The symptoms include autistic behavior, respiratory abnormalities, and skeletal changes. The main cause of RETT syndrome is a mutation in the Mecp2 located on the X chromosome, which encodes a protein called methylation-binding protein 2 that inhibits the expression of the other genes [1]. The Mecp2 encodes an important transcriptional regulator. Mecp2 plays a crucial role in brain development and maintaining neuronal health, among other things. When the Mecp2 is mutated, its function of regulating the expression of the other genes

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is lost, resulting in the expression of genes that are supposed to be suppressed by Mecp2 at the wrong time and the wrong place, thus causing abnormalities in neurological function. In addition, a small number of patients may also be associated with mutations in other genes, such as CDKL5, FOXG1 and the other genes.

Regarding the important role of the Mecp2 in the pathogenesis of RETT syndrome, a large number of studies have shown that more than 200 mutations in Mecp2 are associated with RETT syndrome, and that mutations in the Mecp2 lead to degradation or even loss of function of the Mecp2 protein, which in turn affects neuronal health and even brain development. By knocking out the relevant genes in mice and the other related research tools, researchers will be able to better understand Mecp2 function, mutation mechanism and its molecular mechanism, and then better understand the RETT syndrome and research related therapeutic strategies [2]. Nevertheless, there are still relevant gaps in its study, including the precise molecular mechanism of Mecp2, gender specificity, the role of non-coding RNA, the influence of environmental factors, neuroplasticity and repair. Filling these gaps in the Mecp2 research filed will help scientists to understand and treat RETT syndrome well. and will also help to advance biology.

The Mecp2 is significant not only for the study of the emergence of RETT syndrome, but also for the research of other more human neurodevelopmental disorders. Thus, studying the mechanism of the Mecp2 and its effects on the central nervous system, contributes to development of new strategies for the treatment of the RETT syndrome and also provides new insights into other neurodevelopmental disorders. In addition, because the Mecp2 is located on the X chromosome, the study of Mecp2 also contributes to a deeper understanding of sex-specific genetic diseases. Therefore, the study of the important role of the Mecp2 in the pathogenesis of RETT syndrome not only has a direct contribution to the development of medicine, but also has potential value for the expansion of basic science.

This paper systematically reviews the literature over the past five years to analyze the critical role of the Mecp2 in neurodevelopment and its molecular mechanisms, particularly in relation to RETT syndrome. It examines the correlation between Mecp2 mutations and the syndrome, evaluates current therapeutic approaches, and explores future prospects. The goal is to provide a comprehensive summary of Mecp2's impact on RETT syndrome pathogenesis, offering researchers a broader perspective to advance the field and facilitate more effective treatments.

2. RETT Syndrome

2.1. RETT Syndrome and the Central Nervous System

RETT Syndrome is a neurological disorder caused by mutations in the X-linked gene Mecp2, which severely affects the psychomotor development of female children, and is an important factor affecting the intellectual disability of female children, and the etiology of which is closely related to the central nervous system [3]. RETT syndrome is closely related to the central nervous system and is characterized by abnormal development and functional decline of neurons in the brain, leading to loss of language, motor and social interaction skills; it is accompanied by motor coordination deficits and problems with emotional regulation, which are associated with damage to functional areas of the brain such as the motor cortex, the limbic system, and the prefrontal cortex, respectively, and disturbances in respiratory rhythms that are associated with dysfunctions of the brainstem.

2.2. Clinical Manifestations of RETT Syndrome

The clinical presentation of RETT Syndrome is characterized by distinct stages and changes with age.

In the early stages of RETT syndrome (6 to 18 months after birth), the child's development slows down significantly, with dull eyes, reduced learning ability and lagging development of motor skills.

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As the child enters the first to fourth year of life, stereotyped hand movements occur, leading to loss of hand function, abnormal breathing, unsteady walking, and marked mood swings. In the third stage, loss of hand function, motor deficits, and seizures worsen, and overall health deteriorates despite improvement in autism-like behaviors. In stage 4 (usually after 10 years of age), dystonia and scoliosis are present, and mobility is significantly reduced, with possible dependence on a wheelchair [2]. These distinct stages of RETT Syndrome illustrate the progressive nature of the disorder, highlighting the critical need for early intervention and ongoing support to manage symptoms and improve quality of life.

