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Review

Association of histone modification with the development of schizophrenia

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ABSTRACT

Schizophrenia, influenced by genetic and environmental factors, may involve epigenetic alterations, notably histone modifications, in its pathogenesis. This review summarizes various histone modifications including acetylation, methylation, phosphorylation, ubiquitination, serotonylation, lactylation, palmitoylation, and dopaminylation, and their implications in schizophrenia. Current research predominantly focuses on histone acetylation and methylation, though other modifications also play significant roles. These modifications are crucial in regulating transcription through chromatin remodeling, which is vital for understanding schizophrenia's development. For instance, histone acetylation enhances transcriptional efficiency by loosening chromatin, while increased histone methyltransferase activity on H3K9 and altered histone phosphorylation, which reduces DNA affinity and destabilizes chromatin structure, are significant markers of schizophrenia.

1. Schizophrenia

Schizophrenia is a complex, heterogeneous psychiatric disorder influenced by both genetic and environmental factors, with a lifetime prevalence of approximately 1 % in the general population [1]. This condition manifests through a spectrum of symptoms: (i) positive symptoms such as delusions, hallucinations, paranoia, thought disorders, and psychomotor agitation; (ii) negative symptoms including emotional blunting, social withdrawal, and deficits in motivation and reward processing; (iii) cognitive impairment affecting learning, attention, executive function, and memory, particularly working memory [2,3]. Mood disturbances such as depression and anxiety are also common among patients.

The pathogenesis of schizophrenia is currently explained by several theories, the most notable being the dopaminergic hypothesis. This hypothesis proposes that positive symptoms arise from dysregulated dopaminergic neurotransmission in the limbic system of the midbrain, while disruptions in cortical pathways contribute to negative symptoms [4]. The glutamatergic hypothesis posits that changes in NMDA receptor-mediated glutamatergic transmission affect prefrontal neuronal connectivity [5], and the serotonergic hypothesis attributes disturbances in neuronal activity to serotonin overload from the dorsal raphe nucleus serotonergic hypothesis suggests that stress causes overload of serotonin from the dorsal raphe nucleus [6]. The GABAergic hypothesis suggests that an imbalance between cortical excitation and inhibition, driven by disruptions in GABAergic neurotransmission, underlies the disorder [7]. Additionally, nicotinic receptors play a role in cholinergic transmission; studies have shown that nicotine can improve attention and memory performance in schizophrenic patients [8]. Cognitive dysfunction, a core feature observed in over 80 % of individuals with schizophrenics, involves multiple brain regions, including the dorsolateral and medial prefrontal cortices and the parietal regions [9–11]. Structural abnormalities in the medial temporal lobe, particularly the hippocampus, have been linked to memory deficits and play a significant role in the neural networks responsible for memory and spatial navigation [12–16].

Environmental factors significantly influence the development and function of the central nervous system (CNS), impacting the

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manifestation of psychiatric disorders. Research has established a genetic basis for these disorders, characterized by DNA mutations, while also highlighting a growing focus on epigenetic modifications linked to disease processes [17]. These epigenetic changes include post-translational modifications of histones, DNA methylation, and the roles of non-coding RNA [18]. Unlike genetic mutations, epigenetic alterations do not change the DNA sequence; instead, they modify chromatin structure, thereby regulating gene transcription rates. Such insights are crucial for understanding the pathogenesis of schizophrenia [19].

2. Histone post-translational modifications

Both short- and long-term changes in gene expression are pivotal in neuroplasticity in adult animals. Physiological responses to environmental stimuli, for instance, often involve a rapid and transient transcriptional activation of specific genes. Initial studies indicated that these transcriptional dynamics were primarily governed by transcription factor activities and signal transduction pathways. Recent advancements, however, have elucidated the significant role of chromatin remodeling in regulating gene expression, with post-translational modifications of histone tails being central to this process [20,21].

In eukaryotic cells, nucleosomes—composed of approximately two turns of DNA wrapped around an octameric core of histones (two H3-H4 tetramers and two H2A-H2B dimers)—form the fundamental units of chromatin [22]. The C-terminus of core histones stabilizes the histone structure, facilitating histone-histone and histone-DNA interactions crucial for nucleosome assembly [23].]. In contrast, the N-terminal tail, featuring a flexible charged region, undergoes various reversible post-translational modifications (PTMs). These PTMs adjust the binding affinity of histones to DNA, impacting chromatin structure, nucleosome stability, and chromosome architecture [24,25]. These modifications can transition chromatin into a transcriptionally active state or contribute to gene silencing. Importantly, patterns of PTMs—either on the same histone tail (cis) or on different tails (trans)—create a 'histone code' deciphered by specific 'reader' proteins. These readers bind to modified histones, recruit effector complexes, and drive chromatin remodeling [26,27].

The established pattern of PTM is maintained by cell division during the physiology of the eukaryotic cell itself (in the absence of an initial signal), which allows for the inheritance of cell type-specific gene expression patterns established during cell lineage specification, thereby preserving cell identity [28]. In addition, some specific PTMs appear transiently, both as a link in multiple stages of altered chromatin states and as a result of cellular responses to changes in the extracellular environment [29]. In the nervous system, these histone modifications can serve as a precise regulation of gene expression, allowing cells to adapt to changes in their environment and play an important role in neuronal development, synaptic plasticity and behavioral memory [10].

Studies have shown that the N-terminal amino acid residues of histones can undergo various specific modifications, including acetylation, methylation, phosphorylation, ubiquitination, serotoninylation, lactylation, palmitoylation, dopaminylation, etc. [30,31]. Among them, ubiquitination, serotonylation, lactylation, palmitoylation, and dopaminylation [32–34] are novel histone modifications observed in recent years and attracts numerous attentions [35]. The etiology of schizophrenia related to these modifications needs to be further investigated.

2.1. Histone acetylation

2.1.1. Introduction to histone acetylation

Histone acetylation, a post-translational modification of lysine residues at the N-terminal ends of histone proteins surrounding DNA in eukaryotic chromosomes, is pivotal in CNS research [36]. It is regulated by two main classes of enzymes: histone acetyltransferases (HATs), which add acetyl groups, promoting chromatin relaxation and increased transcriptional activity, and histone deacetylases (HDACs), which remove these groups, condensing chromatin and reducing transcriptional activity [37,38].

