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PSYCHOSIS (R GUR AND B CLEMENTZ, SECTION EDITORS)

Epigenetic Dysregulation in the Schizophrenic Brain

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Abstract Schizophrenia (SCZ) is a severe psychiatric disorder, which lacks a unifying neuropathology. However, reproducible molecular alterations exist, including RNA expression changes affecting GABAergic and other neuronal signaling in cerebral cortex, myelination, and other cellular functions. Yet, for the large majority of RNAs altered in the SCZ brain, the underlying transcriptional and post-transcriptional disease-associated mechanisms remain unclear. Here, we provide an update on epigenetic regulators of gene expression that are potentially affected in some cases with SCZ, including DNA cytosine methylation, histone modifications and histone variants, and chromosomal loop formations facilitating long-range interactions of gene promoters with distal enhancer elements. Exploration of chromatin structure and function, in combination with transcriptome and genome sequencing, is likely to critically advance insight into the molecular mechanisms of disease in specific cases with SCZ.

Keywords 3-dimensional genome · Chromatin-bound RNAs · Chromatin remodeling · Chromosomal loop formation · CpG · DNA cytosine methylation · DNA modification · Enhancer · Epigenetic · GABAergic · GAD1 · Higher-order chromatin · Histone modification · Histone variants · Hydroxymethylation · Methylation · Nucleosome positioning · Postmortem · Post-translational modification · Risk architecture · Schizophrenia · Silencer · Transcriptome

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Introduction

Schizophrenia (SCZ) is a severe psychiatric disorder defined by symptoms such as delusions, hallucinations, and thought disorder, reducing the lifespan of an affected individual on average by 15 years, with cardiovascular risk as the chief cause of increased mortality [1]. Since the second half of the last century, antipsychotic drugs have been the mainstay of treatment but, even now, the majority of schizophrenia patients still suffer from a severe illness that substantially impacts quality of life and increases the risk for suicide, while experiencing incomplete response to treatment [2, 3]. Therefore, there is a pressing need to develop new treatment options in schizophrenia that ideally should go beyond the molecular targets of the currently available antipsychotics, which are primarily aimed at monoaminergic receptor systems [4, 5]. However, rational drug development in schizophrenia is greatly impeded by the lack of a unifying neuropathology and a complex genetic risk architecture, which does not appear to converge onto narrowly defined signaling pathways or molecular mechanisms.

It is now generally accepted that many individuals on the schizophrenia spectrum are affected by dysregulated gene expression influencing widespread areas of the cerebral cortex and other brain regions, thereby pointing to molecular and cellular alterations in the oligodendrocyte lineage [6–11], and compromised inhibitory and excitatory neurotransmission due to altered expression of ligand-gated ion receptors, reuptake transporters, metabolic enzymes, etc. [12–24]. It is largely unclear whether these transcriptional changes are directly related to the underlying etiology or are secondary events in the pathophysiology of disease.

These molecular findings in the postmortem brains of subjects with SCZ often serve as a starting point and, when followed up by experimental work in preclinical and translational laboratories, bear the potential to critically advance

insight into the neurobiology of psychosis. For example, a more recent key advance in the pathophysiology of SCZ concerns molecular defects in cortical inhibitory GABAergic circuitry, which ultimately are thought to contribute to cognitive defects by altering synchronization of electrical activity across widespread cortical areas [25–28]. Remarkably, the empirical framework for this hypothesis was originally rooted in a large body of postmortem literature reporting downregulated gene expression for the rate-limiting GABA synthesis enzyme, 67Kda glutamic acid decarboxylase (GAD67), in multiple subtypes of cortical interneurons, including those commonly defined as fast-spiking parvalbumin+, and low-threshold spiking somatostatin + cells [15, 18, 29–33]. Indeed, it is now thought that 30–40 % of individuals with SCZ are affected by robust deficits in GABAergic gene expression in the prefrontal cortex (PFC) [34].

