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Opinion Article

Molecular Mechanisms and Therapeutic Prospects in Rett Syndrome

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DESCRIPTION

Rett syndrome (Rtt) is a severe X-linked neurodevelopmental disorder that predominantly affects females, with an estimated prevalence of 1 in 10,000 to 15,000 live female births. First described by Andreas Rett in 1966, Rtt is characterized by apparently normal early development followed by developmental regression, loss of purposeful hand skills, gait abnormalities, stereotypic hand movements, and varying degrees of cognitive and motor impairment. In recent decades, advancements in molecular genetics have uncovered the genetic and epigenetic mechanisms underlying Rtt, providing significant insight into its pathophysiology and potential therapeutic targets.

The majority of Rtt cases-over 95%-are caused by mutations in the *MECP2* gene, located on the Xq28 region of the X chromosome. The *MECP2* gene encodes the Methyl-CpG-binding protein 2 (MeCP2), a nuclear protein that binds to methylated DNA and plays a key role in transcriptional regulation, chromatin remodeling, and epigenetic control of gene expression. MeCP2 is highly expressed in the Central nervous system (Cns), particularly in post-mitotic neurons, where it is critical for neuronal maturation, synaptic development, and maintaining neural circuit stability.

Mutations in *MECP2* lead to either loss of function or, in some cases, gain of toxic function. The functional domains of MeCP2 include a Methyl-CpG binding domain (Mbd) and a Transcriptional repression domain (Trd). Mutations affecting either domain can impair the protein's ability to bind methylated DNA or interact with co-repressor complexes such as the Sin3A-histone deacetylase complex, resulting in dysregulation of target gene expression. This dysregulation alters the expression of genes involved in synaptic plasticity, neuronal connectivity, and activity-dependent gene transcription, contributing to the neurodevelopmental phenotype observed in Rtt.

Although *MECP2* is the primary gene implicated in classic Rtt, other genes such as *CDKL5* and *FOXG1* have been associated with atypical variants of the syndrome. Mutations in *CDKL5*, which encodes a cyclin-dependent kinase-like protein, are typically associated with early-onset seizures and severe neurological impairment. Meanwhile, *FOXG1* mutations are linked to congenital Rtt variants characterized by profound intellectual disability and brain structural abnormalities. These genes function in pathways that intersect with MeCP2-mediated regulation, reinforcing the importance of transcriptional and epigenetic control in Rtt pathogenesis.

An essential aspect of Rtt involves the timing and tissue specificity of MeCP2 expression. Studies using mouse models have shown that complete loss of MeCP2 in early postnatal stages leads to severe Rtt-like symptoms, while reactivation of *MECP2* later in life can reverse or alleviate many of these symptoms. This suggests that the neurological phenotype is not solely the result of irreversible developmental defects, but also reflects ongoing dysfunction in mature neurons. This finding has significant implications for therapeutic strategies, indicating that interventions may be effective even after symptom onset.

Another key feature of Rtt is its variability in phenotypic severity, which is influenced by the type and location of the *MECP2* mutation as well as patterns of X-chromosome inactivation (Xci) in females. Skewed Xci, favoring the expression of the normal allele, often results in milder symptoms, while random or unfavorable skewing may lead to more severe manifestations. Male patients with *MECP2* mutations typically experience much more severe symptoms and often do not survive infancy unless mosaicism or Klinefelter syndrome is present.

At the cellular level, Rtt is associated with abnormalities in dendritic morphology, synapse number, neurotransmitter systems, and neurotrophic signaling. Reduced levels of Brain-derived neurotrophic factor (Bdnf), a key target of MeCP2, have been observed in Rtt models and patients. Restoration of Bdnf signaling in experimental systems has shown therapeutic promise, further supporting the role of MeCP2 in regulating genes critical for neuronal health and synaptic function.

Recent therapeutic approaches include gene therapy aimed at reintroducing functional *MECP2*, antisense oligonucleotides to correct splicing defects, and small molecules targeting downstream pathways such as Bdnf-TrkB signaling or glutamate receptor modulation. Clinical trials are ongoing to assess the safety and efficacy of these treatments. The challenge lies in

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achieving precise dosage, as both loss and overexpression of *MECP2* can be detrimental.

CONCLUSION

Rett Syndrome is primarily driven by mutations in the Rett Syndrome is primarily driven by mutations in the MECP2 gene, which disrupts the regulation of gene expression critical for neuronal function and development. The disorder exemplifies how epigenetic dysregulation and transcriptional imbalance can lead to complex neurodevelopmental syndromes. Continued research into the molecular mechanisms of Rtt is crucial for the development of targeted therapies and improving outcomes for affected individuals. Silico gene, which disrupts the regulation of gene expression critical for neuronal function and development. The disorder exemplifies how epigenetic dysregulation and transcriptional imbalance can lead to complex neurodevelopmental syndromes. Continued research into the molecular mechanisms of Rtt is crucial for the development of targeted therapies and improving outcomes for affected individuals.