



Tomasz Bielawski*, Blazej Misiak, Ahmed Moustafa and Dorota Frydecka

Epigenetic mechanisms, trauma, and psychopathology: targeting chromatin remodeling complexes

<https://doi.org/10.1515/revneuro-2018-0055>

Received June 4, 2018; accepted October 19, 2018; previously published online February 7, 2019

Abstract: Environmental pressure affects the genotype throughout different epigenetic processes. There is currently ample evidence on the role of epigenetics in developing various mental disorders. A burden of environmental pressure, such as psychological trauma, and its influence on genotype can lead to a variety of psychopathologies. Thus, this study focuses on the epigenetic activity of the complex protein machinery operating on chromatin – the ATP-dependent chromatin remodeling complexes. Although there are several recent studies on the molecular structure, functions, and taxonomy of ATP-dependent chromatin remodeling complexes, the focus of this paper is to highlight the importance of those ‘protein machines’ in developing psychiatric disorders. Data were obtained from human preclinical and clinical studies. The results of this review indicate an importance of ATP-dependent chromatin remodeling complexes in the interaction between environmental factors, including traumatic events, and genetic vulnerability to stress. Several studies indicate that ATP-dependent chromatin remodeling complexes play a crucial role in the development and consolidation of memory, in neurodevelopmental processes, and in etiology depressive-like behavior. Thus, the activity of those ‘protein machines’ emerges as a key factor in the pathophysiology of various psychiatric diseases. It can also be concluded that the limitations of clinical studies may be explained by inappropriate laboratory methods and research paradigms due to the delayed timeframe of biochemical responses to

environmental stimuli. Future research in this field may enable a better understanding of the pathophysiology of psychiatric diseases and contribute to the development of novel molecular treatment targets.

Keywords: ATP-dependent chromatin remodeling complex; epigenetics; psychiatry; psychopathology; trauma.

Introduction

There is a growing body of evidence that epigenetic processes play an important role in the development of psychopathologies. Historically, epigenetics was defined as an interaction between different molecular pathways, which determines the phenotype under the influence of the environment (Waddington, 1968). However, Jullien and Berger (2009) defined epigenetics as follows: ‘An epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence’. The following processes have been recognized as epigenetic mechanisms: DNA methylation, modification of histones (e.g. methylation, acetylation, and phosphorylation), regulation of DNA expression by microRNA species, and modification via ATP-dependent protein complexes. The effects of these mechanisms as well as the regulatory enzymes involved in biochemical pathways are key epigenetic processes (Ptashne, 2007; Tsankova et al., 2007). Over the past few years, the role played by epigenetic processes in the development of psychiatric disorders became widely accepted. Throughout the human life, the environment puts pressure on individual genotype, initiating various epigenetic mechanisms. One such clinically important environmental pressure is psychological trauma. Recent reports lend support to the considerable impact of traumatic events on epigenetic processes, which contribute to the development of psychopathologies (Sun et al., 2015; Misiak et al., 2017). By targeting epigenetics in psychiatry research, several studies have focused on DNA methylation and histone acetylation (Table 1), yet nucleosome remodeling via ATP-dependent complexes in developing psychopathologies remains an unexplored area. These protein complexes control the histone arrangement

***Corresponding author: Tomasz Bielawski**, Department of Psychiatry, Wrocław Medical University, 10 Pasteur Street, 50-367 Wrocław, Poland, e-mail: tomaszbielawski90@gmail.com

Blazej Misiak: Department of Genetics, Wrocław Medical University, 1 Marcinkowski Street, 50-368 Wrocław, Poland

Ahmed Moustafa: School of Social Sciences and Psychology, Western Sydney University, Sydney, New South Wales 2000, Australia; and Department of Social Sciences, Qatar University Ringgold Standard Institution, Ad Dawhah, Doha, Qatar

Dorota Frydecka: Department of Psychiatry, Wrocław Medical University, 10 Pasteur Street, 50-367 Wrocław, Poland

Table 1: Selected papers targeting epigenetic processes other than ATP-dependent chromatin remodeling complexes.

Epigenetic process	Title	Authors
Methylation	Balancing histone methylation activities in psychiatric disorders	Peter and Akbarian, 2011
	DNA methylation and antipsychotic treatment mechanisms in schizophrenia: Progress and future directions	Ovenden et al., 2018
	DNA methylation in schizophrenia	Pries et al., 2017
	Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: a longitudinal study of discordant monozygotic twins	Ouellet-Morin et al., 2013
	The role of DNA methylation in the central nervous system and neuropsychiatric disorders	Feng and Fan, 2009
	Recently evolved human-specific methylated regions are enriched in schizophrenia signals	Banerjee et al., 2018
Acetylation	Exercise-induced modulation of histone H4 acetylation status and cytokines levels in patients with schizophrenia	Lavratti et al., 2017
	Chemogenomic analysis reveals key role for lysine acetylation in regulating Arc stability	Lalonde et al., 2017

and thereby alter the chromatin structure (Vignali et al., 2000). A tightly packed heterochromatin is unavailable to translation, contrary to a loose form of euchromatin, which enables the initiation of translation because of easy access to genes located within. ATP-dependent complexes use ATP hydrolysis to steer a dynamic process of DNA accessibility. Thus, they are pivotal for adequate temporal and spatial gene expression (Zaghlool et al., 2016). ATP-dependent complexes can be grouped according to a unique ‘taxonomy’ that refers to the specificity of distinct ATPase subunits (Vignali et al., 2000; Becker and Hörz, 2002). Indeed, four groups of ATP-dependent complexes, including switch/sucrose non-fermentable (SWI/SNF), imitation switch (ISWI), chromodomain helicase DNA-binding (CHD), and inositol (INO80), play a role in genomic homeostasis during the lifespan (Zaghlool et al., 2016). Every complex is a ‘protein machinery’ built around ATPase, with many multifunctional protein subunits. The INO80 group is important for DNA repair, checkpoint regulation, DNA replication, telomere maintenance, and chromosome segregation (Morrison and Shen, 2009). Although INO80 is crucial for many processes involved in developmental processes and homeostasis, its impact on human neurobiology is either minor or not yet known. For this reason, this paper focuses on two protein families – the SWI/SNF and ISWI complexes. The protein family CHD is included in this review only in reference to the increased number of reports, suggesting the involvement of CHD proteins in the etiology of autism spectrum disorder (ASD). The aim of this review paper is to both (a) provide basic and initial information about selected epigenetic ‘complex protein machines’ operating on chromatin – ATP-dependent chromatin remodeling complexes – and

(b) highlight the relationship between traumatic stress and those proteins. A detailed description of the molecular and physicochemical properties of ATP-dependent chromatin remodeling complexes is beyond the scope of this article.