While the aforementioned RNA expression changes in the SCZ postmortem brain have had a considerable impact by reshaping current models of the pathophysiology of the disease, mechanistically the disease-associated molecular defects remain incompletely understood. Transcriptional mechanisms are tightly linked to epi- (Greek for *over*, *above*) genetic regulation of chromatin structure and function, including several types of DNA cytosine methylation and an estimated number of more than 100 site- and residue-specific post-translational histone modifications. Importantly, nucleosomes as the elementary unit of chromatin (comprising 146 base pairs of genomic DNA wrapped around an octamer of the four core histones, H2A, H2B, H3, and H4), various histone and DNA methylation markings, and other molecular architectures inside the nucleus (Fig. 1) remain stable for a prolonged period after death. Thus, nucleosomal organization, including epigenetic decorations, is maintained in postmortem brain tissue, which typically is exposed to 5–30 (or more) hours of autolysis time before being safely stored in a freezer [35, 36]. Unsurprisingly, there is a rapidly increasing number of studies that have charted—either locus-specific or even genome-wide—disease-associated changes in DNA cytosine methylation and hydroxymethylation, residue-specific histone methylation and acetylation, and various other types of epigenetic markings in human brain tissue or in some of its surrogates such as the olfactory epithelium. Here, we provide a concise update on epigenetic studies in the SCZ brain and discuss the resulting implications for the neurobiology and treatment of the disease.

DNA Cytosine Methylation

Two related but functionally very different types of DNA modifications, methylation (m) and hydroxymethylation (hm) of cytosine at the carbon 5 position in CpG dinucleotides (DNA sites where a cytosine nucleotide occurs next to a guanine nucleotide), provide the bulk of the epigenetic modifications in vertebrate DNA [37]. In addition, there are chemical intermediates resulting from mC5 and hmC5 synthesis and breakdown (He, et al. 2011, Ito, et al. 2011). The majority of DNA methylation is found at sites of CpG dinucleotides, particularly at sequences enriched with CpGs. In the cerebral cortex, however, up to 25 % of mC5 in the brain is found at non-CpG sites [38]. The hmC5 mark is concentrated toward the 5′ end of genes and the proximal-most portions of transcriptional units, and broadly correlates with local gene expression levels [39, 40]. In the brain, one of the tissues with the highest levels of hmC5, the mark is enriched in many active genes [41] and may play a role in the regulation of intron/exon boundaries and splicing events of neuron-specific gene transcripts [42]. On the other hand, less than 3 % of methyl-cytosine (mC5) markings are positioned around the 5′ end of genes [43]. The classical concept of the transcriptional regulatory role of DNA methylation, which has also guided many brain-related studies, is that DNA methylation at transcription start sites and proximal gene promoters functions as a negative regulator of transcription [44]. Furthermore, it is now generally accepted that DNA methylation, just like the other types of epigenetic markings discussed below, undergoes highly dynamic regulation in the developing brain and maintains the potential for bi-directional regulation and reversibility in the adult brain, particularly in the context of experience, exposure to drugs, and learning.

Some of the early epigenetic studies in SCZ brains were focused on DNA methylation of candidate gene promoters. Examples include hypermethylation of the *REELIN* promoter, hypomethylation of COMT, and hypermethylation of SOX10. REELIN encodes a glycoprotein that is critically important for cortical inhibitory GABAergic circuitry and, more generally, neuronal migration and connectivity formation [45, 46]. *COMT* encodes catechyl-O-methyltransferase, which is a key regulator of monoamine signaling [47]. *SOX10* is a transcription factor gene that is important for oligodendrocyte maturation and myelination [48]. Some of the promoter DNA methylation changes that were found to be associated with corresponding alterations in gene expression in the cerebral cortex from small cohorts of SCZ subjects were independently replicated [49]. There is a general consensus that between-group differences (SCZ vs. control) show at best only subtle changes between cases and controls [50•, 51, 52]. This is not surprising, given the considerable degree of heterogeneity in terms of disease etiology, genetic risk architecture, and between-subject variability in exposure to various drugs that are known to affect brain DNA methylation levels, including alcohol [53], nicotine [54, 55], and stimulants [56, 57]. Genetic variation is likely a major factor for between-subject variability in brain DNA methylation. According to recent genome-scale studies conducted in the cerebral and cerebellar cortex, methylation of several hundred CpG-