2.1.2. Biological role of histone acetylation

Histone acetylation plays a crucial role in regulating genes associated with various diseases, including inflammatory, cardiovascular, neurological disorders, and cancers [39,40]. It is also essential for synaptic plasticity and memory formation. For example, in a situational fear conditioning model, histone acetylation levels were elevated in the hippocampal CA1 area during the early phase of long-term memory consolidation, triggered by NMDA receptors and ERK pathways [41] (Fig. 1). Further, in the Morris water maze, increased acetylation of H3 at lysines 9, 14, and 12 was linked to spatial memory consolidation [42]. Additionally, a hippocampus-dependent learning task showed enhanced acetylation at multiple histone sites, with subsequent genome-wide chromatin immunoprecipitation revealing upregulated expression of the formin2 gene, crucial for synaptic plasticity and memory, in an H4K12 acetylation-dependent manner [43].

Recently, studies that inhibit or activate HDAC confirm the significance of acetylation in memory processes, and HDAC inhibitors increase histone acetylation inducing dendritic sprouting, increased synapse number, restoration of learning behavior and acquisition of long-term memory [44]. Among them, HDAC1 activity was associated with fear memory fading to suppress excessive fear, and HDAC1 overexpression in the adult mouse hippocampus increased this specific form of learning [45]. HDAC2 overexpression was associated with hippocampus-dependent memory formation and impairment of working memory in mice, whereas HDAC2 KO exhibits enhanced memory, a process in which HDAC1 was not involved [46]. The pure-sibling mice with local tissue-specific knockout of HDAC3 in the CA1 region of the hippocampus also exhibited enhanced long-term memory (LTM) through H4K8 acetylation, Nr4a2 and c-fos transcription [47]. In addition, it found that knockdown of HDAC4 (in 2-month-old mice) and HDAC5 (in 10-month-old mice) impaired memory function [48,49]. In animal models, non-specific HDAC inhibitors have also been shown to improve the cognitive phenotype of neurodegenerative diseases [44], and enhance learning and memory in wild-type mice.

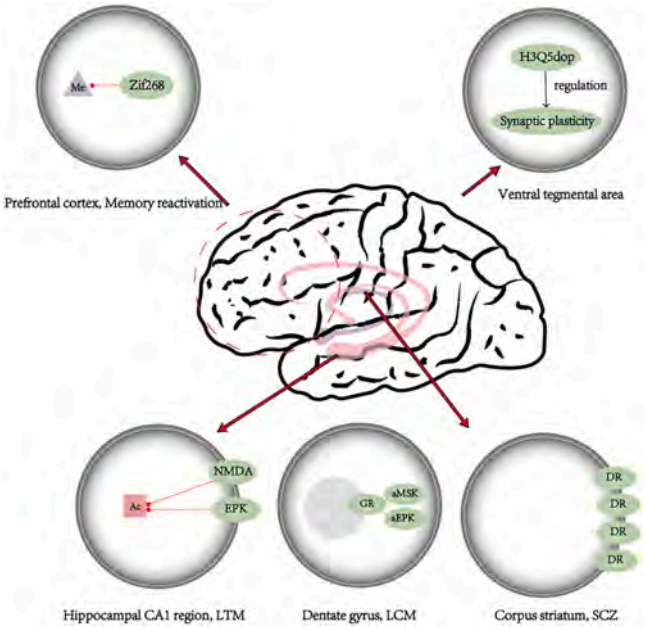

Fig. 1. Location and function of histone modifications in the brain.

2.1.3. The relationship between histone acetylation and schizophrenia

Compared with the control group, the levels of acetylated histone H3 and H4 in peripheral blood mononuclear cells (PBMCs) of schizophrenia patients decreased, while the levels of dimethylated histone H3K9 increased [50–52] (Fig. 2). In autopsy and PET neuroimaging studies, they found that HDAC2 expression decreased in the dorsolateral prefrontal cortex of patients with schizophrenia, while HDAC1 expression levels increased. Moreover, H3K9ac and H3K14ac levels decreased in young subjects with schizophrenia [53,54] (Fig. 1). A strong negative correlation between mRNA expression levels of the schizophrenia candidate gene GAD67 and mRNA expression levels of HDAC1, HDAC3 and HDAC4 has also been reported in other studies [55]. Valproate could increase H3 acetylation as well as H3K9, K14 acetylation in the GAD67 promoter region in lymphocytes from SCZ patients, while clozapine and sulpiride were found to promote valproate-induced chromatin remodeling [56]. The si-RNA-mediated knockdown of HDAC1 and pharmacological inhibition of HDAC1 impair learning and increase cell death, while HDAC1 expression is induced by neurotoxic stimuli and used to prevent ischemic cell death and DNA damage [57]. Hence, the increasing of HDAC1 expression may be a potential outcome and contributor to schizophrenia pathology. One study found that H3K9ac, H3K27ac, and H3K4me3 were overall enhanced and HDAC activity and HDAC4 protein expression were downregulated in the dorsolateral prefrontal cortex (DLPFC) of schizophrenic patients. Interestingly, H3K4me3 and H3K27ac were enhanced and HDAC activity decreased in the antipsychotic (HDAC inhibitor) treated group but not in the none-antipsychotic subgroup [58]. This finding encourages further exploration of the relationship between HPTM and antipsychotics to contribute to the treatment of schizophrenia. In addition to this, acetylation of histone H3 on the promoters of schizophrenia-related genes *GAD1,TOMM70A,HTR2C and PPM1E* has been shown to be associated with the expression of these genes [53]. One of these genes, BRD1, has been shown to be associated with mental health, and one study has investigated the effect of BRD1 knockout on the overall histone modification pattern in the mouse brain by constructing a novel Brd1 knockout mouse model (Brd1 -/-) using mass spectrometry. The results showed that histone H3 acetylation levels (H3K9ac, H3K14ac and H3K18ac) were reduced, suggesting that BRD1 controls gene expression at the epigenetic level by regulating histone H3 protein forms in the brain[59]. Furthermore, a study assessing histone modifications in human induced pluripotent stem cell (hiPSC)-derived forebrain neurons from schizophrenic patients by an unbiased proteomics approach found that acetylation of H2A.Z and H4 was highly expressed in neurons from schizophrenic cases and this result was confirmed in postmortem human brain, where the bromodomain and extra-terminal (BET) protein BRD4 was the true H2A.Z acetylation "reader" and that BET family protein inhibition ameliorates transcriptional abnormalities in patient-derived neurons [60]. Thus, therapies aimed at attenuating the interaction of BET proteins with highly acetylated histones may help prevent or treat schizophrenia.