Materials and methods

To conduct our search, we have used the following databases: PubMed, Scopus, Medline, Google Scholar, and Web of Science, using the following keywords: ‘epigenetic’, ‘trauma’, ‘chromatin remodeling complexes’, ‘psychopathology’, ‘SWI’, ‘SNF’, ‘ISWI’, ‘ATP dependent chromatin remodeling complexes’, ‘CSDS’, ‘chronic social defeat stress’, ‘psychopathology’, ‘autism’, ‘schizophrenia’, ‘bipolar disorder’, ‘depression’, and ‘BAF’. Keywords were used in various combinations to find articles regarding the role of ATP-dependent chromatin remodeling complexes in the development of various psychopathologies. Furthermore, the references section of the publications we found based on the criteria described above was manually reviewed for relevant articles. The following publication records were included: (1) publications in English, (2) publications from peer-reviewed journals or books, and (3) review articles or original studies of human subjects or animal models, presenting data of clinical/psychiatric importance.

Results

After conducting the preliminary search with defined keywords as mentioned above, we obtained 65 articles on

the given topic. We excluded six of these articles based on the following exclusion criteria: (1) articles concerning strictly molecular structure and/or physicochemical properties of ATP-dependent chromatin remodeling complexes, (2) articles concerning the function of ATP-dependent chromatin remodeling complexes outside the nervous system, and (3) articles concerning the role of epigenetic mechanisms other than ATP-dependent chromatin remodeling complexes in the development of mental disorders. A total number of 59 articles were included in this review; 31 of them were experimental studies.

SWI/SNF family

A complex taxonomy of SWI/SNF chromatin remodeling complexes is based on the conserved ATPase subunit that represents the SWI2/SNF2 protein family. In humans, the most common ATPase subunits are hBRM and BRG1 (Vignali et al., 2000; Becker and Hörz, 2002). A complicated machinery of different protein subunits is formed around the ATPase subunit (Table 2). One of those proteins are the BRG1 or HBRM-associated factors (BAF) complexes. The mutations of the polymorphic BAF complexes are often associated with altered cognitive functions. Notably, BAF complexes are expressed by postmitotic neurons [known as neuronal BRG1 or HBRM-associated factors (nBAF)]. Mutations in the neuron-specific subunit known as BAF53b (actin-related protein) result in long-term memory deficits and altered hippocampal synaptic plasticity (Vogel-Ciernia et al., 2013). Transgenic mice with a deletion of the hydrophobic domain of BAF53b perform significantly worse than healthy control mice on the Object Location Memory Test (OLM) and Object Recognition Memory Test (ORM) as well as in a long-term memory version of both tests. In the short-term memory versions of OLM and ORM, mutants did not differ significantly from wild-type (control) individuals. Similar results were obtained in fear conditioning tasks in the lateral amygdala neurons (Yoo et al., 2017). Genetic manipulation

in the BAF53b subunit results in an altered gene expression and leads to an impairment of hippocampal synaptic plasticity (Vogel-Ciernia et al., 2013) and a blunted dendritic outgrowth in the hippocampus (Wu and Liu, 2007). The overexpression of BAF53b does not enhance the already existing memory but plays a crucial role in consolidating and forming a memory trail. BAF53b operates in a late phase of memory creation (after up to 24 h after training) and plays an essential role in creating long-term memory as found in the paradigm of fear conditioning (Yoo et al., 2017). Important recent reports by Marom et al. (2017) confirm the key role of the BAF complex in developing intact cognitive functioning. A pathogenic variant of the *actin-like 6A (ACTL6A)* gene (which encodes another protein component of the BAF complex) was described in three subjects with developmental disabilities, affecting mainly language and memory (Marom et al., 2017). Although the size of a group does not allow us to draw unequivocal conclusions, this report is part of a series of studies confirming the relevance of ATP-dependent complexes and their genetic impact on cognitive functions. Altered hippocampal cytoarchitecture, especially among dendrites, is also observed during the manipulation in other components of BAF, especially the *SWI/SNF-related, matrix-associated, actin-dependent regulator chromatin A2 (SMARCA2)* gene. Some polymorphisms of the *SMARCA2* gene are linked to the animal model of schizophrenia (Loe-Mie et al., 2010) and human schizophrenia (Walsh et al., 2008), whereas mutations in *SMARCA2* are linked to the Coffin-Siris syndrome (Santen et al., 2012; Tsurusaki et al., 2012), Nicolaides-Baraitser syndrome (Van Houdt et al., 2012), and general intellectual disability (Hoyer et al., 2012). In addition, *SMARCA2* (and its protein product) seems to be one of the ‘network centers’ among the SWI/SNF (BAF) complexes. The *SMARCA2* gene is modified by the down-regulation of REST/RFSF, which results in alterations of other interactors and consequences in the development of abnormal dendritic spines. Mouse models revealed impaired social interaction and prepulse inhibition in *Smarca2* knockout mice. Importantly, deficits in both domains – social interaction and prepulse inhibition – are observed in patients with schizophrenia. Moreover, it is possible to manipulate the expression of the *SMARCA2* gene by the application of psychoactive drugs that down-regulate this complex and antipsychotic drugs that in turn up-regulate it. Therefore, *SMARCA2* is considered to be involved in the pathophysiology of schizophrenia (Koga et al., 2009; Loe-Mie et al., 2010). Several mutations in the *SMARCA2* gene seem to be related to the Coffin-Siris syndrome, which is characterized by intellectual disability, growth deficiency, microcephaly, and

Table 2: Few of many genes and protein units/subunits of the SWI/SNF group ATP-dependent chromatin remodeling complexes.

