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Forum

Targeting epigenetic enzymes for autism treatment

Zhen Yan [1,*]

Emerging preclinical autism research has shown the therapeutic promise of pharmacological inhibitors for epigenetic enzymes, such as histone deacetylases (HDAC), euchromatic histone methyltransferases (EHMT), and lysine-specific histone demethylase 1A (LSD1). These interventions restore gene expression, synaptic function, and behavioral performance in autism models, highlighting a new strategy for autism treatment.

Epigenetic enzymes are the most prominent autism risk genes

Autism spectrum disorder (ASD), a prevalent neurodevelopmental disorder (NDD) characterized by social deficits and repetitive behaviors, has no FDA-approved medical treatment for core symptoms. Genetic sequencing has identified ~100 top-ranking, high-confidence ASD risk genes with loss-of-function mutations, many of which are histone modifiers and chromatin remodels, such as *ASH1L*, *KMT5B*, *KDM6B*, *SETD5*, *KDM5B*, *KMT2C*, *ARID1B*, *CHD2*, *CHD8*, *ADNP*, *POGZ*, *SMARCC2*, *PHF12*, etc. [1]. The most prominent ASD risk genes are histone methyltransferases and demethylases that control histone methylation [1]. A histone acetylome-wide association study also uncovers the altered histone acetylation on genes involved in synaptic transmission, ion transport, and histone deacetylation in human ASD postmortem samples [2]. It suggests that aberrant epigenetic machinery plays a key role in ASD pathogenesis. The objective of the forum article is to highlight recent primary research advances on the therapeutic promise of targeting epigenetic enzymes regulating histone acetylation or methylation as a strategy to mitigate synaptic abnormalities and normalize behavioral symptoms in ASD models (Table 1).

Therapeutic potentials of HDAC inhibitors in a variety of ASD models

In the screening of epigenetic mechanism-based treatment strategy for autism, a series of recent studies have uncovered the therapeutic efficacy of HDAC inhibitors in a variety of ASD models [3–8]. HDAC family proteins generally exert their epigenetic silencing of gene expression via condensing of the chromatin architecture. By using a mouse model of Phelan-McDermid syndrome (PMS) that harbors *Shank3* haploinsufficiency, it was found that a brief administration of the class I HDAC inhibitor romidepsin or MS-275 alleviated social deficits persistently, restored the expression of actin regulators (βPIX/Rac1/PAK/cofilin), and normalized *N*-methyl-d-aspartate receptor (NMDAR) trafficking and function in prefrontal cortex (PFC) [3,4]. The nuclear translocation of β-catenin, a Shank3 binding partner at synapses, is critically involved in the upregulation of *HDAC2* transcription in *Shank3*-deficient mice [3]. The rescuing effect of class I HDAC inhibitors is very unique, as many of the pharmacological agents currently used in psychiatric disorders, including fluoxetine, clozapine, risperidone, and aripiprazole, all failed to induce the long-lasting and robust improvement of social behaviors in the *Shank3*-deficient autism model [3].

This original finding on the therapeutic effects of HDAC inhibitors has been validated in several different ASD models. In a mouse model of fragile X syndrome (FXS), **HDAC inhibitor vorinostat (SAHA)** corrected autism-associated repetitive behavior and social interaction deficits, restored memory performances, and induced similar transcriptome changes as antipsychotic trifluoperazine [5]. In transgenic mice carrying 16p11.2 deletion (*16p11*$^{del/+}$), a short treatment with MS-275 or romidepsin led to the prolonged rescue of social and cognitive deficits, which was linked to the normalization of excitability of PFC pyramidal neurons and interneurons, and NMDAR- and $GABA_AR$-mediated synaptic currents [6]. The reduction in histone H3 lysine 9 acetylation was also found in Kat6b$^{+/-}$ mice, a mouse model of Say-Barber-Biesecker-Young-Simpson (SBBYS) syndrome [7]. Treatment with a HDAC inhibitor, valproic acid, or an acetyl donor, acetyl-carnitine, elevated histone acetylation levels, partially reversed gene expression changes, and improved sociability in Kat6b$^{+/-}$ mice [7].

Interestingly, in a high-throughput screening of 1478 compounds using induced pluripotent stem cell (iPSC)-derived cortical glutamatergic neurons from 7q11.23 microduplication ASD patients, three HDAC inhibitors were identified that decreased the abnormal expression level of a pathogenic gene [8]. The efficacy of the lead compounds in rescuing ASD-related phenotypes in 7q11.23 microduplication models awaits to be tested, but it provides a drug target for treating 7q11.23 microduplication and other forms of autism.

Targeting histone methylation/demethylation enzymes for autism treatment

Histone proteins that are mono-, di-, or trimethylated at different lysine (K) residues are associated with gene activation or repression. The balance between histone methyltransferases and demethylases is a tightly orchestrated process during normal development. Mutations in histone methyltransferases, including *EHMT1*, *KMT2C*, *ASH1L*, *SETD5*, and *SETD1A*, and histone demethylases, such as *LSD1* (*KDM1A*), *KDM3A*, *KDM4B*, *KDM5B*, *KDM6A*, and *KDM6B*, have been identified in ASD or NDD [1,9].