3. Relationship between Mecp2 and RETT Syndrome

3.1. Introduction of Mecp2 Location and Coding Product

The Mecp2 is located in the q28 region of the X chromosome, with a total gene length of 76kb, containing the 5'UTR, four exons, and the 3'UTR. The Mecp2 has several distinguishing features, including a large intron 2 that is up to 60kb long, a 3'UTR region that is up to 8.5kb long, and spacing from the upstream genes of up to 40kb. The Mecp2 produces two isoforms, Mecp2e1 and Mecp2e2, through different shearing modes, and although their functional differences have not been clarified, studies have shown that both exhibit the same localization in the nucleus and may overlap in function [4].

The Mecp2 protein encoded by Mecp2 belongs to the family of Mecps with methylated CpG-binding domains (MBD) and transcriptional repressor domains (TRD). Mecp2 recognizes methylated CpG dinucleotides located in the promoter region of genes by interacting with methylated DNA, which in turn recruits the transcriptional repressor Sin3A and histone deacetylase to form a transcription-repression complex that represses downstream gene expression [5]. repressor complex to inhibit downstream gene expression. In addition, Mecp2 can exert transcriptional repression independently of DNA methylation and interact with RNA to participate in the composition of RNA-protein complexes.

3.2. Functions of Mecp2 under Physiological Conditions

Under physiological conditions, as a transcriptional regulator (TF) with dual functions of transcriptional activation and repression, the Mecp2 protein is able to bind methylated DNA and, through its transcriptional The Mecp2 protein, as a TF with transcriptional activation and repression functions, can specifically bind methylated DNA and through its TRD, recruit multiple transcription factors to jointly repress transcription of methylated gene promoters. Meanwhile, the phosphorylation status of Mecp2 protein also affects its transcriptional activity, and the phosphorylated Mecp2 protein is able to recruit transcriptional activation proteins, such as CREB, to promote the transcriptional initiation of related genes.

During the development of the nervous system, Mecp2 protein is involved in neuronal differentiation, maturation and circuit formation. It promotes the aggregation of chromatin centers and thus participates in the establishment of chromatin structure in mature neurons. Meanwhile, Mecp2 protein also affects the function and stability of the nervous system by regulating the synaptic plasticity of neurons, including long duration potentiation (LTP) and long term depression (LTD) [6]. In adulthood, Mecp2 protein is a key factor in maintaining neuronal function by maintaining chromatin structure and regulating the neuronal transcriptome to ensure normal neuronal function. In addition, Mecp2s remain on standby for stimulus-dependent gene transcription, i.e., the arrival of a stimulus promotes Mecp2 dissociation and leads to the initiation of transcription of the gene in question, regulating cognitive function in this way.

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3.3. Role of Mecp2 in Neural Development

During early embryonic development, Mecp2 plays a central role in regulating neuronal differentiation by finely regulating the neuronal maturation process and promoting the formation of complex circuit structures between neurons. During this process, Mecp2 is not only involved in neuronal differentiation, but also promotes the aggregation of chromatin centers, which provides important support for the establishment of chromatin structures in mature neurons.

Upon entering adulthood, the function of Mecp2 did not diminish, but instead became a key factor in maintaining neuronal function. It continues to maintain the stability of the chromatin structure and finely regulates the transcriptome of neurons, ensuring that neurons are able to transmit and process information properly. Notably, Mecp2 has a specific role in regulating the transcription of stimulus-dependent genes. It puts these genes on standby, and once externally stimulated, it can rapidly respond and initiate the transcription process of the relevant genes, thus realizing the flexible regulation of cognitive functions [7].

3.4. Mutation of Mecp2

Mecp2 has various forms of mutations, mainly including point mutations, repeat mutations and deletion mutations. Point mutations refer to the substitution of a base at a specific position on the Mecp2, resulting in a change in the encoded amino acid. Such changes may directly affect the structure and function of the Mecp2 protein, which in turn interferes with its interactions with other molecules, and affects the normal development and function of nerve cells [8]. Duplication mutations, on the other hand, are duplications of some or all sequences of the Mecp2, leading to an abnormal increase in the expression of Mecp2 protein, and this excessive accumulation may interfere with the normal process of neural development and negatively affect the normal function of neurons. In contrast, deletion mutations, in which some or all of the sequences of the Mecp2 are missing, lead to a decrease or complete loss of Mecp2 protein expression, and such mutations may lead to the inability of neurons to develop and maintain their functions normally, which may in turn lead to a series of neurological developmental disorders [9].