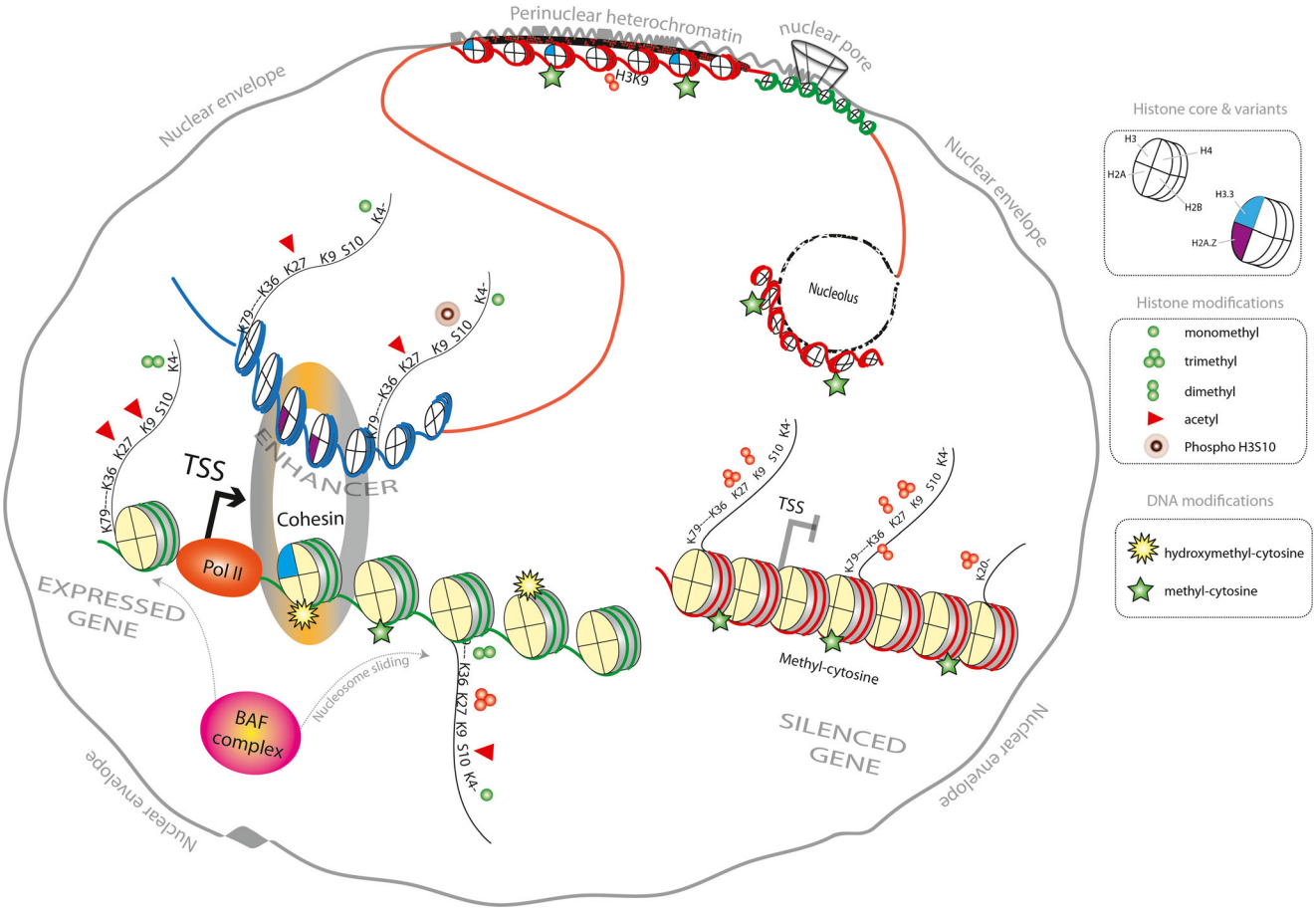

Fig. 1 Epigenetic mechanisms potentially relevant for transcriptional dysregulation in schizophrenia. Schematic illustration of some of the general principles of epigenetic regulation. Gene (green) poised for transcription by polymerase II (Pol II) initiation complex, with nucleosome-free interval at transcription start site (TSS). The distal enhancer sequence (blue), which on the linear genome could be separated by hundreds of kilobases from a gene, is in a loop-like structure moved in close proximity to its promoter target. The subset of heterochromatic portions of the genome (red), including silenced genes, are organized inside the nucleus in a non-random fashion and are bordering the nuclear envelope and the periphery of the nucleolus (intranuclear organelle involved in ribosomal gene expression and assembly). A small subset of representative histone variants and histone H3 site-specific lysine (K) residues at the N-terminal tail (K4, K9, K27, K36, K79) and H4K20 residue are shown as indicated, together with panel of mono- and trimethyl, or acetyl, modifications, which differentiate between active promoters, transcribed gene bodies, and repressive chromatin, as indicated. DNA cytosines that are hydroxymethylated at the C5 position are in the nervous system most prominent at active promoters and gene bodies, while methylated cytosines are positioned around repressed promoters and in constitutive heterochromatin, and within the body of some of the actively transcribed genes. Also shown are the cohesin complex, which tethers together promoter–enhancer and other types of chromosomal loopings, and multiple members of the BAF nucleosome sliding/chromatin remodeling complex as critical regulators for RNA polymerase access and mobility at transcription start sites and active genes. See the text for details, including implications for the SCZ brain

enriched sequences is significantly affected by single nucleotide polymorphisms (SNPs) and variants separated from the CpG site by more than one megabase [58, 59]. An even larger number of genetic polymorphisms have been linked to gene expression differences, including many SNP-based haplotypes within promoters and around the 5′ ends of annotated transcripts [60••]. Therefore, a firm conclusion on whether or not subgroups of SCZ subjects are defined by gene-specific DNA methylation changes in the cerebral cortex or other brain regions will require studies with large cohorts comprising hundreds of specimens and integrative analyses with DNA methylation mapping, genome sequencing, and careful evaluation of drug exposure and other confounding factors.