Examples of genes involved in coding units and subunits	Protein units and subunits	SWI/SNF ATPase unit
<i>ACTL6A</i>	BAF	BRG1
<i>ACTL6A</i>	BAF53a	BRG1
<i>SMARCA2</i>	nBAF	hBRM
<i>SMARCA2</i>	BAF53b	hBRM

a number of dysmorphic features (Tsurusaki et al., 2012). Loe-Mie et al. (2010) revealed how these schizophrenia-related genes, and their protein products, are evolutionary novel. Risk alleles in the *SMARCA2* gene are derived from a point mutation in the conservative region. This mutation leads to altered protein trafficking in the cytoplasm-nucleus pathway. This mechanism is hypothesized to influence both robust primate evolution and schizophrenia. Finally, there is a positive selection among primates and humans toward the *SMARCA2* risk alleles, which reinforce the appearance of this evolutionally novel molecular phenomena (Loe-Mie et al., 2010).

Epigenetic mechanisms regulated by ATP-dependent chromatin remodeling structures within the SWI/SNF family are being affected by other ongoing epigenetic processes or even occur in coordination with other chromatin remodeling complexes (Zaghlool et al., 2016). Gozes (2016) suggested that there is a possible interaction between activity-dependent neuroprotective protein (ADNP) and the SWI/SNF complexes. An increased activity of ADNP (at the mRNA and protein level) has been reported in peripheral blood lymphocytes of patients with schizophrenia as well as in individuals with mild cognitive impairment (Gozes, 2016). The ADNP level has been associated with cognitive functions in patients with Alzheimer's disease (Magen and Gozes, 2014) and correlates with the level of τ protein in an animal model of Alzheimer's disease (Schirer et al., 2014). The altered interaction between ADNP and SWI/SNF is proposed as one of the potential indicators of ASD (Vandeweyer et al., 2014). Helsmoortel et al. (2014) showed that mutations in the *ADNP* gene occur in at least 0.17% of patients with ASD. This estimation may seem irrelevant, but in fact it is among the most prevalent ASD genes, taking into account the fact that no single gene is found to be mutated in more than 1% of patients with autism (Vandeweyer et al., 2014). These findings provide evidence of complex protein-protein and multigene interactions that could be a consequence of epigenetic mechanisms. A biochemical analysis performed by Mandel et al. (2008) revealed that proteins form the SWI/SNF chromatin remodeling complex family (BRG1, BAF250a, and BAF170) immunoprecipitated with ADNP. Furthermore, ADNP binds to *SMARCA2*, *SMARCA4*, and *SMARCC2* by its C-terminal end and possibly positions the whole protein complex in the appropriate DNA location by its zinc finger and homeobox domain. This crucial relationship explains the impact of epigenetic processes, involving nBAF complexes and concomitant enzymes on altered cognitive abilities, intellectual disabilities, and ASD. A specific protein architecture among nBAF complexes regulates the functional characteristics

and tissue specificity during neuronal development. Location shift of 3 of 15 subunits of BAF components initiate dendritic outgrowth and axonal development. Thus, mutations of the nBAF protein components (*SAMRCB1*, *SMARCA4*, *SMARCA2*, *SMARCE1*, *ARID1A*, and *ARID1B*) are reported in syndromic intellectual disability disorders (Santen et al., 2012; Vandeweyer et al., 2014). To date, the reports of exome sequencing analyses of patients with ASD reveal even more important mutations in genes encoding the nBAF proteins, including *BAF155*, *BAF170*, *BAF180*, *BAF250b*, and *BAF100a* (O'Roak et al., 2012; Basak et al., 2015).

ISWI family

A complex taxonomy of the ISWI chromatin remodeling complexes is based on the conserved ATPase subunit that belongs to the ISWI protein family. In humans, the most common ATPase subunit is *SMARCA5* (*hSNF2h*; Vignali et al., 2000; Becker and Hörz, 2002). A complex machinery of protein is formed around the ATPase subunit. The most widely studied protein complex is ATP-utilizing chromatin assembly and remodeling factors (*ACF*) and its subunit bromodomain adjacent to zinc finger domain 1A (*BAZ1A*; Table 3). Animal models imply an overexpression of the *ACF* (and *BAZ1A*) gene in the nucleus accumbens (NAc), which results in greater reductions of social interaction and lower sucrose preference. As much as 65% of experimental mice with up-regulated *ACF* exhibit depression-related behavioral abnormalities, including social avoidance. The up-regulation of *BAZ1A* correlates with a greater susceptibility to social defeat stress in animal models (Sun et al., 2015). This leads to a disruption in nucleosome location and gene silencing (Sananbenesi and Fischer, 2009). The chronic social defeat stress (CSDS) experiment demonstrates the importance and impact of epigenetic processes on the development of pathological behavior (Golden et al., 2011; Sun et al., 2015). It is undeniable that some individuals are characterized by genetic vulnerability to develop depression-like behavior. However, this genetic background is not sufficient; thus,

Table 3: Gene and subunit of the ISWI group AIP-dependent chromatin remodeling complexes.

Example of gene involved in coding units and subunits	Protein subunit	ISWI ATPase unit
<i>BAZ1A</i>	ACF	<i>SMARCA5</i>

an interaction with disadvantageous environment is obviously required for the development of depression (e.g. mice placed in a cage with dominant and an aggressive individuals with high position in the hierarchy). In this experimental paradigm, epigenetic changes are observed, which includes upstream regulation of the ISWI family subunit (BAZ1A), likely due to altered ventral tegmental area neuronal projections to NAc as well as the activation of the BDNF protein (Sun et al., 2015). In the NAc, BAZ1A alters the activity of chromatin remodeling complexes. ATP-dependent ‘protein machinery’ is more likely to position nucleosomes within the transcription start sites (TSS regions), blocking translation and silencing genes (Sananbenesi and Fischer, 2009). Therefore, depressive-like behavior can be observed not due to the activation of some defective or mutated genes but due to epigenetic alterations of ATP-dependent chromatin remodeling complexes (Figure 1).

