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Breaking barriers in fragile X syndrome: a decade of innovations in targeted therapy and molecular modulation

Abstract

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and is a significant genetic contributor to autism spectrum disorders. Herein, we examine recent advancements in targeted therapies and molecular modulation for FXS, emphasizing the breakthroughs and ongoing challenges in the field. Inhibition of metabotropic glutamate receptor 5 (mGluR5) has shown promise in preclinical models, but clinical trials have encountered obstacles such as treatment resistance, necessitating the exploration of intermittent dosing strategies and combination therapies. Gene therapy, particularly CRISPR/Cas9, offers a potential avenue for addressing the root genetic causes of FXS, although technical and safety challenges remain. Additionally, modulation of Rac1 and GABAergic signaling has emerged as a novel approach to restore proper dendritic morphology and reduce neuronal hyperexcitability. These multifaceted strategies highlight the complexity of FXS treatment and the need for continued research to translate these findings into effective clinical interventions. Through an integrated approach, these innovations hold promise for significantly improving the quality of life of individuals affected by Fragile X Syndrome.

Keywords: fragile X syndrome, therapeutics, behavior, clinic, mitochondria

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Introduction

Fragile X Syndrome (FXS) is a genetic disorder caused by a mutation in the Fragile X messenger ribonucleoprotein 1 (FMR1) gene on the X chromosome that leads to intellectual disabilities, behavioral challenges, and distinct physical features. This gene encodes the FMRP protein, which is crucial in regulating synaptic function and plasticity.[1,2] In FXS, a CGG trinucleotide repeat expansion exceeding 200 repeats leads to hypermethylation of the FMR1 gene's promoter region, resulting in transcriptional silencing and subsequent absence of FMRP.[3] This loss disrupts the normal inhibition of mRNA translation, causing excessive synthesis of various proteins at synapses. The overproduction of these proteins interferes with synaptic signaling and plasticity, contributing to the cognitive impairments and behavioral characteristics observed in FXS.[4]

Clinically, FXS is characterized by a range of developmental issues including delayed speech and language development, intellectual disability, and autism spectrum disorder (ASD). The severity of symptoms can vary widely, with males typically being more severely affected due to the presence of only one X chromosome.[5]

Behaviorally, individuals with FXS often exhibit social anxiety, hyperactivity, attention deficits, and repetitive behavior. They may also exhibit sensory sensitivity, such as hypersensitivity to noise or light. Common physical features include a long face, large ears, flat feet, and macroorchidism (enlarged testicles) in men after puberty.[6,7]

Management of FXS involves a multidisciplinary approach, including speech therapy, occupational therapy, and behavioral interventions to address specific symptoms and improve the quality of life. Although there is no cure, medications can help manage symptoms such as hyperactivity, anxiety, and mood instability. Early intervention and supportive educational environments are crucial to maximize developmental potential and functional outcomes.[8]

Over the past decade, significant advances have been made in understanding the molecular underpinnings of FXS and in developing targeted therapies aimed at mitigating its symptoms. Herein, we highlight the key research findings that have shaped the field of FXS treatment.

mGluR5 Inhibition

The metabotropic glutamate receptor 5 (mGluR5) pathway has been the focal point of FXS research because of its role in synaptic plasticity and protein synthesis. Research revealed that the absence of FMRP leads to unchecked mGluR activity. This results in excessive protein synthesis, contributing to the synaptic dysfunction, cognitive impairments, and behavioral abnormalities seen in FXS.[9] Initial preclinical studies demonstrated that inhibiting mGluR5 could correct several FXS phenotypes in animal models, leading to considerable excitement regarding the potential for human treatment. Early trials with mGluR5 negative allosteric modulators (NAMs), such as CTEP (2-chloro-4-((2.5-dimethyl-1H-pyrrol-1-yl)methyl)-5-methylpyrimidine) and mavoglurant, have shown promising results. For example, a study published by Mark Bear's laboratory at the Massachusetts Institute of Technology (MIT), indicated that CTEP treatment could reverse learning and memory deficits, auditory hypersensitivity, and morphological changes in adult FXS mice.[10]

However, the translation of these findings to clinical success has been challenging.[11] Clinical trials with mavoglurant showed initial improvements in patients, but these benefits waned over time because of treatment resistance. This phenomenon, as discussed in studies from the MIT group, likely arises from compensatory mechanisms downstream of mGluR5 signaling that restore pathological protein synthesis despite continued receptor inhibition.[12] The rapid emergence of tolerance underscores the complexity of FXS pathophysiology and suggests that intermittent dosing or combination therapies may be necessary to sustain the therapeutic effects.