2.2. Histone methylation

2.2.1. Introduction to histone methylation

Histone methylation is a post-translational modification involving the addition of methyl groups to lysine or arginine residues on histones H3 and H4, which wrap DNA in eukaryotic chromosomes. This modification commonly occurs at the N terminus, particularly at K4, K9, K27, K36, and K79 of histone H3 and K20 of histone H4 [61] (Fig. 3). Unlike histone acetylation, histone methylation involves varied methylation states—mono-, di-, or trimethylation—regulated by histone methyltransferases (HMTs) and histone demethylases (HDMs). Three main families of HMTs (PRMT1 arginine methyltransferase, SET domain, and non-SET domain DOT1/DOT1L methyltransferases) utilize S-adenosylmethionine (SAM) to transfer methyl groups [62]. Demethylation is mediated by amine oxidase LSD1 and the JmjC protein family.

Histone methylation can either repress or activate transcription, depending on the specific site and degree of methylation. For instance, trimethylation of H3K4 generally promotes chromatin opening, facilitating transcription [63], whereas dimethylation and trimethylation at H3K9 and H3K27 are associated with gene repression [64,65]. Moreover, the polycomb repressor complex 2 (PRC2), which includes the enhancer of Zeste homolog 2 (EZH2), can induce trimethylation at H3K27, playing a crucial role in maintaining cellular transcriptional

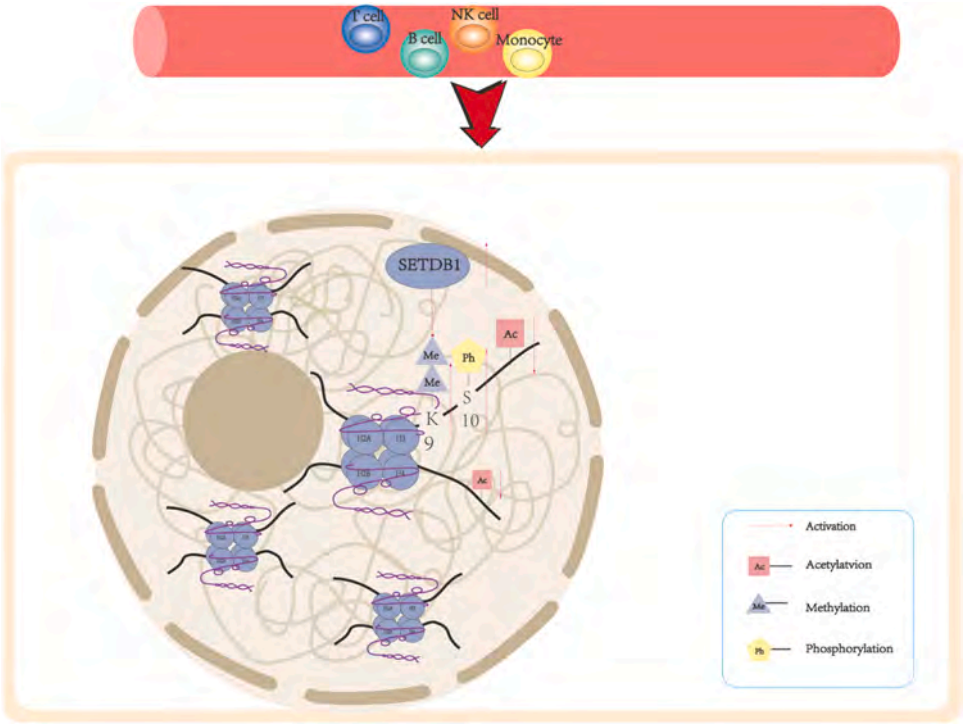

Fig. 2. Histone modifications in single nucleated cell in blood.