The BAZ1B protein, with a similar structure to BAZ1A, works contradictory to BAZ1A and heightens responses to rewarding stimuli as well as promotes adaptive responses to aversive stimuli. BAZ1B appears to be closely related to chronic salient stimuli: cocaine administration and CSDS. Importantly, behavioral effects caused by cocaine and CSDS last longer than remodeled chromatin complex.

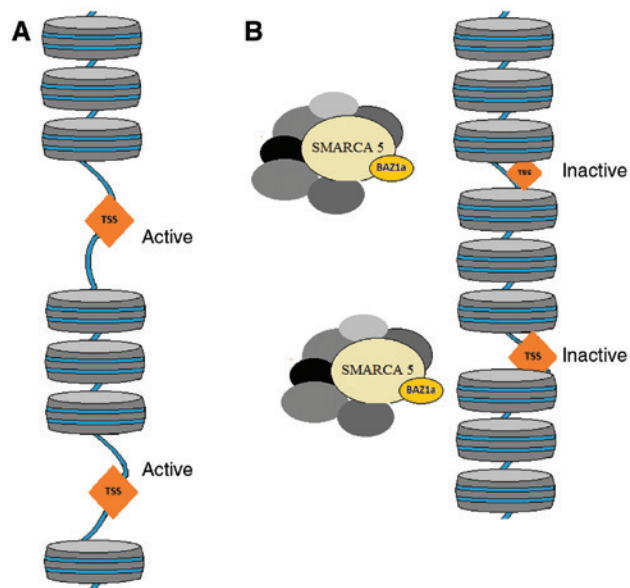


Figure 1: Euchromatin (A) changes to heterochromatin (B) in NAc. ATP-dependent chromatin remodeling complexes position nucleosomes close to the TSS region (B) and therefore unable transcription. In an animal model of CSDS, Sun et al. (2015) showed that such a phenomenon occurs more often among individuals susceptible to CSDS, and it leads to development depression-like phenotype.

BAZ1B levels return to control values within hours after cocaine administration or stress exposure, whereas behavioral repercussions of these treatments can be still observed for a long time afterward. Thus, it is hypothesized that epigenetic changes in chromatin induce further alterations in various genes, which exert longer behavioral effects (Sun et al., 2015). BAZ1A contribute to stress susceptibility maintenance of depressive-like phenotypes, whereas BAZ1B promotes adaptive responses to aversive stimuli, being hypothesized to serve as a stress resilience indicator. Other studies have revealed an interaction between the ACF (ISWI family) and BAF (SWI/SFN) components, particularly between *BAZ1B* and *SMARCA* genes, which can have clinical implications for future studies (Zaghlool et al., 2016). BAZ1B plays a pivotal role in neuron differentiation from pluripotent stem cells. Moreover, the haploinsufficiency of the *BAZ1B* gene plays a crucial role in the development of Williams syndrome (Lalli et al., 2016).

CHD family

In the CHD family, SNF2-like ATPase domain is located in the center of a protein network and the tandem chromodomains are located in the N-terminal region (Marfella and Imbalzano, 2007). There are several human diseases associated with the CHD protein family (e.g. dermatomyositis, Hodgkin’s lymphoma, neuroblastoma, and the CHARGE syndrome) and some reports suggest that it has an anticancer properties (Rother and van Attikum, 2017), but due to the scope of this article we focus on the *CHD8* gene, which is strongly associated with ASD. This gene encodes a protein with the ATP-dependent chromatin remodeling activity. CHD8 binds to posttranslationally trimethylated histone H3 at active promoters and modulates the interaction between DNA and histone (Thompson et al., 2008; Cotney et al., 2015). Krumm et al. (2014) revealed that *CHD8* represents genes with *de novo* loss-of-function mutations in large-scale resequencing studies of ASD. Combined with reports of the CHD8 role in the neurodevelopment of midfetal cortex, these findings suggest an important role of the CHD protein family in the development of cognitive impairments. Other research has confirmed that CHD8 activity targets risk genes for ASD. Indeed, a loss of the *CHD8* gene significantly deregulates the function of ASD-related genes (Cotney et al., 2015). An important role of CHD8 in genomic homeostasis during neurodevelopment, along with reports on BAF protein and the ADNP enzymatic role (discussed in the ‘SWI/SNF family’ section), implies that understanding and

explaining the pathophysiology of ASD might be achieved using epigenetic approaches.

Memory of psychological trauma and ATP-dependent chromatin remodeling complexes

The definition of epigenetic processes emphasizes its crucial role in the mediation between environmental pressure and genotype (Waddington, 1968; Ptashne, 2007). Stressful and traumatic events, as part of environmental burden, have large impact on the development of the phenotype, somatic and mental health state, psychosocial functioning, and general environmental fitness (Weiner, 1992). Clinical studies reveal a number of posttranslational alterations in protein architecture that result in signaling cascade forming short-term memory. Then, epigenetic processes contribute to the conversion of unstable short-term memory to robust long-term memory trail. Thus, new gene expression is hypothesized to be crucial in creating long-lasting memory trail of a stressful event (Barrett and Wood, 2008; Kwapis and Wood, 2014). Animal studies of memory consolidation often use trauma paradigm or fear conditioning due to the necessity of strong stimulus appliance. There are several lines of evidence revealing how various traumatic events affect epigenetic processes, mainly due to histone acetylation, histone phosphorylation, and methylation, but there are also reports about DNA methylation and nucleosome remodeling complexes (Vogel-Ciernia et al., 2013; Kwapis and Wood, 2014; Sun et al., 2015). Epigenetic mechanisms of ATP-dependent chromatin remodeling complexes take part in memory consolidation through the nBAF complex and its BAF53b subunit. Although BAF53b seems to be pivotal for the consolidation of, particularly, visually contextual fear memory, it does not participate in the consolidation of auditory fear (Kwapis and Wood, 2014). The nBAF complexes play a crucial role in the consolidation of the hippocampus-related memory trails, whereas auditory amygdala-dependent trails are autonomous from the BAF53b complex. In animal studies, the CSDS paradigm is used to develop depressive-like features, manifesting in anxiety, anhedonia, and social avoidance in rodents (Golden et al., 2011). Considering the CSDS protocol, results obtained with this paradigm can easily be categorized as consequences of an exposure to trauma. In this protocol, a smaller mouse is placed in a cage with a bigger and more aggressive male. Interindividual interference that lasts for 5–10 min is pivotal for the protocol because, after the defeat of the smaller mouse, both rodents are separated by Plexiglass, allowing visual and olfactory,

