Chapter 6

MECP2 Gene Dysfunction and Emerging Molecular Therapeutics Strategies in Rett Syndrome

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Abstract

Rett Syndrome is a rare X-linked neurodevelopmental disorder that primarily affects females and is mainly caused by mutations in the MECP2 gene. The disorder results in neurological regression, loss of speech and motor skills, seizures, and cognitive impairment. The MECP2 gene plays a crucial role in regulating gene expression and maintaining normal neuronal function. However, recent advances in molecular biology have introduced new therapeutic approaches such as AAV-mediated gene therapy, CRISPR-based gene editing, RNA editing, and MECP2 reactivation strategies. These emerging therapies aim to restore normal gene function and may provide promising disease-modifying treatments for Rett syndrome in the future. This chapter explores the molecular mechanisms of MECP2 dysfunction and highlights current and emerging therapeutic strategies with potential to transform the management of Rett syndrome.

Keywords: Rett Syndrome; MECP2 Gene Mutation;

Neurodevelopmental Disorder; Neuronal Dysfunction; Gene Therapy;

1. Introduction

Rett Syndrome is a rare X-linked dominant neurodevelopmental disorder that primarily affects females and is characterized by severe cognitive and motor impairments. The disorder typically appears after a period of apparently normal early development, followed by progressive neurological regression, loss of acquired speech, impaired motor coordination, and stereotypic hand movements [1]. Rett syndrome is considered one of the most common genetic causes of severe intellectual disability in girls.

The disorder is mainly caused by mutations in the MECP2 (methyl-CpG-binding protein 2) gene located on the X chromosome. The MECP2 gene encodes a protein that plays an essential role in epigenetic regulation of gene expression and neuronal development. Dysfunction of this gene disrupts transcriptional regulation and neuronal communication, ultimately leading to the neurological symptoms observed in affected individuals [2,3].

Recent advances in molecular genetics and neuroscience have significantly improved the understanding of the mechanisms underlying MECP2 dysfunction. These discoveries have also contributed to the development of emerging therapeutic approaches such as gene therapy, genome editing, and epigenetic reactivation strategies aimed at restoring normal MECP2 function [6,8]. This chapter focuses on the molecular mechanisms of MECP2 gene dysfunction and highlights current and emerging therapeutic strategies for the management of Rett syndrome.

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1.1 Etiology

Rett syndrome (RTT) is a severe neurological disorder caused by mutations in the X-linked gene MECP2 (methyl-CpG-binding protein 2)[2]

MeCP2 selectively binds CpG dinucleotides in the mammalian genome and mediates transcriptional repression through interaction with histone deacetylase and the corepressor SIN3A[3].

2. Structure and Functions of MECP2 Gene:

The MECP2 (methyl-CpG binding protein 2) gene encodes the MeCP2 protein, an important epigenetic regulator involved in neuronal development and gene expression. The MeCP2 protein acts as a transcriptional regulator by binding to methylated cytosine residues in DNA. This interaction allows the protein to influence chromatin structure and regulate the expression of multiple genes involved in neuronal development and synaptic function. The protein mainly functions as a transcriptional repressor by recruiting histone deacetylase complexes, leading to chromatin condensation and suppression of gene transcription.

Structurally, the MeCP2 protein contains several functional domains, including the N-terminal domain (NTD), methyl-CpG binding domain (MBD), intervening domain (ID), transcriptional repression domain (TRD), and C-terminal domain (CTD). Among these domains, the MBD domain is responsible for binding methylated DNA, while the TRD domain interacts with co-repressor complexes that regulate chromatin organization and gene transcription. These domains work together to maintain neuronal gene regulation and chromatin stability.

Because MeCP2 regulates large networks of neuronal genes, proper levels of the protein are essential for normal neurological function. Both deficiency and overexpression of the MECP2 gene can lead to neurological disorders such as Rett Syndrome, highlighting its critical role in brain development and epigenetic regulatio[4].

The structural domains of the MeCP2 protein are illustrated in Figure 1, highlighting the major functional regions involved in transcriptional regulation.

Figure 1: Structural organization of the MeCP2 protein

3. Molecular Pathophysiology

MeCP2 is a basic nuclear protein that is highly expressed in the brain. Its amino acid sequence is conserved in vertebrate evolution, being 95% identical between humans and mice. Functional studies have identified a DNA-binding domain (MBD) as the major determinant of chromosome binding through its affinity for short sequences in the genome that contain 5-methylcytosine (mC)[2].

Transfection studies showed that MeCP2 can repress gene transcription when it binds to promoter regions through the GAL4 binding domain. This repression is partly mediated through interaction with histone deacetylase (HDAC) complexes. These findings suggest that MeCP2 acts as a transcriptional regulator targeting genes via DNA methylation. However, later studies indicate that its effect on gene expression is relatively subtle[5].

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3.1 Emerging Therapeutic Strategies

Recent advances in molecular and genetic research have opened promising avenues for developing targeted therapies aimed at correcting the underlying genetic defects associated with Rett syndrome. Since mutations in the MECP2 gene are the primary cause of the disorder, many emerging therapeutic strategies focus on restoring normal MECP2 function in affected neurons.

One of the most promising approaches is adeno-associated virus (AAV)-mediated gene therapy. This strategy involves delivering a functional copy of the MECP2 gene into neurons using viral vectors. Preclinical studies have shown that introducing a normal MECP2 gene can partially restore neuronal function and improve neurological symptoms in experimental models. However, precise regulation of MECP2 expression is essential because both insufficient and excessive levels of the protein can lead to neurological abnormalities[6,7].

Another innovation involves CRISPR-Cas9 gene editing technology, which enables precise modification of disease-causing mutations within the genome. By targeting specific mutations in the MECP2 gene, CRISPR-based systems have demonstrated the ability to repair genetic defects at the DNA level in cellular models. Eventhough, this technology is still in early stages of development for neurological disorders, it offers a promising strategy for correcting the root cause of the disease[7].

Another promising therapeutic strategy involves epigenetic reactivation strategies, that aim to activate the functional MECP2 gene present on the inactive X chromosome. Since females possess two X chromosomes, one copy of the MECP2 gene remains inactive.

Reactivating this silent gene could potentially restore normal levels of MeCP2 protein in neurons and improve neurological function[8].

4. Clinical Features of Rett Syndrome:

The clinical manifestations of Rett Syndrome usually appear between 6 and 18 months of age following a period of apparently normal development. Patients commonly exhibit developmental regression, loss of acquired speech, repetitive hand movements, and impaired motor coordination.

Symptoms such as:

- Sleep disturbance,
- Seizures,
- Breathing irregularities,
- Hand stereotypies,
- Hand function,
- Constipation,
- Use of gastrostomy,
- Communication skills,
- Anthropometry, and
- Bruxism [3,9,10].

4.1 Diagnosis of Rett Syndrome

Diagnosis of Rett Syndrome is primarily based on clinical evaluation and confirmation of mutations in the MECP2 gene through molecular genetic testing. Physicians evaluate developmental history and neurological symptoms such as loss of speech, stereotypic hand movements, and impaired motor coordination. Additional diagnostic investigations including

- electroencaephalography (EEG)
- neurological examination

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- and brain imaging

may also be used to assess associated neurological abnormalities and exclude other neurodevelopmental disorders [9].

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