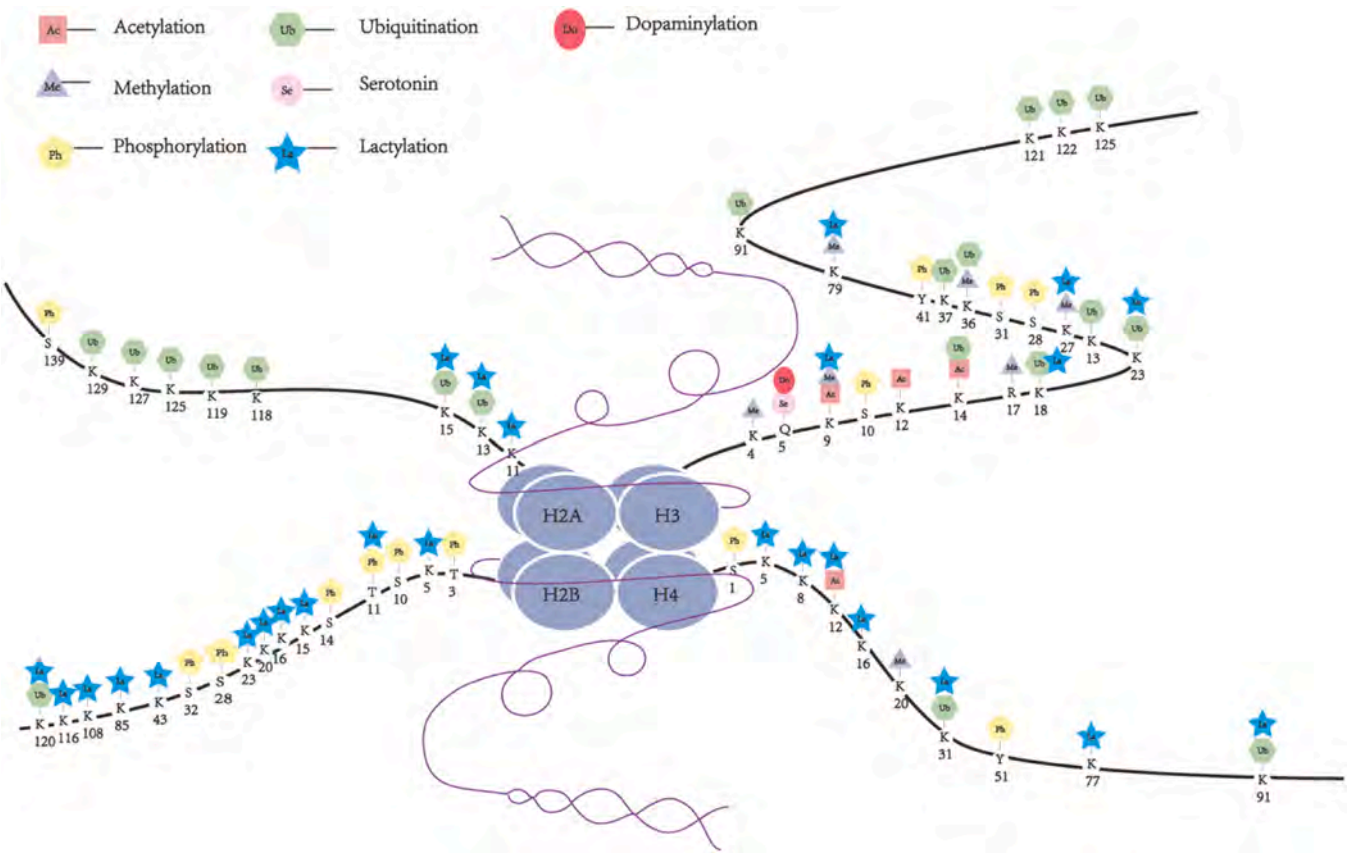

Fig. 3. Methylation modification sites in histone.

programs. The methyl group at H3K27me3 can be removed by demethylases, preventing the persistence of this modification [66].

2.2.2. *Biological role of histone methylation*

Histone methylation is thought to be closely related to cognitive abilities, such as memory formation and the process of learning. Studies have found that mice lacking the histone methyltransferase *mll2/kmt2b* gene in adult excitatory neurons exhibited impairment in hippocampal-dependent memory tasks, while DNA microarray data revealed that the expression levels of 152 genes were downregulated in the dentate gyrus of *kmt2b* knockout mice [67]. Histone H3 methylation, as well as other epigenetic modifications, has been regarded as a viable mechanism for memory storage because it has the potential function to encode experience-driven persistent changes in gene expression [68–70]. Graff *et al.* found that there was an increase in histone H3K4me3 accompanied by an rising in the promoter transcript level of the memory-related gene Zif268 in both the hippocampus of mice with recent memory reactivation (24 h) and in PFC of mice after long term memory reactivation (7d) (Fig. 1) [71]. Gupta *et al.* found that one hour after situational fear conditioning, both histone H3K4me3 and H3K9me2 appeared to be upregulated [72]. Thus, the above results indicated that both active gene expression and repression via histone methylation are necessary for memory formation. Histone methyltransferase inhibitors have been extensively studied in the direction of developing cancer therapeutic agents [73]. Progressively, histone methylation has also become a therapeutic target for cognitive impairment by repairing transcriptional differences in memory-related genes.

2.2.3. *The relationship between histone methylation and schizophrenia*

Increased expression of histone methyltransferases acting on histone H3K9 in brain and blood is an important marker of schizophrenia [74]. SETDB1 is a histone methyltransferase that specifically methylates histone H3K9 and is important for transcriptional repression and local chromatin formation in mice and humans [74]. In postmortem analysis of schizophrenic patients, increased expression of H3K9 histone methyltransferases, including SETDB1, and higher levels of histone H3K9me2 compared to healthy controls were demonstrated [74]. The role of SETDB1 in schizophrenia was also confirmed by the *Setdb1* transgenic mouse model. One study using CK-Setdb1 transgenic mice demonstrated that increased Setdb1 histone methyltransferase expression and activity was associated with an antidepressant-like phenotype in a behavioral paradigm associated with pleasure deprivation, despair, and helplessness [75]. Follow-up studies revealed that SETDB1 represses Htr3a transcription through RMER21B-mediated distal chromatin interactions in the embryonic ganglionic bullae and regulates the development of cortical Htr3a+ IN and emotional behaviors [76]. It provides the potential targets for schizophrenic symptomatic treatment. Moreover, NSD2 is also a histone methyltransferase that mediates the dimethylation of histone 3 lysine 36 (H3K36me2), and it has been suggested that the H3F3B and NSD2 genes, which are associated with histone modifications, may confer susceptibility to schizophrenia in the Chinese population [76]. Furthermore, high levels of histone H3R17 methylation were observed in the PFC of schizophrenic patients and were found to be associated with reduced expression of four metabolic genes, *CRYM*, *CYTOC/CYC1*, *MDH* and *OAT* transcripts [77]. A study suggests that antipsychotic drugs may act by regulating ADRA2A gene expression via H3K27me3 [78]. These findings set the stage for further exploration of the relationship between histone methylation and schizophrenia [79].

2.3. *Histone phosphorylation*

2.3.1. *Introduction to histone phosphorylation*

Histone phosphorylation, a post-translational modification, involves phosphorylating serine, threonine, and tyrosine residues on the histones

H2A, H2B, H3, and H4, which are part of the nucleosome structure surrounding DNA in eukaryotic chromosomes (Fig. 3). This modification is mediated by various protein kinases and is a crucial component of the 'histone code', affecting chromatin assembly and gene regulation [80].

2.3.2. Biological role of histone phosphorylation

In gene expression regulation, histone phosphorylation modulates the interaction between histones and DNA, thereby influencing chromatin structure and transcription activity. Specifically, phosphorylation at sites such as H3 S10 and S28 is linked to mitotic processes, while H4 S1 and H2A.X S139 play roles in meiosis and DNA damage repair. Additionally, phosphorylation at H3 S10 is primarily involved in regulating gene expression, H2B S10 in apoptosis, and modifications like H3 Y41 tyrosine phosphorylation and H3 S31 are associated with tumorigenesis [81–83].