but not physical, contact for the following 24 h. The procedure is repeated for 10 consecutive days, each day with a different aggressor (Golden et al., 2011; Sun et al., 2015). The CSDS procedure attunes with modern trauma definitions that imply the occurrence of various types of traumatic events (Sideli et al., 2012; Misiak et al., 2017). Another important factor is interindividual interference (presenting in abuse, neglect, wars, human-made disaster, technological disasters, or assaults), considering there is a lower prevalence of posttraumatic stress disorder as an aftermath of natural disasters (Galea et al., 2005; Neria et al., 2008). Thus, taking into account all the variables discussed above, we here provide a crucial information about molecular alterations emerging after trauma. In animal models, applying the CSDS paradigm results in alterations among all four families of the ATP-dependent protein complexes (SWI/SNF, ISWI, CHD, and INO80) in the NAc. Particularly robust up-regulation of the BAZ1A protein was observed among stress-susceptible individuals, and the interaction between *BAZ1A* and *SMARCA5* genes in executing transcriptional regulations was noted. Interestingly, the up-regulation of BAZ1A mRNA is observed in the NAc in postmortem brain examinations in individuals with depression (Sun et al., 2015). This allows us to hypothesize similar epigenetic mechanisms among CSDS-susceptible people and animal (rodent) models. Moreover, a significant up-regulation in the prefrontal cortex of *BAZ1A* genes was observed in genome-wide expression profiling of schizophrenia patients performed by Mistry et al. (2013). This is in agreement with several studies showing an increased risk of psychosis in individuals with a history of childhood trauma (Varese et al., 2012). In addition, novel theoretical models consider childhood trauma (and concomitant epigenetic alterations) to be essential components of the etiology of psychosis (Misiak et al., 2017). Early-life adversities cause significant alterations in NAc activity (Tidey and Miczek, 1996; Gambarana et al., 2001; Salamone and Correa, 2012), which is a structure of great dependency from the ATP-dependent chromatin remodeling complexes (Sun et al., 2015).

Discussion

Epigenetic processes may not be a primary cause of psychiatric diseases, but their alterations can have an important downstream effect on mental health. Recent reports suggest a presence of an interrelation between chromatin remodeling complexes and even alcohol

dependence. Animal studies of the nematode *Caenorhabditis elegans* reveal a relationship between the SWI/SNF chromatin remodeling complexes and acute behavioral response to ethanol (Mathies et al., 2015). The results are significant for human studies mainly due to a similar and conservative molecular mechanism in mammals and worms. This relationship can be observed in clinical research, where an association among ATP-dependent chromatin remodeling complexes, antisocial behavior, and alcohol dependence has been shown (Mathies et al., 2015). It is highly plausible that ATP-dependent chromatin remodeling complexes assist in many neural processes and possibly even play a crucial role in the development of pathological mechanisms, but they are difficult to examine due to their subtle and intermediary functions. A mediation on the molecular level between environmental stimuli and an adequate genetic response is difficult to be investigated mainly because our methods and research paradigms may not be appropriate. Yoo et al., 2017 showed that ATP complexes that are pivotal in consolidating memory trials can peak up to 24 h after stimulation. If other ATP-dependent chromatin remodeling complexes work in a similar manner, we have to change our testing paradigms and stop looking for direct and rapid stimulus-based effects. The complexity of multiprotein constructions, diversity in subunit functions, and family ‘taxonomy’, along with a complex cooperation between various ATP-dependent chromatin remodelers, dims overall the picture of what we know about those molecules. Some studies (Larrieu et al., 2017) provide important reports about the neurochemical modifications and metabolic alterations in distinct brain regions, such as the NAc, which is known for being widely regulated by ATP-dependent chromatin remodelers (Sun et al., 2015). Extending our knowledge about epigenetic processes may contribute to explain these discrepancies. Novel theoretical models on the development of psychosis among people with childhood trauma emphasize the importance of environmental factors in developing psychopathology (Misiak et al., 2017). It seems inevitable that epigenetic mechanisms, such as chromatin remodeling complexes, play a pivotal role in the interdependence between environmental factors (like trauma) and genetic vulnerability, further leading to biological alterations that result in pathological and psychological mechanisms and psychiatric diseases. ATP-dependent chromatin remodeling complexes may predetermine mental disorders and constitute triggering factors for psychiatric diseases. Furthermore, epigenetic alterations of genes involved in the regulation of ATP-dependent chromatin remodeling complexes and

