Epigenetic mechanisms in schizophrenia

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Schizophrenia is a major psychiatric disorder that lacks a unifying neuropathology, while currently available pharmacological treatments provide only limited benefits to many patients. This review will discuss how the field of neuroepigenetics could contribute to advancements of the existing knowledge on the neurobiology and treatment of psychosis. Genome-scale mapping of DNA methylation, histone modifications and variants, and chromosomal loopings for promoter-enhancer interactions and other epigenetic determinants of genome organization and function are likely to provide important clues about mechanisms contributing to dysregulated expression of synaptic and metabolic genes in schizophrenia brain, including the potential links to the underlying genetic risk architecture and environmental exposures. In addition, studies in animal models are providing a rapidly increasing list of chromatin-regulatory mechanisms with significant effects on cognition and complex behaviors, thereby pointing to the therapeutic potential of epigenetic drug targets in the nervous system.

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Introduction

Schizophrenia (SCZ) is a psychiatric disorder defined by positive symptoms such as delusions, hallucinations and disorganized thought, and negative symptoms such as anhedonia (inability to experience pleasure), social withdrawal, and apathy. SCZ reduces the lifespan of an affected individual on average by 15 years, with cardiovascular disease and suicide among the chief causes for increased mortality.[1-3] In addition, the mainstay of antipsychotic intervention is medicinal treatment targeting dopaminergic, serotonergic, and monoaminergic receptor systems,[4,5] but the majority of patients still experience an incomplete response to treatment.[6,7] Currently prescribed antipsychotics exert therapeutic effects on psychosis in up to approximately 75% of patients, but it is the cognitive impairment which is often the more disabling and persistent feature of schizophrenia.[8] It has been a challenge to promote rational drug development in SCZ, mainly because of the lack of a unifying neuropathology[9,10] and a complex genetic risk architecture,[11,12] which so far have defied

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any narrowly defined signaling pathways or molecular mechanisms representing the majority of affected cases.

This review will outline how neuroepigenetic approaches[13]—broadly defined as the study of chromatin structure and function in the developing and adult nervous system, including its role for neuronal and behavioral plasticity—could advance our knowledge on SCZ pathophysiology and the underlying genetic risk architecture and pave the way for novel treatment approaches. Epigenetic marks, such as DNA cytosine methylation and histone modifications and variants, could be viewed as a "molecular bridge" by which myriads of external ("environmental") or internal factors mold and shape the nascent genetic material throughout the entire lifespan of a brain cell.[14] While a comprehensive discussion on epi- (*Greek for "over," "above"*) genetic regulation in the nervous system would be beyond the scope of this review (the reader is referred to recent handbooks and special journal volumes in this field, see refs 14-17) we have now clearly entered a period with a heightened level of enthusiasm for epigenetic approaches in neurology and psychiatry, and SCZ research is no exception to this trend. This phenomenon is due to a coalescence of multiple factors: First, there is knowledge that many epigenetic markings remain "plastic" throughout all periods of brain development and aging, with ongoing and highly dynamic regulation even in neurons and other differentiated cells. Second, some of the chromatin-modifying drugs—histone deacetylase inhibitors are a well-known example—exert profound effects on brain metabolism and behavior in the animal model.[18-21] Third, monogenetic disorders associated with widespread chromatin defects in brain cover a much wider continuum of neurological disease than previously thought, ranging from neurodevelopmental defects of early life to adult onset psychosis and dementia.[22] And fourth, there is the emerging concept of transgenerational epigenetic inheritance, including early evidence for a role of environmental conditions and nutrition, as well as the physical and emotional health of a parent, as potential factors modulating the epigenetic state at the site of brain-relevant genes in the offspring.[23]

Epigenetic regulation in the brain—basic principles

This section is limited to a very brief discussion of epigenetic markings that have been implicated in SCZ (discussed in the next section). The elementary unit of chromatin in the eukaryote cell is the nucleosome, or 146 bp of genomic DNA wrapped around an octamer of core histones, connected by linker DNA and linker histones. The collective set of covalent DNA and histone modifications and variant histones provide the major building blocks for the "epigenome," or the epigenetic landscapes that define the organization of the genomic material into many tens of thousands of transcriptional units, clusters of condensed chromatin and other features that are differentially regulated in different cell types and developmental stages in a multicellular organ such as brain *(Figure 1)*.[24-28]