2.3.2.1. Histone phosphorylation is involved in DNA damage repair. The integrity and stability of DNA are constantly challenged by environmental factors and stressors. In the mammalian cellular DNA damage response (DDR), H2AXS139ph is an important histone modification, often referred to as γH2AX [84,85]. It is involved in a variety of DDR pathways, including non-homologous terminal junction (NHEJ), homologous recombination (HR), and replication-coupled DNA repair, and is widely used as a marker of double-strand break DNA damage. DDR begins with the activation of ATM and ATR (ATM and Rad3-related) kinases, which phosphorylate many of the proteins that activate the DDR cascade reaction. Several phosphatases are regulated by their actions, including PP2A, PP1, Wip1 (wild-type p53-inducible phosphatase 1) and PP5. This broad distribution of γH2AX around the break is thought to create a specific signaling platform for the recruitment as well as retention of DNA damage repair and signaling factors, including the key mediator protein MDC1 recognized through the BRCT structural domain [86,87]. It is also thought that γH2AX allows the recruitment of other chromatin-modifying complexes (e.g., the ATP-dependent remodeler INO80 and SWR1) to DNA double-strand break (DSB) sites, and that the synergistic effect of these complexes enhances DNA accessibility to facilitate the repair process [88–90]. Once DNA is repaired, γH2AX must be removed from chromatin to prevent retention of repair proteins at the DSB and to allow efficient recovery from DNA damage-induced cell cycle arrest. It has been shown that both H2AZ (mammalian Htz1) and γH2AX are removed from chromatin near the DSB in an INO80-dependent manner [91]. In addition to this, γH2AX is also dephosphorylated by γH2AX phosphatases such as PP2A, Wip1, PP6 and PP4 [92–96].

In mammals, phosphorylation of H2BS14 was also detected during ionizing radiation-induced DNA damage and showed co-localization with γH2AX lesions [97]. However, the role of this modification in DDR is still unclear. Phosphorylation of histone H4 by CKII at Ser1 plays a role in the later stages of DDR[98]. Another recent identified histone modification associated with DNA damage is the phosphorylation of Tyr51 on H4 by TIE-2 under ionizing radiation [99]. H4Y51ph is recognized by ABL1 (a kinase involved in DDR) and other DDR-related proteins, suggesting an active role of this modification in the DNA repair machinery.

2.3.2.2. Histone phosphorylation is involved in mitotic processes. A marker when a cell enters mitosis is the overall phosphorylation of histone H3. Histone H3 can be phosphorylated at serines 10 and 28 and threonines 3 and 11 [100–103] and four sites have been shown to be phosphorylated in mitotic chromatin and exhibit a highly coordinated spatiotemporal distribution [104–106]. During G2/M, three different kinases are involved in H3 phosphorylation: Aurora B kinase (serine 10 and 28 sites), haspin kinase (threonine 3 site), and death-associated protein-like kinase (Dlk) (threonine 11 site). Aurora B kinase participates in phosphorylation of histone H3S10 and S28 sites. The phosphorylation starts from the chromatin and spreads along the entire length of the chromosome arm, reaching maximum abundance at mid-phase before rapidly decreasing during the transition to homophase [107,108]. Such a pattern is highly consistent with the characteristics of chromosome condensation, suggesting a potential role for these two loci in the process of chromosome condensation [109]. The Haspin-mediated H3T3ph [110] plays an important role in mitotic dynamics, acting as a docking site for Survivin to mediate the accumulation of chromosome passenger complexes (CPCs) in mitotic granules and some Aurora B activation [111–114]. Aurora B phosphorylates Haspin, which further promotes H3T3 phosphorylation at the mitophagus, thus establishing a positive feedback loop [115]. H3T11 is also phosphorylated by Dlk in mitosis and phase-shift localized to the mitophagus from prophase to early phase and this modification appears to play a role in kinetic assembly [103]. Additionally, histone H1 is also regulated in a cell cycle-dependent manner, and its phosphorylation is significantly increased in mitosis and S phase [116].

2.3.2.3. Histone phosphorylation is involved in transcriptional regulation. Transcriptional regulation involving histone phosphorylation is a hot issue of interest, as gene expression is regulated by chromatin structure and several histone modifications have been associated with specific processes in response to stimuli. In the face of various extracellular stimuli, signaling protein kinases phosphorylate transcription factors, chromatin modification complexes, and components of the transcriptional machinery in the nucleus by transferring signals recorded at the plasma membrane through the phosphorylation cascade [117,118], a process called the nucleosome reaction, and histone is one of the substrates of the signaling kinase. In mammalian cells, histone H3 phosphorylation at serine 10 or 28 is associated with the induction of immediate early (IE) genes and is part of the downstream nucleosome response activated by the ERK1/2 or p38 MAPK pathways. H3 phosphorylation is a downstream target of all major MAPK pathways (JNK, ERK, and p38) [119–122] and is a response to a large number of extracellular stimuli such as growth factors, stressors such as UV, ethanol, neurotransmitters, and other toxic factors that further affect immediate early gene expression [119,123–130]. In the case of epidermal growth factor (EGF) subunits, for example, H3S10, H3S28 and H2BS32 are associated with the regulation of proliferation genes, phosphorylation in response to EGF stimulation, and transcription of growth factor responsive genes including c-fos, c-jun and c-myc [131–133].

Chandramohan *et al.* showed that histone H3P(Ser10)-Ac(Lys14) appeared increased in the granule cell layer of the mouse hippocampal dentate gyrus, both of which are markers of transcriptional activation in a study of forced swimming-induced immobility responses, and this process requires the mediation of NMDA receptors and MAPK/ERK signaling pathways, ultimately inducing the expression of the immediate early gene c-fos, suggesting that histone nucleosome responses involved in phosphorylation are physiologically relevant to stress-related memory formation [134]. In the striatum of mice exposed to drug abuse (psychostimulant drugs, D-amphetamine and cocaine, and morphine) and intensive learning, increased dopamine signaling leads to nuclear accumulation of DARPP-32 *via* a signaling cascade of dopamine D1 receptors, cAMP-dependent activation of PP-2A, dephosphorylation of DARPP-32 at Ser-97, and inhibition of its nuclear export, resulting in induces increased phosphorylation of Ser-10-H3. Thus, histone phosphorylation is associated with long-term effects of drugs of abuse and physiologically rewarding controlled learning [135].