schizophrenia pathophysiology are observed in our ancestral, phylogenetic tree. This validates the relevance and utility of psychiatric animal model studies. It is not difficult to hypothesize about the potential clinical importance of more robust research in this area. Examples of translating epigenetic mechanisms into clinical trials can be found in some diseases associated with neurodegeneration, such as Huntington’s disease. Although it is a hereditary and fatal disorder caused by dynamic mutations, epigenetic modifications are critical in the development of Huntington’s disease. Promising drugs that are being investigated in preclinical studies inhibit neurodegeneration in Huntington’s disease via modifications of chromatin (Kim and Kaang, 2017). The majority of mental disorders cannot be described as monogenic phenotypes and one disease approach. The ‘multiprotein machinery’ of ATP-dependent chromatin remodeling complexes, alongside different regulatory enzymes, is involved in complex protein-protein networks and multigene systems. Improving our knowledge in this field may be challenging, but the complexity of environmental factors and genetic vulnerability creates a vast range of methods for both the prevention and management of various psychopathologies. Recent reports of epigenetic mechanisms, other than ATP-dependent chromatin remodeling complexes (like histone or DNA methylation and histone modifications), imply that substantial molecular changes can be induced by various lifestyle factors. Changes in the physical activity of schizophrenia patients may induce hypoacetylation of histone 4 as well as down-regulation of inflammatory processes in the peripheral blood (Lavratti et al., 2017). Another important relationship was pointed out by Alam et al. (2017), who highlighted the relationship among diet, gut microbiota, and different epigenetic processes (like DNA methylation), with relevance to mental disorders (Malan-Muller et al., 2018). It can be hypothesized that similar, yet undiscovered, relationships between lifestyle-dependent environmental factors and significant molecular alterations may be induced by epigenetic mechanisms related to ATP-dependent chromatin remodeling complexes. It seems evident that we are facing an uncharted field, where the association between environmental stress and genetic adaptation can be observed at the molecular level *in vivo*. Some authors hypothesized epigenetics to carry the potential of transgenerational inheritance (Woodhouse, 2018; Yeshurun and Hannan, 2018). It is possible that we are yet to discover a whole new ‘layer’ of mechanisms that not only simply control gene expression but also serve as potential treatment and diagnostic targets.

Main findings

Our review of the current literature provides a framework to better understand the role of epigenetic mechanisms of ATP-dependent chromatin remodeling complexes in developing psychopathologies. Environmental pressure, manifesting in various forms, via epigenetic processes, interacts with genetic vulnerability and plays an important role in the development of psychiatric disorders. ‘The protein machinery’ of ATP-dependent chromatin remodeling complexes, as well as different accompanying enzymes, steers a dynamic process of DNA accessibility, up-regulate and down-regulate gene expression, and affect neuronal development. Three ‘families’ of proteins – SWI/SNF, ISWI, and CHAD, representing ATP-dependent chromatin remodeling complexes – play a crucial role in the development of various psychopathologies that are often accompanied by cognitive impairment. In this article, we reviewed the role of ATP-dependent chromatin remodeling complexes in forming long-term memory trails and attuned these findings to modern models of psychological trauma. We reasoned that psychological phenomena, including helplessness, forced submission, and low in-hierarchy position, lead to epigenetic changes. We showed evidence of the crucial role of chromatin remodeling complexes in the development of depressive-like behavior in the social defeat paradigm. We also provided potential limitations of laboratory methods (examining the molecular background of memory trials) due to the delayed timeframe of biochemical responses to environmental stimuli. The role of ATP-dependent chromatin remodeling complexes in neurodevelopmental disorders, including schizophrenia, ASD, and various intellectual disabilities, was described.

Finally, we noted that the multidependency of environmental factors and genetic vulnerability creates a vast range of therapeutic methods for both the prevention and management of different psychopathologies. We hypothesized that research in this field can not only broaden our knowledge in the area of pathophysiology of mental diseases but may also contribute to the development of swift diagnostic procedures as well as novel treatment targets.

References

- Alam, R., Abdolmaleky, H.M., and Zhou, J.R. (2017). Microbiome, inflammation, epigenetic alterations, and mental diseases. *AJGM: Neuropsychiatr. Genet.* *174*, 651–660.
- Banerjee, N., Polushina, T., Bettella, F., Giddaluru, S., Steen, V.M., Andreassen, O.A., and Le Hellard, S. (2018). Recently evolved human-specific methylated regions are enriched in schizophrenia signals. *BMC Evol. Biol.* *18*, 63.
- Barrett, R.M. and Wood, M.A. (2008). Beyond transcription factors: the role of chromatin modifying enzymes in regulating transcription required for memory. *Learn. Mem.* *15*, 460–467.
- Basak, A., Hancarova, M., Ulirsch, J.C., Balci, T.B., Trkova, M., Pelisek, M., and Dymont, D.A. (2015). BCL11A deletions result in fetal hemoglobin persistence and neurodevelopmental alterations. *JCI.* *125*, 2363–2368.
- Becker, P.B. and Hörz, W. (2002). ATP-dependent nucleosome remodeling. *Annu. Rev. Biochem.* *71*, 247–273.
- Cotney, J., Muhle, R.A., Sanders, S.J., Liu, L., Willsey, A.J., Niu, W., and Reilly, S.K. (2015). The autism-associated chromatin modifier CHD8 regulates other autism risk genes during human neurodevelopment. *Nat. Commun.* *6*, 6404.
- Feng, J. and Fan, G. (2009). The role of DNA methylation in the central nervous system and neuropsychiatric disorders. *Int. Rev. Neurobiol.* *89*, 67–84.
- Galea, S., Nandi, A., and Vlahov, D. (2005). The epidemiology of post-traumatic stress disorder after disasters. *Epidemiol. Rev.* *27*, 78–91.
- Gambarana, C., Tolu, P.L., Masi, F., Rinaldi, M., Giachetti, D., Morazzoni, P., and De Montis, M.G. (2001). A study of the antidepressant activity of *Hypericum perforatum* on animal models. *Pharmacopsychiatry* *34*, S42–S44.
- Golden, S.A., Covington, H.E., Berton, O., and Russo, S.J. (2011). A standardized protocol for repeated social defeat stress in mice. *Nat. Prot.* *6*, 1183–1191.
- Gozes, I. (2016). The cytoskeleton as a drug target for neuroprotection: the case of the autism-mutated ADNP. *Biol. Chem.* *397*, 177–184.
- Helsmoortel, C., Vulto-van Silfhout, A.T., Coe, B.P., Vandeweyer, G., Rooms, L., Van Den Ende, J., and Yntema, H.G. (2014). A SWI/SNF-related autism syndrome caused by *de novo* mutations in ADNP. *Nat. Genet.* *46*, 380.
- Hoyer, J., Ekici, A.B., Ende, S., Popp, B., Zweier, C., Wiesener, A., and Zweier, M. (2012). Haploinsufficiency of ARID1B, a member of the SWI/SNF-a chromatin-remodeling complex, is a frequent cause of intellectual disability. *Am. J. Hum. Genet.* *90*, 565–572.
- Jullien, P.E. and Berger, F. (2009). Gamete-specific epigenetic mechanisms shape genomic imprinting. *Curr. Opin. Plant Biol.* *12*, 637–642.
- Kim, S. and Kaang, B.K. (2017). Epigenetic regulation and chromatin remodeling in learning and memory. *Exp. Mol. Med.* *49*, e281.
- Koga, M., Ishiguro, H., Yazaki, S., Horiuchi, Y., Arai, M., Niizato, K., and Ozaki, N. (2009). Involvement of SMARCA2/BRM in the SWI/SNF chromatin-remodeling complex in schizophrenia. *Hum. Mol. Genet.* *18*, 2483–2494.
- Krumm, N., O’Roak, B.J., Shendure, J., and Eichler, E.E. (2014). A *de novo* convergence of autism genetics and molecular neuroscience. *Trends Neurosci.* *37*, 95–105.
- Kwapis, J.L. and Wood, M.A. (2014). Epigenetic mechanisms in fear conditioning: implications for treating post-traumatic stress disorder. *Trends Neurosci.* *37*, 706–720.
- Lalli, M.A., Jang, J., Park, J.H.C., Wang, Y., Guzman, E., Zhou, H., and Tutulan-Cunita, A.C. (2016). Haploinsufficiency of BAZ1B contributes to Williams syndrome through transcriptional dysregulation of neurodevelopmental pathways. *Hum. Mol. Genet.* *25*, 1294–1306.