Histone Modifications

Epigenetic regulation of chromatin by virtue of histone modifications is extremely complex, with an estimated number of more than 100 residue-specific post-translational modifications (histone PTMs) molding and shaping the epigenome of a vertebrate cell [61]. These include, but are not limited to, mono- (me1), di- (me2)-, and tri- (me3) methylation, acetylation, and crotonylation, polyADP-ribosylation, and small-protein (ubiquitin, SUMO) modification of specific lysine residues, as well as arginine (R) methylation and "citrullination", serine (S) phosphorylation, tyrosine (T) hydroxylation, etc. [61–63]. An epigenetic histone code, or a

combinatorial set of multiple types of histone PTMs, is thought to define promoters, gene bodies, enhancer and repressor elements, and other regulatory sequences [64•]. It is important to emphasize that histone PTMs rarely occur in isolation; instead, multiple histone PTMs appear to be co-regulated and, as a group, they define the aforementioned chromatin states [65]. Many active promoters, for example, are defined by high levels of histone H3 lysine 4 methylation in combination with various histone lysine acetylation markings [64•]. Likewise, repressive histone PTMs, including the trimethylated forms of H3K9, H3K27, and H4K20, potentially co-localize to some of the same loci in the genome. There is evidence for coordinated and sequential regulation of histone PTMs. To mention one example, phosphorylation of histone H3 at the serine (S)10 position often serves as a trigger for subsequent acetylation of neighboring lysine residues histone H3 lysine 9 (H3K9) and lysine 14 (H3K14) in the context of transcriptional activation, while at the same time blocking repression-associated methylation of H3K9 [66]. The brain is no exception to this type of coordinated histone PTM regulation, and it has been observed, for example, in striatal neurons after exposure to antipsychotic drugs that are acting as dopamine D_2 receptor antagonists [67].