Table 1. Pharmacological agents targeting epigenetic enzymes that are used in the treatment of ASD models

Disease	Genetic cause	Pharm. agent	Drug action	Refs
Phelan-McDermid syndrome (PMS)	SHANK3	Romidepsin, MS-275	Class I HDAC inhibitor	[3,4]
Fragile X syndrome (FXS)	FMR1	Vorinostat (SAHA)	HDAC inhibitor	[5]
16p11.2 deletion	KCTD13, MAPK3, KIF22, etc. (chr 16p11.2)	Romidepsin, MS-275	Class I HDAC inhibitor	[6]
SBBYS syndrome	KAT6B	Valproic acid, acetyl-carnitine	HDAC inhibitor, acetyl donor	[7]
7q11.23 microduplication syndrome (7Dup)	GTF2I, LIMK1, STX1A, etc. (chr 7q11.23)	Vorinostat, mocetinostat, RG2833	Pan or class I HDAC inhibitors	[8]
PWS	SNORD116, SNRPN, etc. (chr 15q11–q13)	UNC0638, UNC0642	EHMT1/2 inhibitors	[10]
PMS	SHANK3	UNC0642	EHMT1/2 inhibitor	[11]
PMS	SHANK3	GSK-LSD1, ORY-1001	LSD1 inhibitors	[12]
Maternal exposure to valproate or poly I:C	N/A	TAK-418	LSD1 inhibitor	[13]
Williams-Beuren syndrome (WBS) and 7Dup	GTF2I, LIMK1, STX1A, etc. (chr 7q11.23)	DDP-38003	LSD1 inhibitor	[14]
Schizophrenia	SETD1A	RN-1, TCP, ORY-1001, SP2509	LSD1 inhibitors	[15]

In a high-content screen of >9000 small molecules using cells from Prader–Willi syndrome (PWS) patients, two selective inhibitors for H3K9 methyltransferases EHMT1/2, UNC0638 and UNC0642, were discovered to activate imprinted PWS-associated genes on the maternal chromosome via selective reduction of H3K9me2 and improve the survival and growth of a mouse model of PWS [10], providing the first proof of principle for an epigenetics-based therapy for an imprinting disorder.

A significant increase of EHMT1, EHMT2, and H3K9me2 was found in PFC of *Shank3*-deficient mice and autistic human postmortem brains [11]. Treatment with EHMT1/2 inhibitor UNC0642 or knockdown of EHMT1/2 in PFC induced a robust rescue of autism-like social deficits in *Shank3*-deficient mice [11]. Among the large set of genes restored by UNC0642, activity-regulated cytoskeleton-associated protein (Arc), a synaptic plasticity gene regulating cognitive processes, was identified as a key factor underlying the rescuing effects of UNC0642 on NMDAR function and social behaviors in *Shank3*-deficient mice [11].

An important component in HDAC/EHMT-containing chromatin-associated complex is the histone demethylase LSD1, which causes the loss of permissive histone mark H3K4me2 and ensuing gene suppression. Significantly decreased H3K4me2 is found in PFC of autistic human patients and *Shank3*-deficient mice [12]. A brief treatment of several autism models with a highly potent and selective inhibitor of LSD1, GSK-LSD1, led to the robust rescue of two core symptoms of autism: social deficits and repetitive behaviors. These behavioral effects of LSD1 inhibition in *Shank3*-deficient mice could be attributable to the restoration of NMDAR function in PFC, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) function in striatum, and the expression and H3K4me2 occupancy of downregulated genes enriched in synaptic signaling and developmental processes, such as *Egr1* (early growth response 1) [12]. Another LSD1 inhibitor, TAK-418, normalized the dysregulated gene expression in the brain and ameliorated some ASD-like behaviors in NDD models, such as maternal exposure to valproate or poly I:C [13]. Inhibition of LSD1 was also sufficient to normalize neuronal differentiation and social behavior in 7q11.23 NDDs [14]. In addition, antagonizing LSD1 activity reversed schizophrenia-related cognitive and morphological phenotypes in mice carrying a heterozygous loss-of-function mutation of the schizophrenia susceptibility gene SETD1A [15].

Taken together, these studies have provided a framework for understanding the complex mechanisms linking chromatin and transcriptional and synaptic dysregulation to behavioral deficits associated with ASD and uncovered epigenetic enzyme-based intervention avenues for ASD (Figure 1).

Concluding remarks

Emerging genomic, epigenomic, and preclinical studies have implicated epigenetic dysregulation as a primary hallmark of ASD. Targeting epigenetic enzymes may hold the key to restore gene expression homeostasis, leading to the normalization of synaptic function and the mitigation of behavioral abnormalities in ASD.

Epigenetic drugs are promising for ASD due to their ability to modulate gene expression, potentially influencing complex networks involved in neuronal function.