- Lalonde, J., Reis, S.A., Sivakumaran, S., Holland, C.S., Wesseling, H., Sauld, J.F., and Haggarty, S.J. (2017). Chemogenomic analysis reveals key role for lysine acetylation in regulating Arc stability. *Nat. Commun.* *8*, 1659.
- Larrieu, T., Cherix, A., Duque, A., Rodrigues, J., Lei, H., Gruetter, R., and Sandi, C. (2017). Hierarchical status predicts behavioral vulnerability and nucleus accumbens metabolic profile following chronic social defeat stress. *Curr. Biol.* *27*, 2202–2210.e4.
- Lavratti, C., Dorneles, G., Pochmann, D., Peres, A., Bard, A., de Lima Schipper, L., and Elsner, V.R. (2017). Exercise-induced modulation of histone H4 acetylation status and cytokines levels in patients with schizophrenia. *Physiol. Behav.* *168*, 84–90.
- Loe-Mie, Y., Lepagnol-Bestel, A.M., Maussion, G., Doron-Faigenboim, A., Imbeaud, S., Delacroix, H., and Moalic, J.M. (2010). SMARCA2 and other genome-wide supported schizophrenia-associated genes: regulation by REST/NRSF, network organization and primate-specific evolution. *Hum. Mol. Genet.* *19*, 2841–2857.
- Magen, I., and Gozes, I. (2014). Davunetide: Peptide therapeutic in neurological disorders. *Curr. Med. Chem.* *21*, 2591–2598.
- Malan-Muller, S., Valles-Colomer, M., Raes, J., Lowry, C.A., Seedat, S., and Hemmings, S.M. (2018). The gut microbiome and mental health: implications for anxiety-and trauma-related disorders. *OMICS* *22*, 90–107.
- Mandel, S., Spivak-Pohis, I., and Gozes, I. (2008). ADNP differential nucleus/cytoplasm localization in neurons suggests multiple roles in neuronal differentiation and maintenance. *J. Mol. Neurosci.* *35*, 127–141.
- Marfella, C.G. and Imbalzano, A.N. (2007). The Chd family of chromatin remodelers. *Mutat. Res.* *618*, 30–40.
- Marom, R., Jain, M., Burrage, L.C., Song, I.W., Graham, B.H., Brown, C.W., and Gavrilova, R.H. (2017). Heterozygous variants in *ACTL6A*, encoding a component of the BAF complex, are associated with intellectual disability. *Hum. Mutat.* *38*, 1365–1371.
- Mathies, L.D., Blackwell, G.G., Austin, M.K., Edwards, A.C., Riley, B.P., Davies, A.G., and Bettinger, J.C. (2015). SWI/SNF chromatin remodeling regulates alcohol response behaviors in *Caenorhabditis elegans* and is associated with alcohol dependence in humans. *Proc. Natl. Acad. Sci.* *112*, 3032–3037.
- Misiak, B., Krefft, M., Bielawski, T., Moustafa, A.A., Sasiadek, M.M., and Frydecka, D. (2017). Toward a unified theory of childhood trauma and psychosis: a comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neurosci. Biobehav. Rev.* *75*, 393–406.
- Mistry, M., Gillis, J., and Pavlidis, P. (2013). Genome-wide expression profiling of schizophrenia using a large combined cohort. *Mol. Psychiatry* *18*, 215–225.
- Morrison, A.J. and Shen, X. (2009). Chromatin remodeling beyond transcription: the INO80 and SWR1 complexes. *Nat. Rev. Mol. Cell Biol.* *10*, 373–384.
- Neria, Y., Nandi, A., and Galea, S. (2008). Post-traumatic stress disorder following disasters: a systematic review. *Psychol. Med.* *38*, 467–480.
- O’Roak, B.J., Vives, L., Girirajan, S., Karakoc, E., Krumm, N., Coe, B.P., and Turner, E.H. (2012). Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations. *Nature* *485*, 246.
- Ouellet-Morin, I., Wong, C.C.Y., Danese, A., Pariante, C.M., Papadopoulos, A.S., Mill, J., and Arseneault, L. (2013). Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: a longitudinal study of discordant monozygotic twins. *Psychol. Med.* *43*, 1813–1823.
- Ovenden, E.S., McGregor, N.W., Emsley, R.A., and Warnich, L. (2018). DNA methylation and antipsychotic treatment mechanisms in schizophrenia: progress and future directions. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* *81*, 38–49.
- Peter, C.J. and Akbarian, S. (2011). Balancing histone methylation activities in psychiatric disorders. *Trends Mol. Med.* *17*, 372–379.
- Pries, L.-K., Gülöksüz, S., and Kenis, G. (2017). DNA methylation in schizophrenia. *Adv. Exp. Med. Biol.* *978*, 211–236.
- Ptashne, M. (2007). On the use of the word ‘epigenetic’. *Curr. Biol.* *17*, R233–R236.
- Rother, M.B. and van Attikum, H. (2017). DNA repair goes hip-hop: SMARCA and CHD chromatin remodelers join the break dance. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* *372*, 1–13.
- Salamone, J.D. and Correa, M. (2012). The mysterious motivational functions of mesolimbic dopamine. *Neuron* *76*, 470–485.
- Sananbenesi, F. and Fischer, A. (2009). The epigenetic bottleneck of neurodegenerative and psychiatric diseases. *Biol. Chem.* *390*, 1145–1153.
- Santen, G.W.E., Aten, E., Sun, Y., Almomani, R., Gilissen, C., Nielsen, M., and Wessels, M.W. (2012). Mutations in SWI/SNF chromatin remodeling complex gene ARID1B cause Coffin-Siris syndrome. *Nat. Genet.* *44*, 379–380.
- Schirer, Y., Malishkevich, A., Ophir, Y., Lewis, J., Giladi, E., and Gozes, I. (2014). Novel marker for the onset of frontotemporal dementia: early increase in activity-dependent neuroprotective protein (ADNP) in the face of tau mutation. *PLoS One* *9*, e87383.
- Sideli, L., Mule, A., La Barbera, D., and Murray, R.M. (2012). Do child abuse and maltreatment increase risk of schizophrenia? *Psychiatry Investig.* *9*, 87–99.
- Sun, H., Domez-Werno, D.M., Scobie, K.N., Shao, N.Y., Dias, C., Rabkin, J., and Cahill, M.E. (2015). ACF chromatin-remodeling complex mediates stress-induced depressive-like behavior. *Nat. Med.* *21*, 1146–1153.
- Thompson, B.A., Tremblay, V., Lin, G., and Bochar, D.A. (2008). CHD8 is an ATP-dependent chromatin remodeling factor that regulates β -catenin target genes. *Mol. Cell. Biol.* *28*, 3894–3904.
- Tidey, J. and Miczek, K.A. (1996). Social defeat stress selectively alters mesocorticolimbic dopamine release: an *in vivo* microdialysis study. *Brain Res.* *721*, 140–149.
- Tsankova, N., Renthal, W., Kumar, A., and Nestler, E.J. (2007). Epigenetic regulation in psychiatric disorders. *Nat. Rev. Neurosci.* *8*, 355.
- Tsurusaki, Y., Okamoto, N., Ohashi, H., Kosho, T., Imai, Y., Hibi-Ko, Y., and Fukushima, Y. (2012). Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. *Nat. Genet.* *44*, 376–378.
- Van Houdt, J.K.J., Nowakowska, B.A., Sousa, S.B., van Schaik, B.D., Seuntjens, E., Avonce, N., and Castori, M. (2012). Heterozygous missense mutations in SMARCA2 cause Nicolaides-Baraitser syndrome. *Nat. Genet.* *44*, 445–449.
- Vandeweyer, G., Helsmoortel, C., Van Dijk, A., Vulto-van Silfhout, A.T., Coe, B.P., Bernier, R., and Wilson, M. (2014). The transcriptional regulator ADNP links the BAF (SWI/SNF) complexes with autism. *Am. J. Med. Genet. Pt. C Semin. Med. Genet.* *166*, 315–326.
- Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., and Bentall, R.P. (2012). Childhood adversities

- increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr. Bull.* **38**, 661–671.
- Vignali, M., Hassan, A.H., Neely, K.E., and Workman, J.L. (2000). ATP-dependent chromatin-remodeling complexes. *Mol. Cell. Biol.* **20**, 1899–1910.
- Vogel-Ciernia, A., Matheos, D.P., Barrett, R.M., Kramár, E.A., Azzawi, S., Chen, Y., and Jia, Y. (2013). The neuron-specific chromatin regulatory subunit BAF53b is necessary for synaptic plasticity and memory. *Nat. Neurosci.* **16**, 552–561.
- Waddington, C.H. (1968). Towards a theoretical biology. *Nature* **218**, 525.
- Walsh, T., McClellan, J.M., McCarthy, S.E., Addington, A.M., Pierce, S.B., Cooper, G.M., and Stray, S.M. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* **320**, 539–543.
- Weiner, H. (1992). *Perturbing the Organism: The Biology of Stressful Experience* (University of Chicago Press).
- Woodhouse, R.M., Buchmann, G., Hoe, M., Harney, D.J., Low, J.K., Larence, M., and Ashe, A. (2018). Chromatin modifiers SET-25 and SET-32 are required for establishment but not long-term maintenance of transgenerational epigenetic inheritance. *Cell Rep.* **25**, 2259–2272.
- Wu, L. and Liu, Y.J. (2007). Development of dendritic-cell lineages. *Immunity* **26**, 741–750.
- Yeshurun, S., and Hannan, A.J. (2018). Transgenerational epigenetic influences of paternal environmental exposures on brain function and predisposition to psychiatric disorders. *Mol. Psychiatry*, **1**. <https://doi.org/10.1038/s41380-018-0039-z> [Epub ahead of print].
- Yoo, M., Choi, K.Y., Kim, J., Kim, M., Shim, J., Choi, J.H., and Han, J.H. (2017). BAF53b, a neuron-specific nucleosome remodeling factor, is induced after learning and facilitates long-term memory consolidation. *J. Neurosci.* **37**, 3686–3697.
- Zaghlool, A., Halvardson, J., Zhao, J.J., Etemadikhah, M., Kalushkova, A., Kanska, K., and Feuk, L. (2016). A role for the chromatin-remodeling factor *BAZ1A* in neurodevelopment. *Hum. Mutat.* **37**, 964–975.

Article note: The publication of this article was funded by the Qatar National Library.