The bulk of DNA modifications exist as cytosine methylation (m) and hydroxymethylation (hm).[29] The mC5 and hmC5 markings show a differential (but not mutually exclusive) pattern of genomic occupancy. The hmC5 mark broadly correlates with local gene expression levels[30,31] while methyl-cytosine (mC5) markings, particularly when positioned around the 5' end of genes is thought to function primarily as negative regulator of transcription.[32,33] The regulation of chemical histone modifications is even more complex than the DNA methylation discussed above, and it is now thought that there are far more than 100 amino acid residue-specific post-translational modifications (PTMs) in a typical vertebrate cell,[34] including mono (me1), di (me2)- and tri (me3) methylation, acetylation, and crotonylation, poly adenosine triphosphate (ADP)-ribosylation and small protein (ubiquitin, small ubiquitin-like modifier—SUMO) modification of specific lysine residues, as well as arginine (R) methylation and "citrullination," serine (S) phosphorylation, tyrosine (T) hydroxylation, and several others.[34-36] It is thought that multiple combinatorial sets of histone PTMs contribute to functional chromatin states that differentially define gene proximal promoters and gene bodies as opposed to enhancer and other regulatory sequences, condensed heterochromatin, and the "insulator" sequences that compartmentalize and provide boundaries for these various domains of chromatin *(Figure 1)*.[26] Proteins associated with the regulation of histone PTM are sometimes referred to as "writers," or "erasers," or "readers," essentially differentiating between the process of establishing or removing a mark as opposed to its docking functions for chromatin remodeling complexes that regulate transcription, or induce and maintain chromatin condensation.[36-38] In addition to these chemical modifications of

the genomic DNA and the nucleosomal histones, other types of epigenetic regulation include histone variants (H3.1, H3.3, H2A.X, H2A.Z, etc) which differ from the canonical histones (H3/H4/H2A/H2B) only at very few amino acid positions, but robustly affect nucleosome stability and compaction.[39] In addition there is "supra-nucleosomal" or "higher-order chromatin" regulation, which, at least in the nervous system, has barely been explored until now. For example, chromosomal loopings provide scaffolds that enable distal regulatory enhancer or silencer elements positioned potentially hundred kilobases apart from a gene, to physically interact directly with that gene's promoter sequences at the transcription start site.[40]