The relationship between Mecp2 mutations and RETT syndrome is complex and diverse. The type of mutation is closely related to the clinical phenotype, and different types of mutations may lead to different degrees of clinical symptoms. Mutation location also significantly affects function, with different regions of the Mecp2 being responsible for different functions, e.g., mutations in the DNA-binding and transcriptional repressor domains affect MeCP2's DNA binding and transcriptional repression functions, respectively, leading to different clinical phenotypes, including differences in motor, language, and social skills. In addition, although mutations in the Mecp2 are the primary cause of RETT syndrome, genetic background and environmental factors also influence the severity of symptoms and developmental trajectory of patients.

3.5. Mecp2 Epigenetics

Regulation of the Mecp2 is a multifaceted process involving DNA methylation, histone modification, the role of noncoding RNAs, and chromatin remodeling. DNA methylation plays a key role in CpG islands, and the hypermethylated state leads to gene silencing by attracting Mecp2 proteins and repressor complexes, whereas hypomethylation promotes gene expression [10]. Histones affect gene activity by altering chromatin structure through modifications such as acetylation and methylation, with acetylation usually associated with activation and specific methylation marks with repression [11]. Non-coding RNAs, including microRNAs and long-stranded non-coding RNAs, regulate Mecp2 expression by binding to mRNAs or altering chromatin structure. Chromatin remodeling complexes affect gene accessibility and transcriptional activity by adjusting the position and

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composition of nucleosomes. In addition, non-coding RNAs, including microRNAs (miRNAs) and long-chain non-coding RNAs (lncRNAs), can also regulate the stability and translational efficiency of Mecp2 mRNAs, either directly or indirectly. Together, these epigenetic mechanisms act to finely regulate the expression level of the Mecp2, and any dysregulation may lead to neurodevelopmental disorders such as RETT syndrome. Therefore, understanding the epigenetic regulation of Mecp2 is crucial to unraveling the pathogenesis of RETT syndrome and finding potential therapeutic strategies.

3.6. Regulation of Genes Upstream and Downstream of Mecp2

Mecp2 is a protein that occupies a central position in epigenetic regulation, acting as a bridge between DNA methylation and the regulation of gene expression. Mecp2 specifically recognizes and binds to methylation sites on DNA molecules, which are usually located on CpG islands, and is important for the maintenance of genome stability and the regulation of gene expression. important for maintaining genome stability and regulating gene expression [12].

Upstream, Mecp2 regulates the transcription of CpG promoter-rich genes in neurons by directly interacting with RNA polymerase II, involving more than 4,000 genes, including genes associated with autism risk, and extends its regulatory network by affecting microRNA processing through modulation of the DGCR8/Drosha complex. Downstream, Mecp2 affects neuronal development by regulating gene expression through the recognition of hydroxymethylated CA repeat sequences. Inactivation of Mecp2 function leads to RETT syndrome, which causes widespread gene expression changes and chromatin structural abnormalities leading to neurodevelopmental abnormalities, such as mental retardation, motor deficits, and autism-like behaviors.

In addition, Mecp2 is involved in multiple signaling pathways (e.g., Wnt/β-catenin, Notch, and mTOR) that work together to maintain normal development and function of the nervous system. When Mecp2 is mutated, this complex regulatory network is disrupted, leading to Rett syndrome.

4. Molecular Mechanisms Mediated by Mecp2

4.1. How Mecp2 Affects Neuronal Plasticity and Function

Mecp2 is a key protein that is widely expressed in the nucleus of mammalian cells, and its main function is to regulate gene expression by binding to methylated CpG islands on DNA and thus regulating gene expression. This regulatory role has profound implications for neuronal plasticity and function.

Mecp2 plays a crucial role in neuronal plasticity. Synaptic plasticity is a key component of neuronal plasticity, which determines the efficiency and accuracy of information transfer between neurons, and Mecp2 regulates synaptic plasticity by modulating the expression of BDNF (Brain Derived Neurotrophic Factor), which affects the functional balance between excitatory and inhibitory synapses. In addition, deletion or mutation of Mecp2 leads to abnormalities in neuronal morphology and connectivity, such as impaired maturation of dendritic spines and abnormalities in the frequency of excitatory postsynaptic currents (mEPSCs), all of which affect the normal function of neurons and information transmission [13].

Mecp2 also plays an important role in neuronal function. It can directly interact with RNA polymerase II, thereby regulating the gene transcription process in human neurons and affecting gene expression levels. This regulatory role is essential for maintaining normal neuronal function and electrical activity. For example, in the striatum, Mecp2 affects the overall function of neurons by regulating dopamine levels and the electrical activity of neurons, which in turn affects the overall function of neurons [14]. In addition, Mecp2 is involved in the regulation of stimulus-dependent gene transcription, which is important for maintaining neuronal cognitive function.