Allosteric modulation of other mGluR receptors

The theory that mGluR receptors play an important role in FXS continues with studies of other allosteric modulators of metabotropic glutamate receptor 7 (mGluR7). Researchers have activated the mGluR7 using the allosteric modulator AMN082 to repress protein synthesis via ERK1/2 and eIF4E signaling.[13] This study showed promising results in reducing neuronal excitability, audiogenic seizure susceptibility, repetitive behavior, and improved learning and memory in Fmr1 knockout (KO) mice, suggesting potential therapeutic approaches for FXS.

Rac1 modulation

Another emerging area of research involves the modulation of Rac1. Rac1, a member of the Rho family of GTPases, is pivotal in regulating neuronal plasticity, the actin cytoskeleton, and dendritic spine morphology.[14] Upon activation, Rac1 influences actin dynamics by promoting the polymerization of actin filaments, leading to the formation and remodeling of dendritic spines, key structures for synaptic transmission, and plasticity.[15] This modulation of the actin cytoskeleton is essential for the structural changes in spines that underlie learning and memory processes.[16] Disruptions in Rac1 signaling can result in abnormal spine morphology and impaired synaptic function, highlighting its critical role in maintaining neuronal connectivity and cognitive function.

Abnormal Rac1 activity has been implicated in the synaptic abnormalities observed in FXS.[1] Recent studies have explored the potential of Rac1 inhibitors to restore dendritic morphology and improve synaptic function.[17,18] Those studies have revealed that targeting Rac1 activity could correct structural defects in neurons in FXS animal models. By modulating Rac1, researchers have been able to restore normal dendritic spine structure, leading to improvements in cognitive and behavioral functions.[1,18] This approach represents a novel therapeutic strategy that addresses the synaptic basis of FXS and complements the efforts to modulate protein synthesis pathways.

GABAergic signaling

Gamma-aminobutyric acid (GABA) signaling has also been the focus of FXS research because of its role in maintaining the balance between neuronal excitation and inhibition. Dysfunctional GABAergic signaling contributes to hyperexcitability and cognitive deficits observed in FXS. Enhancing GABAergic signaling through pharmacological means has shown promise in preclinical studies.[19,20]

Studies have reviewed the role of the GABAergic system in Fragile X Syndrome (FXS), highlighting significant impairments in inhibitory neurotransmission within key brain regions such as the amygdala, cortex, and hippocampus. These deficits contribute to the characteristic symptoms of FXS, including intellectual disability, sensory hypersensitivity, and increased prevalence of autism spectrum disorders and epilepsy. Thus, targeting the GABAergic system could be a promising therapeutic strategy for FXS.[19] Additionally, several other critical findings about the role of GABAergic dysfunction in FXS have been reported. Among them, deficits in GABAergic circuits were linked to hyperexcitability and disrupted balance between excitation and inhibition, contributing to the neurological and behavioral symptoms of FXS. The expression of GABA receptor subunits was found to be altered, leading to compromised inhibitory synaptic function. GABAergic dysfunction was directly associated with behavioral phenotypes in FXS, such as increased anxiety, hyperactivity, and cognitive impairments. Lastly, all these outcomes had a therapeutic implication. The findings highlight the potential of restoring GABAergic function as a therapeutic strategy to alleviate FXS-related symptoms, pointing to pharmacological approaches targeting the GABAergic system.[20]

Investigating the effects of GABA agonists in FXS models has revealed that these compounds could reduce neuronal hyperexcitability and improve cognitive performance. These findings suggest that targeting the GABAergic system could provide symptomatic relief in individuals with FXS. However, translating these findings into clinical practice requires further research to optimize dosing and minimize potential side effects.[21,22]

The potential of gene therapy

Gene therapy represents a promising avenue for addressing the root cause of FXS, which is the silencing of the FMR1 gene. Advances in CRISPR and other gene-editing technologies have opened the door to potentially correcting genetic defects at their source. Preclinical models have shown that restoring Fragile X mental Retardation Protein (FMRP) expression can ameliorate several FXS symptoms. Although still in its infancy, this approach has the potential for long-lasting and possibly curative effects.[23]

One notable study demonstrated the feasibility of using CRISPR/Cas9 to reactivate the silenced FMR1 gene in neuronal cells derived from patients with FXS. Researchers designed single-guide RNAs (sgRNAs) targeting sequences flanking the expanded CGG-repeat in the 5' untranslated region of *FMR1*. By introducing double-strand breaks on either side of the repeat, they aimed to excise the expanded segment. They constructed sgRNAs to target regions upstream and downstream of the CGG-repeat expansion in *FMR1* using human somatic cell hybrids containing the fragile X chromosome and induced pluripotent stem cells (iPSCs) derived from FXS patients. Then, transfected cells with CRISPR/Cas9 components, isolated clonal lines, and assessed the excision of the CGG-repeat and subsequent *FMR1* expression. With this approach, approximately 67% of edited somatic cell hybrid clones and 20% of edited FXS iPSC clones showed reactivation of *FMR1* transcription, and those reactivated clones exhibited production of FMRP, indicating functional gene expression.