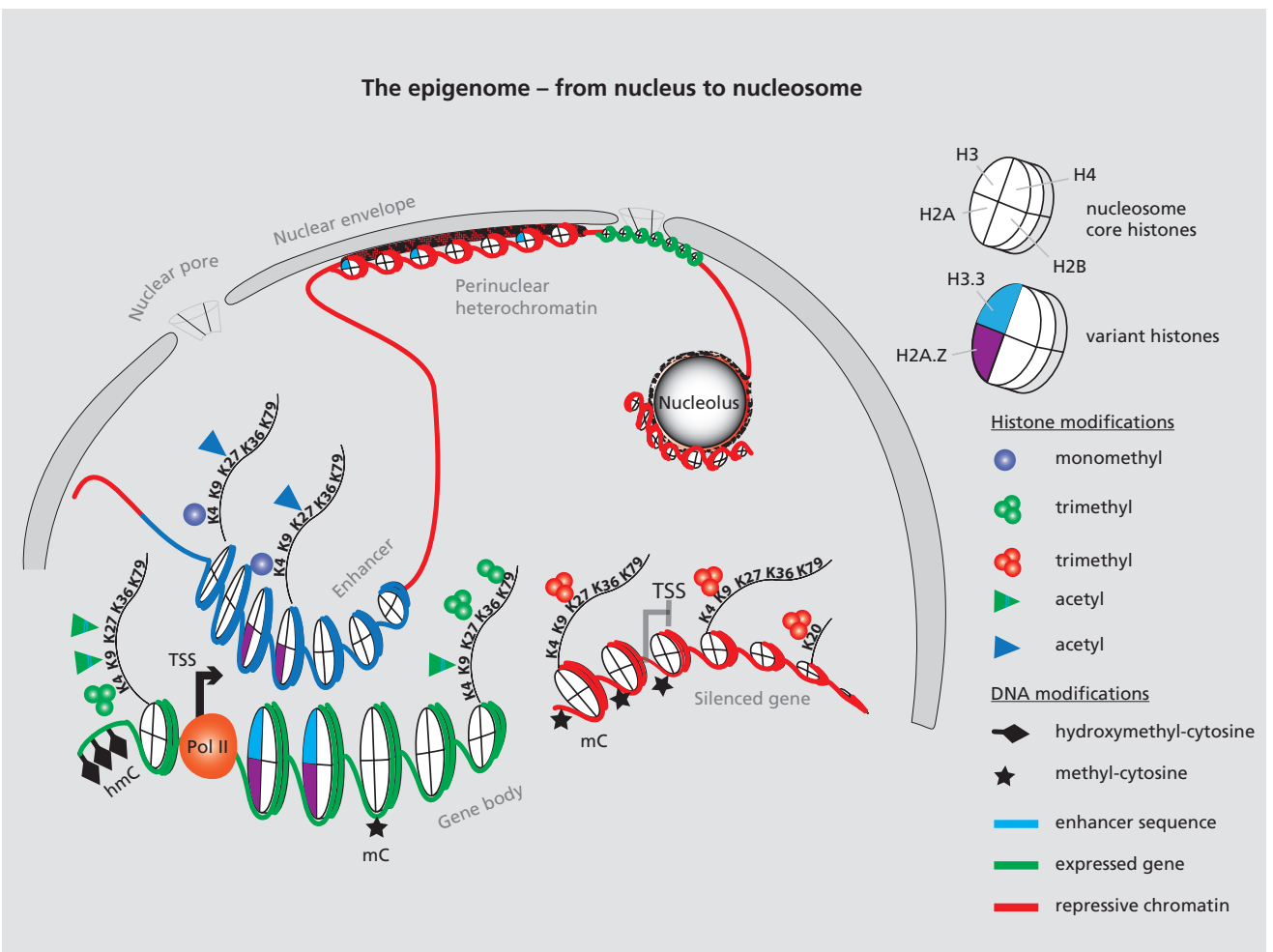

Figure 1. Basic building blocks of the epigenome. The epigenome of a eukaryote (a cell with a well-defined nuclear membrane) is comprised of DNA modifications, including (but not limited to) cytosine methylation and hydroxymethylation, and a large number of site and residue-specific histone modifications and histone variants, only some of which are shown in this figure as representative examples. These molecular building blocks largely define the epigenetic landscapes that organize genomic DNA, often in a locus-specific fashion into active transcriptional units (green) including promoter and enhancer sequences (blue) and condensed chromatin including silenced genes (red). These epigenetic signatures are thought to distinguish between various cell types and developmental stages sharing the same genome.[24,25] Many heterochromatic sequences are tethered to the nuclear envelope and pore complex, and also enriched at the periphery of the nucleolus (an intranuclear compartment for ribosomal biogenesis). A representative subset of histone variants and site-specific lysine (K) residues at histone H3 and H4 N-terminal tail that are potentially modified by methylation and/or acetylation, two types of covalent modifications among many others (see text). TSS, transcription start site; Pol, polymerase; hm, hydroxymethylation

Epigenetic studies in SCZ postmortem brain and peripheral tissues—past and future

There can be little doubt that despite of the lack of a unifying neuropathology, many cases of SCZ are affected by gene expression alterations in the cerebral cortex and other brain regions, often including transcripts important for oligodendrocyte function and myelination,[41-46] or inhibitory and excitatory neurotransmission,[47-59] among others. It is almost always unclear whether these transcriptional changes are directly related to the underlying etiology or secondary events in the pathophysiology of disease. Given that transcriptional mechanisms are tightly linked to the chromatin remodeling and histone modification machinery in the nucleus,[60,61] it would come as no surprise if some of the genes affected by altered expression in SCZ brain showed concomitant changes in the epigenetic architecture of their promoters, enhancers, repressor elements and other regulatory sequences. To date, the majority of studies were focused on the quantification of DNA methylation (as a repressive mark) at candidate gene promoters, with some of the early work focused on the *REELIN* glycoprotein, the catechyl-O-methyltransferase *COMT*, the *SOX10* developmental transcription factor.[62-64] A few studies have measured changes in promoter-bound nucleosomal histone modifications, including histone acetylation and methylation.[65,66] Interestingly, DNA methylation and histone modification changes at some of the promoters with altered epigenetic status in SCZ postmortem brain, including *REELIN, Glutamate decarboxylase (GAD)1* (encoding GAD67 GABA synthesis enzyme) and *BDNF (brain-derived neurotrophic factor)* were also found in lymphocyte extracts from patients,[67-70] which if independently confirmed would warrant further examination as potential epigenetic biomarkers.

At the time of writing, however, very few studies have pursued DNA methylation or histone modification changes in SCZ on a genome-wide scale in brain tissue or peripheral cells,[67,71-74] and none of these studies has harnessed the full power of modern ("next-generation") sequencing technology that provides a near unbiased view of the distribution of an epigenetic mark across the entire genome.[75] These modern epigenomic mapping technologies, when applied in conjunction with whole genome sequencing of specific individuals, are expected to inform on epigenetic alterations that could be driven by the underlying genetic risk architecture.[76] As an illustrative example for the potential benefits when epigenome mappings are combined with genotyping, consider a recent report on risk-associated genetic variants for the autoimmune disorder multiple sclerosis, which showed a striking enrichment for regulatory sequences subject to distinct epigenetic decorations in immune cells, with disease-associated chromatin signatures that specifically affected promoters and enhancer elements.[77] Given that, according to recent genome-scale studies conducted in cerebral and cerebellar cortex of control subjects, many hundreds of DNA methylation sites are significantly affected by single nucleotide polymorphisms (SNPs) and variants, some of which separated from the methylation site by more than one megabase.[78,79] From this, there can be little doubt that in SCZ too, a significant portion of the epigenetic risk architecture is likely to be ultimately driven by the underlying genetic risk variants. Importantly, many of the DNA polymorphisms— according to some estimates, several thousand SNPs each could contribute a small but nonetheless significant SCZ risk[80,81]—do not change protein coding sequence and do not locate to exonic sequence. Therefore, cell-type specific epigenome mappings in normal and diseased human brain will be among the few options currently available to illuminate the functional and biological significance for many of these disease-relevant DNA polymorphisms.[81]