2.3.2.4. Learning and memory processes. Phosphorylation of histone H3S10 is most described in studies involving learning and memory, and phosphorylation of this residue is associated with transcriptional activation. H3S10 may affect transcription by directly altering chromatin structure, or by recruiting other proteins and crosstalking with other

epigenetic markers [136]. There are many similarities between histone phosphorylation and histone acetylation with respect to learning and memory. As with histone acetylation, H3S10 phosphorylation is increased in the hippocampus in response to fear conditions in an ERK- and mitogen- and stress-activated protein (MSK)-dependent manner [137,138]. MSK is a histone kinase that is activated by ERK signaling. Interestingly, reduction of histone phosphorylation by MSK mutation leads to deficits in spatial memory in mice, whereas enhancement of histone phosphorylation by deletion of histone phosphatase PP1 improves spatial memory [139,140]. Therefore, an increase in histone phosphorylation along with histone acetylation appears to enhance memory formation.

In addition, glucocorticoids are thought to be necessary to enhance memory consolidation during periods of stress. Glucocorticoids are released in response to stress(acts by binding to the glucocorticoid receptor GR), a classical nuclear receptor [141]. Its function depends on SWI/SNF signaling and other epigenetic regulators to induce changes in gene transcription [141]. GR is required for LTM in the forced swim test, a stress-related form of learning and memory that requires glucocorticoid activity in the dentate gyrus. During forced swimming, GR binds directly to activated ERK and MSK, while during forced swimming GR is required to increase MSK activation and downstream H3S10 phosphorylation [142].

2.3.3. The relationship between histone phosphorylation and schizophrenia

Differences in histone phosphorylation were found in both peripheral blood and central nervous system of schizophrenic patients compared to healthy controls. Sharma *et al.* found increased phosphorylation levels of histone H3 at Ser10 in peripheral blood mononuclear cells of schizophrenic patients compared to healthy controls (Fig. 2). This effect was negatively correlated with PANSS scores [143]. Moreover, a combined increase in histone H3S10 phosphorylation and H3K14 acetylation in the postmortem prefrontal cortex was observed in schizophrenic subjects [77]. However, the mechanism and causality of the increased histone phosphorylation in schizophrenic patients still need to be further investigated. It has been demonstrated that antipsychotic risperidone activates the GPCR kinase cascade reaction, phosphorylating the H3S10 terminus and remodeling chromatin along the targeted promoter [144]. It has also been found that MSK1 regulates gene expression through the regulation of H3 phosphorylation, the transcription factor CREB, and DNA-binding proteins, and that MSK1 deletion impedes BDNF-dependent striatal neurodevelopment and leads to symptoms of schizophrenia [145]. Encouragingly, the above results provide potential targets for antipsychotic therapy.

2.4. Histone ubiquitination

2.4.1. Introduction to histone ubiquitination

Histone ubiquitination, a post-translational modification, involves the addition of an 8.5 kDa ubiquitin molecule to lysine residues on histones H2A and H2B, which surround DNA in eukaryotic chromosomes. The primary sites for this modification are K119 on H2A and K120 and K34 on H2B, which are notably abundant in mammalian nuclei. This process is facilitated by a cascade involving ubiquitin activating enzyme (E1), ubiquitin conjugating enzyme (E2), and ubiquitin ligase (E3), and is reversible through the action of deubiquitinating enzymes (DUBs), a group of thiol proteases [146] (Fig. 3).

Histone ubiquitination plays a critical role in the DNA damage response (DDR) by influencing transcriptional regulation, cell cycle progression, and DNA repair mechanisms. Specifically, ubiquitination at these sites is crucial for mediating transcriptional reprogramming and managing cell cycle checkpoints, thereby enhancing the cell's ability to repair DNA (Table 1) [147].

Table 1
Histone ubiquitination functions and sites.

Enzyme	Function	Target lysine site	Category
RNF168	DNA damage repair (DDR)	H2AK13/H2AK15	Monomer
RING1B	DNA damage repair (DDR)	H2AK119	Monomer
BRCA1/BAED1	DNA damage repair (DDR)	H2AK127/ H2AK129	Monomer
RNF20/40	DNA damage repair (DDR)	H2BK120	Monomer
Cul4-DDB-ROC1	DNA damage repair (DDR)	H3	Monomer
BBAP (also known as Dtx3L)	DNA damage repair (DDR)	H4K91	Monomer
UFL1	DNA damage repair (DDR)	H4K31	Monomer
RNF111	DNA damage repair (DDR)	H4	Monomer
Cul4-DDB-ROC1	DNA damage repair (DDR)	H4	Monomer
RNF8	DNA damage repair (DDR)	H1	Polyurea
HUWE1	DNA damage repair (DDR)	H1	Monomer
RNF168	DNA replication	H2AK13/H2AK15	Monomer
RNF20/40	DNA replication	H2BK120	Monomer
UHRF1	DNA replication	H3K14 /H3K18/ H3K23	Multibody
Cul4-DDB1	DNA replication	H3K121/H3K122/ H3K125	Multibody
RING1A/B	Transcriptional regulation	H2AK188/H2A199	Monomer
RNF20/40	Transcriptional regulation	H2BK120	Monomer
NEDD4	Transcriptional regulation	H3K23/H3K36/ H3K37	Monomer
Cul4	Heterochromatin regulation	H3K14	Monomer

2.4.2. Biological role of histone ubiquitination

2.4.2.1. Histone ubiquitination is involved in DNA damage repair. The primary function of histone ubiquitination is the involvement of the DDR, which mediates rapid chromatin responses and promotes the availability of various histone post-translational modifications in response to and resolution of potentially hazardous situations [148]. Ubiquitination of histones H2A and H2B is an important post-translational modification in the DNA damage response, and the modifications of H2A and H2B have rare site-selectivity. RNF168, RING1B and BRCA1/BARD1 in the multiple comb repressor complex 1 (PRC1) modify H2A at K13/K15, K119, K127/K129, respectively, while RNF20/RNF40 modify H2B at K120 [149–153]. Among them, ubiquitination of H2A by BRCA1/BARD1 is thought to promote homologous recombination, while ubiquitination of RNF168 appears to promote non-homologous end-joining. Ubiquitination of H2A by the PRC1 complex has a global function in transcriptional silencing, and it may play the same role locally around the damage site. Moreover, H2B ubiquitination in the context of DNA damage is essential for damage checkpoint activation and timely initiation of repair [154]. Additionally, H2AK119ub1 dosage changes is more sensitive to DNA damage than the regulation of gene expression [155]. Mono-ubiquitination is essential for transcriptional regulation, DNA damage signaling, and protein translocation, whereas polyubiquitination serves as a tagging mechanism for proteins, tagging them for degradation or activation through specific signaling pathways [156].