There is a rapidly increasing literature on histone PTM alterations in the SCZ brain, with the majority of studies exploring facilitative or repressive markings at candidate gene promoters that are important for GABAergic or glutamatergic signaling in the PFC and other cortical areas. For example, the *GAD1(GAD67)* GABA synthesis enzyme gene promoter shows in the SCZ cortex a shift from facilitative histone acetylation and H3K4 methylation toward repressive histone methylation markings [68, 69]. Interestingly, such histone PTM changes have been reported in animals exposed to suboptimal postnatal care and parenting [70] or antimitotic drugs during prenatal development [71], which would be consistent with the neurodevelopmental hypothesis of schizophrenia. These findings may be relevant for future treatments of SCZ because, in the adult cerebral cortex, promoter-bound histone PTM at *GAD1* and various other genes are altered after exposure to antipsychotic and mood-stabilizing drugs [69, 72–74].

In addition to these pioneering histone PTM studies on candidate gene promoters in the SCZ brain, early genome-scale findings have been reported. In one pilot study on dissociated olfactory epithelium in four SCZ subjects, 22 genes showed altered expression in conjunction with changes in histone H3K4 and H3K27 methylation. Brain tissue is usually obtained postmortem. In vivo studies have consequently relied on peripheral blood, which has limits when comparing tissue-specific epigenetic changes. In an elegant approach, the authors addressed this challenge by using (olfactory) nervous tissue, which is more complementary to postmortem brain tissue [75].

Histone Variants

Histone variants—well known examples of which include H3.3, H2A.Z, and H2A.X—differ from the canonical histones only at very few amino acid positions but could play an important role in replication-independent assembly of nucleosomes and chromatin fibers [76]. Several histone variants robustly affect nucleosome stability and compaction [77]. One model postulates that during the process of gene expression, RNA polymerase and the transcriptional activation and elongator complexes destabilize nucleosomes, which, in turn, promote nucleosome remodeling and variant histone incorporation, which then further potentiate or stabilize the process of gene expression [78, 79]. Transcriptome changes in SCZ could include altered expression of histone *H2B type 1D* (*HIST1H2BD*) and other variants [80] that are positioned in the SCZ susceptibility locus on chromosome 6p22.1 [81].

Chromatin-Bound RNAs (CBRs)

The process of gene expression results in the nascent RNA molecule emerging from genomic DNA. In contrast, CBR applies to an RNA species that regulates chromatin function. CBRs and nascent RNA transcripts are not mutually exclusive. According to some estimates, up to 2–3 % of the nucleic acid content in chromatin is contributed by polyadenylated RNAs [82]. Among the best-known examples of a CBR is provided by the *X-chromosome Inactive Transcript (XIST)* [83, 84].

Perhaps one of the most illustrative and complex examples, as it pertains to a CBR with a critical role for normal brain development and function, includes chromosome 15q11–13—a highly regulated locus, which is subject to genomic imprinting (parent-of-origin-specific gene expression) and is responsible for a range of neurodevelopmental syndromes, including Prader–Willi and Angelman [85]. Furthermore, DNA structural variants within this locus could contribute to the genetic risks of schizophrenia and bipolar disorder, further emphasizing that this locus is broadly relevant for a range of neuropsychiatric disease [85]. Of note, a very large non-coding (nc) RNA arises from *15q11–13*, covering 1 Mb in the mouse and 600 kb in humans, with 148 exons and introns [86]. This long *SNPRN-UBE3A* ncRNA, which normally is highly expressed on the paternal chromosome but not on the maternal chromosome, includes clusters of smaller ncRNAs, which are thought to modulate nucleolar functions in neurons, and an antisense transcript, *UBE3A-AS*, which suppresses UBE3A sense transcription of the same gene on the paternal chromosome [85]. There is evidence that the *SNPRN-UBE3A* ncRNA, and the smaller RNAs derived from it, produce an "RNA cloud" in *cis* (at the site of the genomic locus), which contributes to lasting decondensation of this locus on the

paternal chromosome, including epigenetic decoration with open chromatin-bound histone modifications and loss of repressive chromatin-associated histone and DNA methylation [85, 87]. UBE3A, which is also known as E6-AP, encodes a ubiquitin ligase, which regulates RING-1B, a component of a repressive chromatin remodeling complex PRC1 [88]. Because PRC1 is a key regulator for genome-wide repressive histone (H3K27) methylation, dysregulated expression of long *SNPRN-UBE3A* ncRNA may affect orderly activity of the PRC1 complex in the developing brain [89–91], perhaps resulting in chromatin defects across widespread portions of neuronal or glial genomes, with serious implications for brain function and behavior.