The potential benefits of including genotype information when analyzing epigenetic alterations in brain (or peripheral tissues) of specific cases diagnosed with SCZ also became apparent in some of the aforementioned candidate gene studies. The *GAD1* promoter (chr. 2q31), which regulates GAD67 γ-aminobutyric acid (GABA) synthesis enzyme expression, could serve as an illustrative example. The GAD67 transcript is downregulated in cerebral and cerebellar cortex of a significant portion of subjects diagnosed with schizophrenia, depression, or autism, and this type of alteration may contribute to desynchronization of cortical networks and cognitive dysfunction due to defective GABAergic inhibition.[50,82-87] Interestingly, a haplotype (a group of neighboring SNPs that are in linkage dysequilibrium with each other) positioned within few Kb from the *GAD1* transcription start site confers genetic risk for accelerated loss of frontal lobe gray matter[88,89] and, via epistatic interaction with catechol-o-methyl-

transferase (COMT) alleles regulating synaptic dopamine, modulates prefrontal GABA levels. [90] Notably, subjects with schizophrenia who are biallelic for this *GAD1* promoter-associated risk haplotype, in striking contrast to cases with the protective alleles, show a significant deficit in prefrontal *GAD67* transcript together with a shift in the epigenetic decoration of the surrounding chromatin, with loss of a facilitative histone methylation marking (histone H3 trimethyl-lysine 4) and excess of a repressive mark, histone H3 trimethyllysine 27 *(Figure 2)*.[66] Interestingly, these disease-associated changes in local chromatin templates at specific gene promoters apparently are accompanied by additional alterations in higher order chromatin structures, because decreased *GAD1/GAD67* expression in SCZ prefrontal cortex (PFC) is accompanied by a weakening of a long range promoter-enhancer loop that normally interconnects regulatory sequences positioned