This reactivation led to the restoration of normal protein synthesis levels and a reduction in the pathological phenotypes associated with FXS.[24] Although these findings are encouraging, translating gene therapy into a viable clinical treatment faces numerous hurdles, including delivery mechanisms, off-target effects, and long-term safety concerns.

Addressing mitochondrial dysfunction

Emerging research indicates that mitochondrial dysfunction plays a significant role in the pathology of FXS. The absence or reduction of FMRP disrupts normal mitochondrial function, leading to impaired energy production and increased oxidative stress, which contribute to the neurodevelopmental deficits observed in FXS.[4]

Addressing mitochondrial dysfunction presents a promising therapeutic avenue for FXS. For instance, studies have shown that enhancing mitochondrial function can rescue brain cells damaged by the lack of FMRP. Additionally, inhibiting specific mitochondrial channels has been found to restore normal synaptic activity and behavior in FXS mouse models.[25] These findings suggest that targeting mitochondrial pathways could mitigate some of the neurological symptoms associated with FXS. A recent study by Vannelli et al.,,[26] investigated the use of 5-HT1A receptor agonist, eltoprazine, as a therapeutic potential for FXS-related impairments using a drosophila

model. This 5HT1A agonist ameliorated synaptic transmission anomalies, corrected mitochondrial dysfunctions, and improved motor behaviors, suggesting that targeting the 5-HT1A receptor with eltoprazine may offer a promising strategy for mitigating certain neurological deficits associated with FXS. Overall, therapies aimed at correcting mitochondrial dysfunction hold the potential for improving outcomes in individuals with FXS, though further research is needed to fully understand these mechanisms (Table 1).

Table 1 Summary of the targeting approaches studied as a therapeutic potential for Fragile X syndrome

Targeting approach	Research articles
mGluR5 Inhibition	Dölen et al.,[9] Stoppel et al.,[10] Berry-Kravis et al.,[11]
mGluR7 Allosteric Modulation	Kumar et al.,[13]
Rac1 Modulation	Bongmba et al.,[1] Tejada-Simón,[17] Martínez et al.,[18]
GABAergic Signaling	Paluszkiewicz et al.,[19] Lozano et al.,[21] Gao et al.,[20] Schaefer et al.,[22]
Gene Therapy	Xie et al.,[24] Yrigollen,[23]
Mitochondrial Dysfunction	Shen et al.,[25] Pagano et al.,[4] Vannelli et al.,[26]

Conclusion

The past decade has seen significant advancements in our understanding and treatment of Fragile X Syndrome. The modulation of mGluR5 and 7, Rac1, GABAergic signaling, along with the growing field of gene therapy and mitochondrial function, represents a multifaceted approach to tackling this complex disorder.

Despite extensive research on Fragile X Syndrome, there remains a critical need to translate preclinical findings into effective clinical interventions. There has been an inconsistency between promising results from animal models and the challenges encountered in clinical trials, especially concerning the mGluR5 pathway. This represents the translational obstacles we face in FXS and suggests the need for adopting innovative approaches, such as intermittent dosing strategies and combination therapies, to overcome treatment resistance observed in human patients. By integrating findings from recent studies on mGluR5 inhibition, Rac1 modulation, GABAergic signaling, and, more recently, mitochondria dysfunction, we might develop a multifaceted strategy that not only targets the synaptic abnormalities characteristic of FXS but also opens new avenues for therapeutic development.

The exploration of gene therapy as a future frontier further underscores the potential for groundbreaking advancements in treating the root causes of this disorder. While challenges such as treatment resistance and intricacies of gene editing remain, the progress made thus far provides a strong foundation for future breakthroughs.

Continued research and clinical trials are essential to refine these therapies and ultimately provide effective and long-lasting treatments for individuals with FXS. As we move forward, the integration of these strategies holds the promise of transforming the lives of those affected by FXS, breaking barriers, and paving the way for innovative and effective interventions.

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Conflict of interest

The author declares that there is no conflict of interest.

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