2.4.3. Relationship between histone ubiquitination and schizophrenia

Psychiatric disorders are often accompanied by circadian rhythm disorders, and it has been found that the schizophrenia-associated gene TRRAP is involved in circadian rhythm regulation, and knockdown of

the Drosophila homolog of human TRRAP, Nipped-A, leads to prolonged motor rhythm cycles in Drosophila. Moreover, they found that NIPPED-A may contribute to the deregulation of the core clock gene timeless (tim) and Par structural domain protein (Pdp1ε) through the deubiquitination of the transcriptional co-activator Spt-Ada-Gcn5 acetyltransferase complex. The module promotes the deubiquitination of histone H2B and thus the transcription of the core clock gene timeless (tim) and the Par structural domain protein (Pdp1ε) [157]. However, the specific molecular basis for the link between histone ubiquitination and schizophrenia remains unclear. The recent study found that learning in a contextual fear conditioning paradigm increases overall and gene-specific levels of H2BubiK120 in the rat hippocampus, which regulates a histone "crosstalk" mechanism that is critical for memory formation [158].

2.5. Histone serotonylation

2.5.1. Introduction to histone serotonylation

Histone serotonylation, a novel post-translational modification identified in 2019, involves the covalent attachment of serotonin to the glutamine residues of histones surrounding DNA in eukaryotic chromosomes, notably through tissue transglutaminase (TGM)-catalyzed transamidation. This modification, mediated by tissue transglutaminase 2 (TGM2), targets the glutamine at the fifth position of histone H3, transforming it into 5-hydroxytryptamine (H3Q5ser), which subsequently enhances TFIID binding and modifies gene expression patterns [32,159].

This process not only involves the modification of histone H3 by serotonylation but also often occurs concurrently with the trimethylation of histone H3 at lysine 4 (H3K4me3), further influencing transcriptional activity. Specifically, histones that are doubly modified with K4me3 and Q5ser show increased transcriptional activation, playing critical roles in neuronal differentiation and the development of the central nervous system [32].

2.5.2. Biological role of histone serotonylation

WDR5 was later found to interact with the N-terminal tail of histone H3 and act as a "reader" for H3Q5ser, which functions as a core subunit of the mixed-spectrum leukemia (MLL) complex and catalyzes the methylation of H3K4 upon interaction with the N-terminal tail of histone H3. WDR5 plays a role in neuroblastoma. WDR5 co-localizes with H3Q5ser in the promoter region of oncogenes in neuroblastoma cells, and it promotes gene transcription to induce cell proliferation, i.e. This WDR5-H3Q5ser-mediated epigenetic regulation apparently promotes tumorigenesis [160].

2.5.3. Relationship between histone serotonylation and schizophrenia

Abnormal 5-hydroxytryptamine (5-HT)-dependent signaling is associated with psychiatric disorders during critical periods of neurodevelopment [161,162]. The 5-hydroxytryptamine receptor, whose typical signaling pathway consists of activation of the heterotrimeric Gs protein and the cyclic adenosine monophosphate (cAMP) pathway, may regulate neuronal development. Recent findings also demonstrate the involvement of another 5-HT6 receptor-dependent signaling pathway in the control of neuronal migration [163]. It has been reported that the carboxy-terminal recruitment signaling protein cluster of the 5-HT6 receptor [164], for example, cell cycle protein-dependent kinase 5 (Cdk5), which is associated with various neuropsychiatric disorders, including schizophrenia, major depression, and Alzheimer's disease [165,166]. This 5-HT6/Cdk5-dependent signaling pathway affects neuronal migration, synapse growth, and dendrite structure through a mechanism that requires phosphorylation of the Cdk5 substrate histone H1 [164]. Furthermore, these structural effects are independent of the coupling of 5-HT 6 receptors to G proteins [164]. This effect on primary neuronal synapse growth was also reduced by mutating the carboxy-terminal Ser350 of the 5-HT 6 receptor to alanine [164]. Although these findings suggest that both Cdk5 and 5-HT_6 are involved in the epigenetic regulation of neurite growth and neuronal migration, these events may be disrupted in developmental disorders, and therefore further work is needed to determine the precise epigenetic role of histone H1 as a Cdk5 substrate in neuronal differentiation.

Long-term memories last a lifetime, and the RNA or protein markers that may constitute these memory traces are replaced by new functional copies within hours or days [167]. An attractive hypothesis that could explain how memories remain stable in the face of constant molecular turnover is related to epigenetic mechanisms that may affect the intrinsic properties of neurons over time. An example of this model is the epigenetic control of 5-hydroxytryptamine-dependent regulation of synaptic plasticity. Using the central nervous system of sea rabbits as a model, researchers found that serotonin induces methylation of conserved CpG islands in the promoter region of the *CREB2* gene, thereby enhancing long-term synaptic vulnerability [168]. Interestingly, recent findings further support this epigenetic hypothesis, suggesting that serotonin-induced long-term memory (LTM) in sea rabbits requires epigenetic changes [169]. LTM is associated with functional strengthening of existing synapses and other processes, including ab initio synaptogenesis [167]. One operation that can permanently remove LTM is to inhibit the constitutively active catalytic fragment of the atypical protein kinase *C ζ* (PKM) [170]. The LTM can be permanently cleared. Researchers have found that LTM can persist after reconsolidation of PKM blockade and inhibition, suggesting that consolidation memory may be more difficult to modify or eliminate than commonly believed. If these findings are confirmed in mammals, it would challenge the notion that synapses are cellular sites of long-term memory storage [171].

2.6. Histone lactylation

2.6.1. Introduction to histone lactylation

Histone lactylation, a reversible post-translational modification, involves the addition of lactate groups to lysine residues on histones that package DNA in eukaryotic chromosomes. This modification is predominantly regulated by the EP300 enzyme and class I histone deacetylases (HDAC1–3), which can both add and remove lactate groups [172]. Significant research has identified 26 lactylation sites in human HeLa cells and 16 in mouse bone marrow-derived macrophage core histones, indicating the widespread nature of this modification [173]. The lactyl coenzyme A is the lactyl donor for lactylation of lysine [174]. The lactylation sites of histones are shown in Table 2.