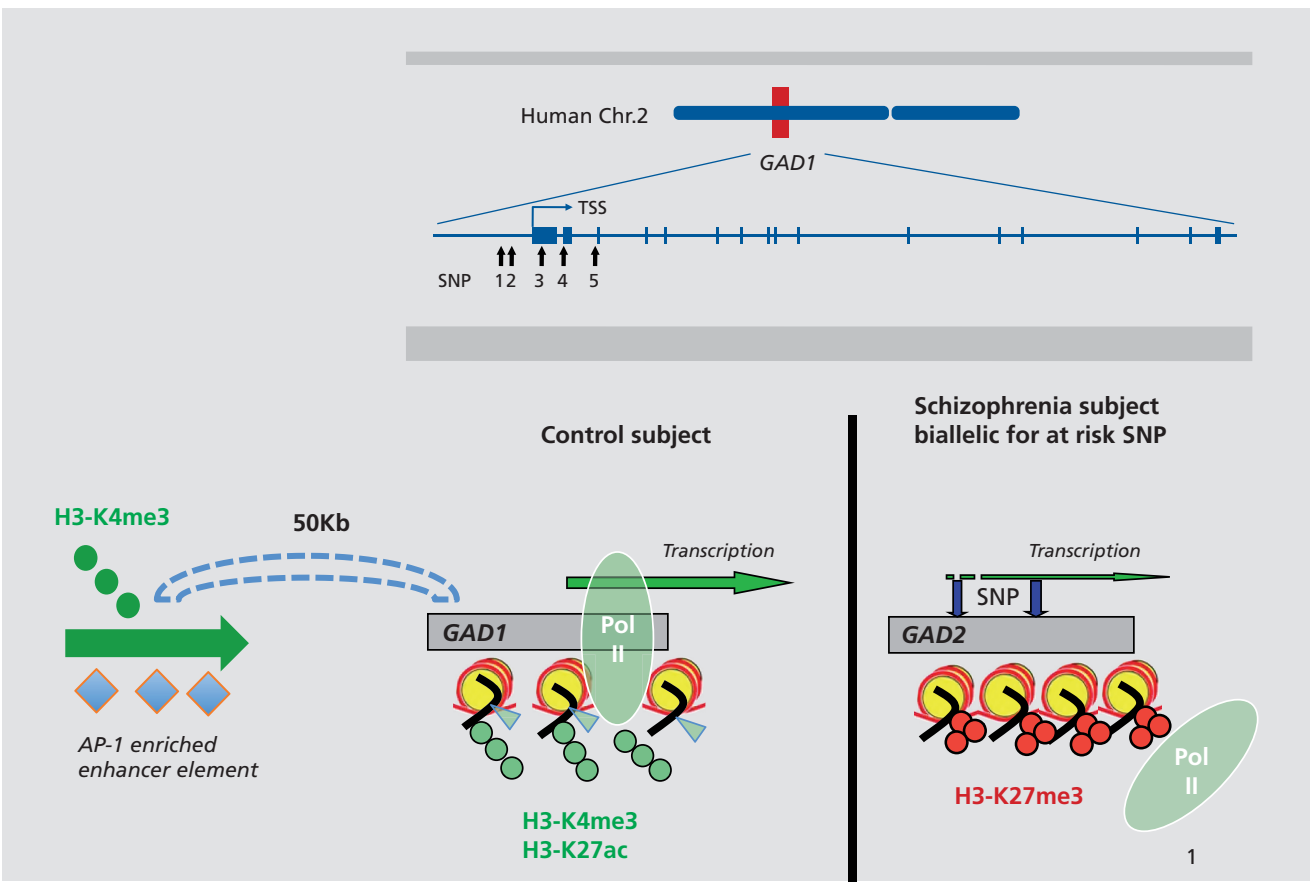

Figure 2. Multiple layers of epigenetic dysregulation for the *GAD1* promoter in SCZ prefrontal cortex. (top) A haplotype, comprised of at least five single-nucleotide polymorphisms within a few Kb from glutamate decarboxylase *(GAD)1* transcription start site confers genetic risk for childhood-onset schizophrenia and accelerated loss of gray matter[88] and is associated with decreased *GAD1* gene expression in cerebral cortex of subjects on the psychosis spectrum. The at-risk haplotype, through yet unknown mechanisms, is in diseased individuals associated with decreased *GAD1* gene expression, and a shift from open chromatin with high levels of the permissive marks, histone H3-trimethyl-lysine 4 (H3K4me3) and H3-acetyl-lysine 27 to a more repressive state with the open marks H3K4me3 and H3K27ac replaced by a restrictive mark, H3K27me3. As a result, there are lower levels of transcription factors and phospho-activated RNA II polymerase (POl) at the proximal portions of the *GAD1* gene.[65,66] In addition to these changes in the epigenetic architecture of the *GAD1* promoter, there are additional alterations in higher order chromatin. These include a chromosomal loop formation that physically connects enhancer sequences 50 kilobases upstream of the GAD1 gene with the *GAD1* promoter and transcription start sites. These regulatory sequences are enriched with AP-1 (activating protein 1) transcription factor binding site and likely to promote GAD1 gene expression. In the PFC of some subjects with SCZ, there is a significant decrease in the GAD1 promoter-enhancer interaction frequency.[91]

50Kb upstream of *GAD1* with the gene's transcription start site and proximal promoter. [91] Therefore, some of the risk-associated DNA polymorphisms at regulatory noncoding sequences could impact not only the epigenetic status of local chromatin structures but even exert "long-range" effects and impact epigenetic regulation of sequences that are positioned many kilobases further up- or downstream *(Figure 2)*. Hence, one could expect that future epigenetic studies in SCZ postmortem brain will increasingly harness genotype information to explore whether epigenetic changes at the site of regulatory noncoding sequences are affected by underlying genetic variation related to disease risk[81] or working memory and other cognitive functions often compromised in psychosis.[92]