Chromatin Remodeling and Nucleosome Positioning

Chromatin-remodeling complexes, according to their classical definition, regulate sliding and mobility of nucleosomes, powered by ATP hydrolysis, thereby regulating gene expression and RNA polymerase II access at transcription start sites [92]. Examples of well-known chromatin remodelers with a critical role in brain development include the BAF (SWI/SNF) complex and the CHD family of proteins [92]. Interestingly, mutations in numerous members of the BAF complex and multiple CHD proteins have now been linked to psychiatric disease, including SCZ [92–94].

Higher-Order Chromatin

Epigenetic decoration of nucleosomes, including the DNA and histone PTM and histone variants described, does not adequately portray chromatin architecture. This is because chromosomal arrangements in the interphase nucleus show a non-random organization. For example, loci at sites of active gene expression are more likely to be clustered together and positioned toward a central position within the nucleus, while heterochromatin and silenced loci move more toward the nuclear periphery [95, 96]. Chromosomal loopings, in particular, are highly regulated structures and are associated with transcriptional regulation and the process of gene expression. Chromosomal loopings enable regulatory enhancer or silencer elements—which, on the linear genome, are potentially positioned hundred of kilobases further up- or downstream from their target gene—to interact directly with that specific promoter [97–99]. The regulation of higher-order chromatin is certainly of critical importance for human health, including orderly brain development and function. For example, Cornelia de Lange syndrome (CdLS)—with an estimated incidence of 1:10–30,000 live births among the more frequent genetic disorders, as per http://ghr.nlm.nih.gov —is associated with neuropsychiatric symptoms, including psychosis [100]. CdLS (including *Online Mendelian Inheritance of Man (OMIM)* 122470 and 300590) involves causative mutations in the cohesin complex—a multisubunit protein, which includes, among others, nipped B-like protein (NIPBL), structural maintenance of chromosomal proteins SMC1A and SMC3, and histone deacetylase HDAC8 [101, 102]. Cohesin is thought to form ring-like structures bringing together DNA segments from different locations, and could provide a structural foundation for chromosomal loop formations, including promoter–enhancer loopings for cell-type specific gene expression programmes [103]. Importantly, chromosomal loop formations and 3-dimensional genome architectures are to some degree preserved in postmortem brain tissue [104•], and early findings indeed suggest that dysregulated gene expression in the SCZ brain could be associated with weakening of longer-range promoter–enhancer loopings [105••].

Conclusion and Outlook

Molecular alterations in SCZ include altered DNA methylation and histone PTM at a subset of genes. While none of the reported postmortem findings are expected to be consistently present across all cases diagnosed with the disorder, epigenetic dysregulation of gene promoter chromatin could contribute to alterations in GABAergic circuitry and other signaling defects of the cerebral cortex in SCZ. Larger studies are now necessary, ideally in hundreds of postmortem brain specimens, to undertake comprehensive mapping of neuronal and non-neuronal epigenomes, including DNA methylation, histone PTM, and chromosomal loop mapping in diseased and control brains. Ideally, this should be undertaken with whole-genome sequencing of the same cases, because both candidate gene studies and genome-scale surveys point to a connection between the epigenetic alterations in the diseased brain and the genetic risk architecture of the underlying psychiatric disorder [69, 106, 107]. There can be little doubt that epigenomic exploration of the brain and other tissues will provide critical insights into the molecular pathology of specific cases diagnosed with SCZ and other psychiatric disease.

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Compliance with Ethics Guidelines

Conflict of Interest Schahram Akbarian declares no conflicts of interest. Tobias Halene declares no conflicts of interest. Cyril Peter declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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