Notably, EP300 plays a critical role in several histone acylations, including acetylation, lactylation, and crotonylation, underscoring its versatility in histone modification [175]. Histone lactylation is particularly impactful in gene regulation, often competing with acetylation for lysine residues, and is implicated in essential cellular functions such as energy metabolism and responses to hypoxia. 2.6.2 Relationship between protein palmitoylation and schizophrenia

One study using a rabbit polyclonal anti-pan-lactoyl lysine antibody to assess Kla levels in neuronal cultures in vitro and in brain tissue in vivo found that Kla may be prevalent in neuronal cells of the brain and that lysine lactylation (Kla) in brain cells is regulated by neuronal excitation and social stress, with parallel changes in lactate levels. Moreover, histone H1 lactylation may be involved in gene expression by competing with acetylation [176]. In addition, HDAC1–3 and EP300 have been associated with schizophrenia and side effects of

Table 2
Histones lactylation sites.

Histones	Lysine targets
H2A	K11/K13/K115
H2B	K5/K11/K16/K20/K23/K43/K85/K108/K116/K120
H3	K9/K18/K23/K27/K79
H4	K5/K8/K12/K16/K31/K77/K91

antipsychotic drugs through their interactions with brain-derived neurotrophic factor (BDNF). Modifications of the BDNF gene on histones are crucial for fear extinction, and dysfunctions in this process may lead to Kla-related neuropsychiatric symptoms, including excitation, social defeat, anxiety, and stress [177]. Histone lactylation is a recently discovered PTM, and its relationship with the SCZ needs to be explored in further studies.

2.7. Protein palmitoylation

2.7.1. Introduction to protein palmitoylation

Protein palmitoylation, the most prevalent form of protein lipidation, typically occurs as thioesters or amides. Known as S-palmitoylation, this reversible modification has recently emerged as a crucial regulator of cellular function [178]. The process is facilitated by palmitoyltransferases (PATs), particularly those in the DHHC family with a zinc finger structure, which are key to this activity [179].

2.7.2. Relationship between protein palmitoylation and schizophrenia

Notably, DHHC8, a member of this family, has been linked to schizophrenia; mutations in the dhhc8 gene, located within the microdeletion region of chromosome 22q11, are associated with an increased risk of the disorder [180]. Recent studies have employed biotin and switch assays to investigate S-palmitoylation in the human postmortem brain, revealing distinct patterns of palmitoylation across 17 molecular mass bands, many of which are tied to receptor signal transduction. Mass spectrometry analyses identified 219 palmitoylated proteins in the human frontal cortex, and further validation confirmed the palmitoylation status of several of these proteins. Comparative analyses in the dorsolateral prefrontal cortex of schizophrenic patients and control subjects found significantly reduced S-palmitoylation in most of the schizophrenia-associated bands. Notably, studies in mice have shown that this reduction in palmitoylation is not attributable to long-term antipsychotic drug treatment [181].

2.8. Histone dopaminylation

Histone dopaminylation, a post-translational modification, involves the attachment of dopamine to glutamine residues on histones around DNA in eukaryotic chromosomes. The pathogenesis theory of schizophrenia has significantly relied on the role of neurotransmitters, particularly dopamine, since the 1960 s. Numerous experimental and clinical studies support a link between dopamine dysregulation and schizophrenia, notably through mutations in the DRD2 gene, which encodes the dopamine D2 receptor [182]. The mutations increased dopamine receptor density in the striatum of schizophrenic patients [183] and heightened dopamine synthesis and uptake [184].

The ventral tegmental area (VTA), a primary source of dopamine neurons within the brain's reward pathway, plays a crucial role in the dysregulation seen in psychiatric disorders and drug addiction. Epigenetic mechanisms, including histone modifications, are now understood to significantly influence dopamine signaling in the VTA, affecting the transcription of key genes involved in synaptic plasticity and memory formation [185]. Furthermore, our research has demonstrated that histone H3 glutamine 5 dopaminylation (H3Q5dop) is instrumental in cocaine-induced transcriptional changes in the midbrain, highlighting its importance in neural plasticity [186] (Fig. 1).

2.9. Summary

In conclusion, a deeper understanding of the pathogenesis of schizophrenia will significantly enhance the diagnosis and treatment of this complex disorder. Schizophrenia is influenced by both genetic factors and environmental conditions such as substance abuse and stress, which can induce epigenetic changes leading to alterations in gene and genomic expressions. Therefore, epigenetic studies are crucial for further elucidating the etiology and pathogenesis of schizophrenia, potentially revolutionizing its identification and treatment strategies.

This review has thoroughly examined the connections between histone modifications and the development of schizophrenia. We have delved into how modifications like acetylation, methylation, phosphorylation, ubiquitination, serotoninization, lactylation, palmitoylation, and dopaminylation influence schizophrenia's neurobiological aspects through chromatin remodeling and gene expression regulation. Although current research has begun to uncover these relationships, the specific functions of these modifications and their interactions remain insufficiently defined. Moreover, the precise mechanisms through which these modifications affect gene expression in various brain regions are still not fully understood. Additionally, developing drugs that target specific histone modifications requires a clear understanding of these modification sites.

Ongoing research and further investigation into these areas are expected to yield significant advancements in the prevention, diagnosis, and treatment of schizophrenia. Such progress will not only deepen our comprehension of its complex pathology but also lead to the development of more effective therapeutic options for patients.

Ethical approval

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Authors' contributions

J.Y. and X.G. conceived and designed the project. Y.C., Z.D., X.Z., P. L., and A.L. collected the literature and wrote the draft. J.Y. wrote the paper. J.Y. and K.L. revised the paper. All authors reviewed and approved the final manuscript.

CRediT authorship contribution statement

Xiaochong Guo: Data curation, Conceptualization. **Jia-xin Xing:** Data curation, Conceptualization. **Jin-feng Xuan:** Data curation, Conceptualization. **Zhe Du:** Data curation, Conceptualization. **Xi-kai Hou:** Formal analysis, Data curation, Conceptualization. **Xiu-mei Zhu:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yun-zhou Chen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jun Yao:** Writing – review & editing. **Ying Pan:** Data curation, Conceptualization. **Kun Liu:** Writing – review & editing. **Peng Lv:** Data curation, Conceptualization. **Ang Li:** Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declares that they have no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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