Epigenetics and "gene x environment" interactions

It is obvious that the very concept of epi- ("over," "above") genetics lends itself towards molecular models for "gene x environment" interactions in the field of biological psychiatry and virtually any other field of biomedical research.[93] From a heuristic perspective, the idea that myriads of external or internal factors could leave a long-lasting molecular imprint in the genome of our brain cells is extremely appealing to the neurobiological models of SCZ and related disorders, which often are viewed as neurodevelopmental in origin but cannot be fully explained by genetic risk. Some of the well-established risk factors, such as maternal infection during prenatal development with various types of viruses, pathogenic bacteria or parasites, are estimated to play a significant role ("population-attributable risk") in more than 30% of SCZ cases.[94] Indeed, symptoms of psychosis may not surface until early adulthood, but a multitude of primary disease mechanisms could have operated as early as the prenatal period and in infancy.[95] Furthermore, DNA and histone methylation mappings in the developing human cerebral cortex suggest that neuronal epigenomes specifically (and to some degree the non-neuronal constituents of cortex as well) are in the prenatal period and early childhood subject to presumably preprogrammed waves of DNA hydroxymethylation and methylation and histone H3K4 lysine (de) methylation at thousands of loci. In contrast, changes during the subsequent phases of maturation and aging are comparatively minor in relation to these earlier periods.[78,96-99] Thus, there is considerable potential for "epigenetic plasticity," particularly during the critical periods of human cortical development. Whether or not adverse environmental influences operating during these early time windows could indeed result in lasting and maladaptive "imprints" in our brain cells' chromatin is difficult to test. However, evidence from postmortem studies is in support of the hypothesis that early life experience may indeed leave a lasting epigenetic imprint in the human brain. For example, abnormal neuronal expression and DNA methylation of the *NR3C1* glucocorticoid receptor distinguishes suicide victims who experienced childhood abuse from those who did not (100) and there is evidence other additional genes and loci are epigenetically altered in adult brain after exposure to early life trauma.[101-103] In addition, some of the genes that become frequently dysregulated in the cortex of adult SCZ, including aforementioned *GAD1/GAD67* GABA synthesis gene,[104] are highly regulated across the extended period of prefrontal development, with expression levels ramping up slowly from the prenatal period at least until early adolescence,[66,105] with dynamic changes in promoter-bound DNA methylation and histone methylation and acetylation continuing across the entire lifespan.[65,66,96] This would, just as in the case of the aforementioned glucocorticoid receptor gene, indicate heightened epigenetic vulnerability of the GAD1 gene in early life. Indeed, this hypothesis received recent report from animal studies, because in the adult male rat, hippocampal *Gad1* expression and open chromatin-associated histone acetylation are positively influenced by the level of maternal care in the postnatal period, while repressive Gad1-promoter DNA methylation was negatively influenced.[106] Likewise, prenatal exposure to the alkylating and antimitotic agent methylazoxymethanol (MAM) causes decreased Gad1 expression and histone H3K4 methylation in adult rat prefrontal cortex,[107] a finding that is of interest given that similar changes were observed in clinical samples.[66,108] Other types of prenatal adverse events, such as excessive maternal immune activation and activation of cytokine signaling, could result in prefrontal cortex of adult offspring in widespread changes of the GABAergic transcriptome, including *Gad1*,[109] together with altered expression and epigenetic regulation of other SCZ susceptibility genes, including *Disrupted-in-Schizophrenia 1* (*DISC1*) in the prefrontal cortex of adult offspring.[110,111] These types of epigenetic vulnerability

may extend to other brain regions and an even wider developmental period. For example, it had recently been reported that stress in adolescent animals could, in the context of a *Disc1* mutation, result in altered DNA methylation at the tyrosine hydroxylase gene promoter in dopaminergic projection neurons of the ventral midbrain.[112] Furthermore, a number of genes epigenetically dysregulated in SCZ could be modulated, even in a fully matured brain. For example, in the cortex of adult mice, the synthetic nicotinic acetylcholine receptor agonist varenicline, like nicotine in doses comparable to those reported in heavy smokers, reduces DNA methylation load at the *Gad1* gene promoter, thereby increasing *Gad1* expression.[113,114] These findings, taken together, leave little doubt that environmental factors are likely to impact proper epigenetic regulation of SCZ-relevant genes across the entire lifespan.

Chromatin regulators linked to SCZ via evidence from genetics and functional genomics

To date, mutations and structural variants in perhaps up to 50 genes, each encoding a different chromatin regulator, have been linked to a wide range of neurodevelopmental syndromes, including rare monogenic forms of autism.[115] Importantly, however, chromatin defects in brain were traditionally considered static lesions of early development that occurred in the context of rare genetic syndromes, but it is now clear that mutations and maladaptations of the epigenetic machinery cover a much wider continuum, including adult-onset neurodegenerative disease.[22,116,117] Thus, there is a small but rapidly growing list of cases diagnosed with schizophrenia who harbor mutations in genes encoding chromatin regulators, including methyl-DNA binding proteins, histone modifiying enzymes and transcription factors. Thus, mutations and changes in the amino acid sequence of the neurodevelopmental susceptibility gene *Methyl-CpG-binding protein 2* (*MECP2*, best known as the "Rett Syndrome" gene) are thought play causal roles in some SCZ cases.[118,119] Furthermore, gene duplication of the histone methyltransferase *KMT1D/EHMT1* or the *MYTL1* transcription factor have been linked to some cases with SCZ.[120,121]

Such types of mono- or oligogenic forms of psychosis due to mutations in gene encoding a chromatin regulator are believed to be very rare and certainly not representative for the large majority of subjects on the SCZ spectrum. However, biological pathway analyses, after combining a diverse group of datasets, including risk loci from genome-wide association (GWAS) and copy number variant (CNV) studies and transcriptomics from diseased brain tissue, point to a broader contribution of the chromatin and nucleosome assembly machinery to the genetic risk architecture and neurobiology of schizophrenia.[122,123] This includes the major histocompatibility (MHC) locus, spanning 4 to 7.6 Mb on chromosome 6p21.32-p22.2, and as one of the most intensely explored regions of the human genome, it has been consistently implicated in SCZ genetics as early as 1974.[124,125] Interestingly, in a recent study on whole-genome gene expression profiles in lymphoblastoid cell lines (LCLs) from 413 SCZ cases and 446 controls, multiple histone variants encoded within the MHC region, including *HIST1H2BD*, *HIST1H2BC*, *HIST1H2BH*, *HIST1H2BG* and *HIST1H4K,* emerged among the top differentially expressed transcripts in the disease cohort[126] and are likely to take part in complex chromosomal loopings that define local genome architectures at this locus in brain cells.[127]

Epigenetic therapies for SCZ?