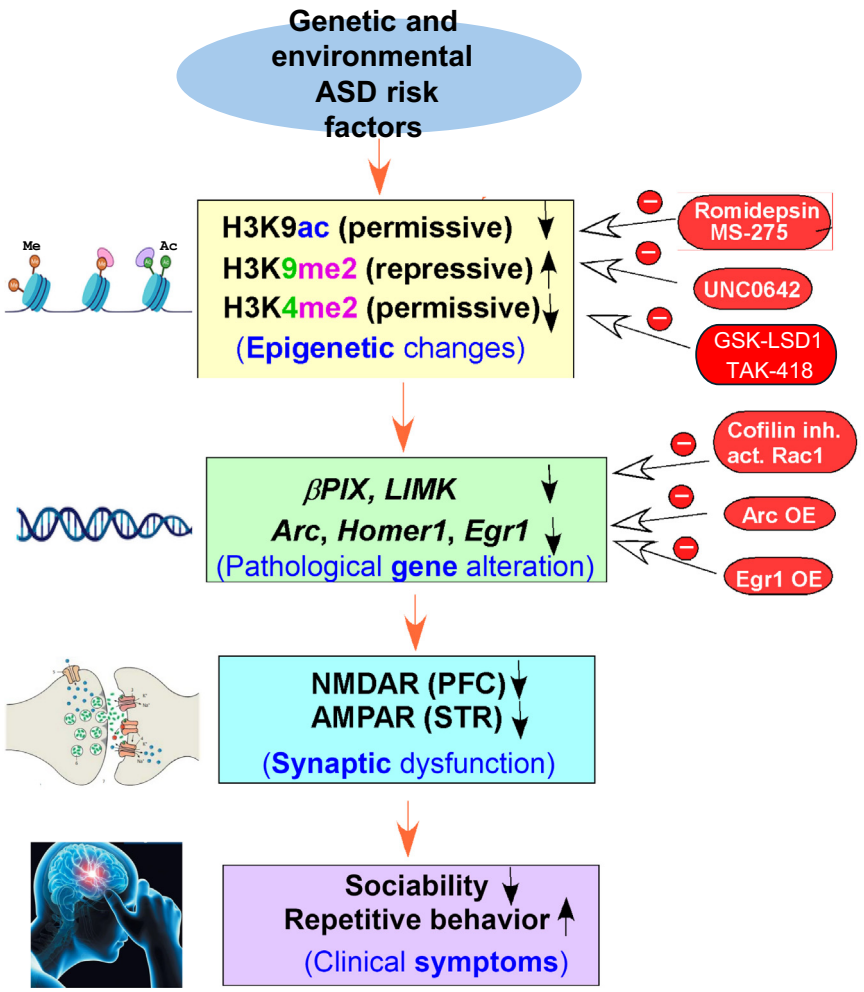

Figure 1. A schematic model summarizing the convergent epigenetic mechanism and treatment strategy for autism. In autism spectrum disorder (ASD), multiple genetic and environmental factors, such as haploinsufficiency of ASD risk genes (chromatin and transcription regulators), lead to epigenetic changes (e.g., decreased H3 acetylation, increased H3K9me2, reduced H3K4me2). These changes result in alterations of gene expression (e.g., downregulation of *βPIX*, *Arc*, *Egr1*), which causes synaptic dysfunction [e.g., reduced *N-methyl-d-aspartate receptor* (NMDAR)-mediated synaptic currents in prefrontal cortex (PFC)] and clinical symptoms (e.g., social interaction deficits). One therapeutic approach involves targeting epigenetic enzymes to reverse these modifications, such as using histone deacetylase (HDAC) inhibitors (romidepsin, MS-275), euchromatic histone methyltransferase (EHMT)1/2 inhibitors (UNC0642, UNC0638), or lysine-specific histone demethylase 1A (LSD1) inhibitors (GSK-LSD1, TAK-418) to restore normal histone acetylation/methylation and gene expression levels. Another strategy focuses on the direct modulation of downstream molecular targets, such as using cofilin inhibitors, Rac activators, Arc overexpression, or Egr1 overexpression to recover synaptic function and improve behavioral outcomes.

However, their broad actions raise possibilities of unintended effects on genes unrelated to the targeted pathways, which could lead to off-target side effects. Moreover, ASD is highly heterogeneous with individuals carrying a wide range of symptoms and genetic variations. This diversity poses a challenge for treatment strategies aiming to address the underlying biology of ASD. Consequently, while epigenetic drugs represent a fascinating avenue for ASD treatment, further research is necessary to fully understand their efficacy, safety, and applicability across different subtypes of the disorder. Additionally, personalized approaches that consider the unique genetic and epigenetic profiles of individuals with ASD may be necessary for maximizing therapeutic benefits while minimizing adverse effects.

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Declaration of interests

The author has no interest to declare.

[1]Department of Physiology and Biophysics, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY 14203, USA

*Correspondence:
zhenyan@buffalo.edu (Z. Yan).

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