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4.2. Role of Non-coding RNAs and Other Regulators

Mecp2 plays a key role in the regulation of gene expression, as it can either repress gene expression by binding to DNA methylation sites and recruiting transcriptional repression complexes, or interact with other transcription factors to activate gene transcription. In addition, non-coding RNAs (e.g. miRNAs, lncRNAs, and circRNAs) are also involved in this regulatory process, and they can indirectly regulate gene expression by modulating Mecp2 expression, affecting chromatin structure, or acting as sponges for miRNAs [15]. Meanwhile, transcription factors and epigenetic modifying enzymes (e.g., DNA methyltransferases and HDAC) also interact with Mecp2 to co-regulate gene expression [16]. These complex interactions constitute a multilevel regulatory network that enables cells to precisely respond to environmental changes and maintain normal physiological functions, and also provides new ideas for the treatment of related diseases.

5. Molecular Mechanisms Mediated by Mecp2

5.1. Exploration of New Therapies Based on Mecp2 Mechanism

The exploration of new therapies based on the Mecp2 mechanism mainly includes gene therapy, protein replacement therapy, modulation of downstream signaling pathways, non-coding RNA regulation, neuroprotective and supportive therapies, cell transplantation and regenerative medicine, as well as environmental interventions and behavioral therapies [17]. These new therapies aim to bring new hope to the treatment of RETT by repairing or replacing mutated Mecp2s, regulating related signaling pathways, protecting neural cell function, and improving the development and quality of life of patients.

5.2. Current Status of Gene Therapy

Gene therapy for RETT syndrome is a potential treatment for neurodevelopmental disorders caused by mutations in the Mecp2 [18]. The core concept is to correct or replace the mutated Mecp2 in order to restore normal Mecp2 protein function, thereby improving the patient's neurodevelopment, motor skills, cognitive abilities and behavioral problems. However, there are many challenges to achieving this goal, including how to effectively deliver gene vectors to target cells in the brain, avoiding immune reactions and potential side effects, and ensuring the safety and stability of the treatment.

In this context, AVVs have shown great potential as an efficient and safe gene delivery tool for gene therapy in RETT syndrome. AVVs are particularly suitable for targeting the nervous system due to their broad host range, ease of modification, and efficient delivery. In particular, AAV9-Mecp2 therapy, which delivers normal Mecp2 copies into neurons in the brain by using AVV9 vectors, has achieved remarkable results in animal experiments, including improved motor function and cognitive behavior [19].

Overall, AVV vectors provide new ideas and approaches for the treatment of RETT syndrome. Although it is still in the research and trial stage, the positive effects it has shown in animal experiments and preliminary clinical trials are encouraging. In the future, with further research and technological advances, it is believed that this therapy is expected to become one of the standard treatment options for patients with RETT syndrome.

6. Conclusion

This paper systematically reviews the critical role of the Mecp2 in neurodevelopment and its association with RETT, an X-chromosome-linked neurodevelopmental disorder primarily affecting female children, characterized by neurodevelopmental arrest or regression, loss of language and

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motor skills, autistic behaviors, respiratory anomalies, and skeletal changes that occur after early normal development. Mutations in the Mecp2 result in loss of function of the Mecp2 protein, which in turn triggers a dysregulation of gene expression leading to neurological dysfunction.

The results presented herein indicate that Mecp2 represses downstream gene expression under physiological conditions by binding methylated DNA and recruiting transcriptional repression complexes, and also participates in RNA composition, exerting transcriptional repression independent of DNA methylation. During neural development, Mecp2 maintains neuronal function by regulating neuronal differentiation and maturation, synaptic plasticity, and chromatin structure. Mutations in Mecp2 come in various forms, including point, duplication, and deletion mutations, and different types of mutations may lead to different clinical symptoms.

The study herein provides an important scientific basis for understanding the pathogenesis of RETT syndrome and offers new ideas for future therapeutic strategies. However, further studies are still needed to fill the gaps in Mecp2 research, including its precise molecular mechanisms, sex specificity, the role of non-coding RNAs, the effects of environmental factors, and neuroplasticity and repair. Future studies should aim to gain a deeper understanding of the role of Mecp2 in neurodevelopment and develop more effective therapeutic strategies to improve the quality of life of patients with RETT syndrome.

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