Antipsychotics are the mainstay of the pharmacological treatment of SCZ, but the majority of patients show an incomplete response with an unfavorable disease course.[128] Much of the problem revolves around the negative and cognitive symptoms that are responsible for the debilitating effects of SCZ and often do not respond to pharmacological treatment.[129] It remains to be seen whether or not the knowledge gained by the field of neuroepigenetics will contribute towards improved treatment options in the future. Interestingly, both typical antipsychotics acting as dopamine D_2 receptor antagonists and atypicals with a more mixed receptor profile affect DNA methylation and histone modification levels in cerebral cortex and striatum, two key nodes in the neural circuits of psychosis.[19,130-132] It is currently unclear whether these observations, which are mostly of a correlative nature, indeed would indicate a critical role of chromatin regulatory mechanisms for antipsychotic drug action. In the following, inhibition of histone deacetylase activity will be discussed as one of the potential avenues for new antipsychotic drug research. As further discussed below, there are significant challenges that need to be overcome

before such type of epigenetic therapy would be given serious considerations.

Histone acetylation is associated with a more flexible and "open" chromatin state, thereby facilitating gene expression; one example of this is that it enables enhancer and other regulatory sequences separated from a gene target site by thousands of kilo- or even megabases, to engage with distant promoters in chromosomal loop formations.[133] Histone acetylation is regulated by the opposing effects of histone acetyltansferases (HATs) and deacetylases (HDACs). There are at least 18 different HDACs encoded in the human genome, which are commonly divided into four classes, based on their equivalents in yeast.[134] Class I includes HDAC1, 2, 3, and 8, class II/IIa include HDAC 4,5,6,7,9, and 10, and HDAC11 is the sole representative of class IV (134); all these HDACs are defined by a zinc ion site in the catalytic binding pocket which also explains why many classical HDAC inhibitor (HDACi) drugs, including short-chain fatty acids (eg, butyrates), related compounds (eg, sodium valproate) and trichostatin A,[134] have a broad profile and act on multiple HDACs (note that the clinically effective doses of valproate, as a mood stabilizer and anticonvulsant, are below those required to induce histone hyperacetylation in brain).[135] Class III HDACs, which are also known as sirtuins, are defined by a different catalytic site, without the zinc ion but with nicotineamide dinucleotide (NAD+) as an essential cofactor.[134] Most, or perhaps all of the HDACs are thought to target various nuclear and cytoplasmic non-histone proteins for deacetylation.[134]

Interestingly, expression of the class I histone deacetylase, *HDAC1* was increased (on average 30% to 50%) in the prefrontal cortex and hippocampus of multiple SCZ postmortem brain cohorts.[84,136-138] Therefore, abnormal *HDAC1* expression in corticolimbic circuitry is a type of molecular pathology representative for a significant portion of subjects with SCZ. Furthermore, overexpression of *Hdac1* in young adult mouse prefrontal cortex resulted in robust impairments in working memory, increased repetitive behaviors and abnormal locomotor response profiles in novel environments, in conjunction with dysregulated expression of more than 300 transcripts, including several that are located in the MHC risk locus on chromosome 6p21.3-22.1. [138] Interestingly, *Hdac1* expression becomes successively downregulated during the course or postnatal development, which could point to a neurodevelopmental etiology for the observed excessive *HDAC1* expression in adult SCZ.[138] Interestingly, *Hdac2* which like Hdac1 is a class I HDAC (see above) has also recently been implicated in SCZ. Specifically, overexpression of *Hdac2* in a mouse prefrontal cortex resulted in SCZ-like phenotypes, including diminished prepulse inhibition.[19] On the other hand, conditional deletion of *Hdac2* in postnatal forebrain neurons resulted in improved attentional set-shifting in the adult,[139] which would suggest that alterations in expression or activity of HDAC2 result in very complex brain phenotypes, dependent on cell type and developmental stage.

These findings would suggest that drug-induced inhibition of neuronal and/or glial HDACs could result in a therapeutic effect for SCZ. However, there are significant challenges to explore this hypothesis in a clinical context. As discussed in in a recent review,[135] there are newly developed potent HDAC inhibitor drugs (HDACi) either approved or in clinical trials, such as the benzamide-based MS-275 (tradename Entinostat), which crosses the blood-brain barrier and when orally administered indeed exerts a therapeutic effect in preclinical models of traumatic brain injury and neurodegeneration.[140,141] However, these drugs, which are mostly used as anticancer agents, broadly inhibit multiple HDAC isoforms, lack CNS specificity, and, while not directly cytotoxic, nonetheless exhibit a safety profile that would mandate additional investigations prior to any experimental use in psychiatric patients.[135] In addition, animal studies suggest that HDACi potentially augment therapeutic effects of atypical antipsychotic drugs[19,142] and antidepressants.[143-146] However, such types of combination treatments and polypharmacy would require even stricter safety criteria as compared with single drug regimens. We have argued that it may be premature to initiate trials with HDACi or other epigenetic drug targets in SCZ, but given that this is a rapidly evolving field, pending the availability of HDACi with favorable safety profiles, such trials should then given serious consideration.[135] Interestingly, the human genome also encodes 50 proteins containing "bromodomains," which essentially recognize and bind acetylated histone lysine residues[147] and are thought to provide an important scaffold to recruit transcriptional proteins. [148] The interaction acetyl-lysine binding pocket of these proteins is considered "druggable" and already identified as potential therapeutic target in some cancers and inflammatory disease.[148] Some of the bromodomain

containing proteins, including *BRD1*, are differentially regulated in cerebral cortex and hippocampus after electronconvulsive seizures[149] and could provide important drug targets to treat conditions such as SCZ that are associated with transcriptional dysregulation in the cerebral cortex and other forebrain areas.

Conclusion

An increasing number of genes encoding chromatin regulators are linked to mono- and polygenic forms of neurodevelopmental disease, including some cases with schizophrenia. Furthermore, it is generally accepted that a significant portion of the genetic risk architecture of schizophrenia is positioned outside of coding sequences and in regulatory elements for gene expression (promoter, enhancers, repressors etc). Such types of regulatory elements are commonly defined by virtue of specific types of histone modifications and other types of epigenetic decorations, and therefore the combined epigenomic/genomic analyses in specific disease cases is expected to provide deep insights into the underlying molecular mechanisms of disease. Early findings from postmortem brain studies link some of the gene expression alterations in schizophrenia to changes in promoter-bound DNA methylation and post-translational histone modifications. However, the field lacks larger-scale studies that map on a comprehensive and genome-wide scale the various epigenetic markings in diseased tissue. Such studies are urgently needed, particularly because a number of animal studies link developmental risk factors, including maternal immune activation during pregnancy and rearing conditions in the early postnatal period, and certain drugs and toxins, to lasting epigenetic alterations in offspring brain. Finally, many chromatin regulators are considered "druggable" and bear potential promise for novel treatments of schizophrenia and other neuropsychiatric diseases. ❑

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Mecanismos epigenéticos en la esquizofrenia

La esquizofrenia es un importante trastorno psiquiátrico que carece de una neuropatología única, y que los tratamientos farmacológicos disponibles en la actualidad solo aportan beneficios limitados para muchos pacientes. Esta revisión discute cómo el campo de la neuroepigenética podría contribuir a los avances del conocimiento existente sobre la neurobiología y el tratamiento de las psicosis. Es probable que el mapeo a gran escala del genoma de la metilación del ADN, las variantes y modificaciones de la histona, y los lazos cromosómicos para las interacciones entre el reforzador y el promotor, y otros determinantes epigenéticos de la organización y función del genoma proporcionen pistas importantes acerca de los mecanismos que contribuyen a la mala regulación de la expresión de los genes sinápticos y metabólicos en el cerebro de pacientes con esquizofrenia, incluyendo los potenciales vínculos con los riesgos genéticos subyacentes a la arquitectura y a las exposiciones ambientales. Además, los estudios en modelos animales están aportando una lista rápidamente creciente de mecanismos reguladores de la cromatina con efectos significativos en la cognición y en conductas complejas, lo que apunta al potencial terapéutico de fármacos epigenéticos para blancos en el sistema nervioso.

Mécanismes épigénétiques dans la schizophrénie

La schizophrénie, trouble psychiatrique majeur, manque d'une neuropathologie unifiée, les médicaments actuellement disponibles n'offrant que des bénéfices limités à de nombreux patients. Cet article étudie la façon dont la neuroépigénétique pourrait faire progresser les connaissances actuelles en neurobiologie et en thérapeutique de la psychose. La cartographie à l'échelle du génome de la méthylation de l'ADN, des modifications et des variantes de l'histone, des boucles chromosomiques des interactions promoteur-activateur et d'autres déterminants épigénétiques de l'organisation et de la fonction du génome sont probablement des pistes importantes menant aux mécanismes participant à l'expression dérégulée des gènes métaboliques et synaptiques au sein du cerveau schizophrène, y compris les liens éventuels avec l'architecture sous-jacente du risque génétique et les expositions à l'environnement. De plus, des études de modèles animaux fournissent une liste exponentielle de mécanismes de régulation de la chromatine ayant des effets significatifs sur la cognition et les comportements complexes, suggérant donc des cibles médicamenteuses épigénétiques à potentiel thérapeutique dans le système nerveux .

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