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Review Article

Depression and the Epigenetic Code: Role of Histone Marks

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ABSTRACT

Major depressive disorder (MDD) is a highly prevalent and multifactorial psychiatric illness characterized by persistent low mood, anhedonia, cognitive impairments, and functional disability. While traditional research has focused on neurotransmitter imbalances, recent advances highlight the crucial role of epigenetic mechanisms—particularly histone modifications—in the pathophysiology of depression. Histone acetylation and methylation, two key epigenetic processes, regulate chromatin structure and gene transcription without altering the DNA sequence. These modifications dynamically influence the expression of genes involved in neuroplasticity, stress response, neurotransmission, and immune function—biological systems often dysregulated in depression. Histone acetylation, generally associated with gene activation, is modulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Altered HDAC activity has been observed in preclinical models of depression, and HDAC inhibitors show promise as novel antidepressants. Histone methylation, depending on the specific residues and methylation states, can either activate or repress gene expression. Dysregulation of histone methyltransferases and demethylases has also been linked to depressive-like behaviors and altered stress reactivity. This review comprehensively explores the roles of histone acetylation and methylation in shaping the epigenetic landscape of the depressed brain. It also discusses therapeutic strategies targeting these histone modifications, including pharmacological agents and environmental interventions that may reverse maladaptive gene expression patterns. Understanding how environmental stressors interface with epigenetic machinery provides new insights into the neurobiology of depression and offers novel avenues for personalized, mechanism-based treatments.

INTRODUCTION

Depression is a complex and multifactorial neuropsychiatric disorder affecting more than 280 million people worldwide, significantly

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contributing to the global burden of disease (World Health Organization, 2021). While genetic, environmental, and psychological factors have been traditionally recognized in its pathophysiology, recent advances in molecular biology have brought attention to the pivotal role of epigenetic mechanisms, particularly histone modifications, in the regulation of gene expression associated with depressive phenotypes.

Epigenetics refers to heritable changes in gene function that do not involve alterations in the DNA sequence. Among the various epigenetic mechanisms, histone modifications—including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation—play a crucial role in chromatin remodeling and transcriptional regulation (Jaenisch & Bird, 2003). These histone marks can dynamically alter the accessibility of transcriptional machinery to DNA, thereby influencing gene expression relevant to mood regulation, neuroplasticity, and stress responses (Nestler et al., 2016).

Epigenetic regulation of gene expression generally falls into three major categories: (i) modifications

of histone proteins after translation and the replacement of histone variants; (ii) remodeling of chromatin structure; and (iii) methylation of DNA. Although each of these mechanisms plays a distinct role, they function in coordination to finely tune gene expression and cellular phenotype in mammalian systems. The role of noncoding RNAs is also significant in epigenetic regulation, but it is not covered in this discussion due to space constraints.

Studies have shown that environmental stressors, such as chronic social defeat or early life stress, can induce persistent histone modifications in key brain regions like the hippocampus, prefrontal cortex, and nucleus accumbens—areas implicated in the pathogenesis of depression (Tsankova et al., 2006; Bagot et al., 2014). For instance, increased histone H3 lysine 27 trimethylation (H3K27me₃), a repressive histone mark, has been associated with the downregulation of brain-derived neurotrophic factor (BDNF), a protein essential for neuronal survival and synaptic plasticity (Kundakovic et al., 2013).

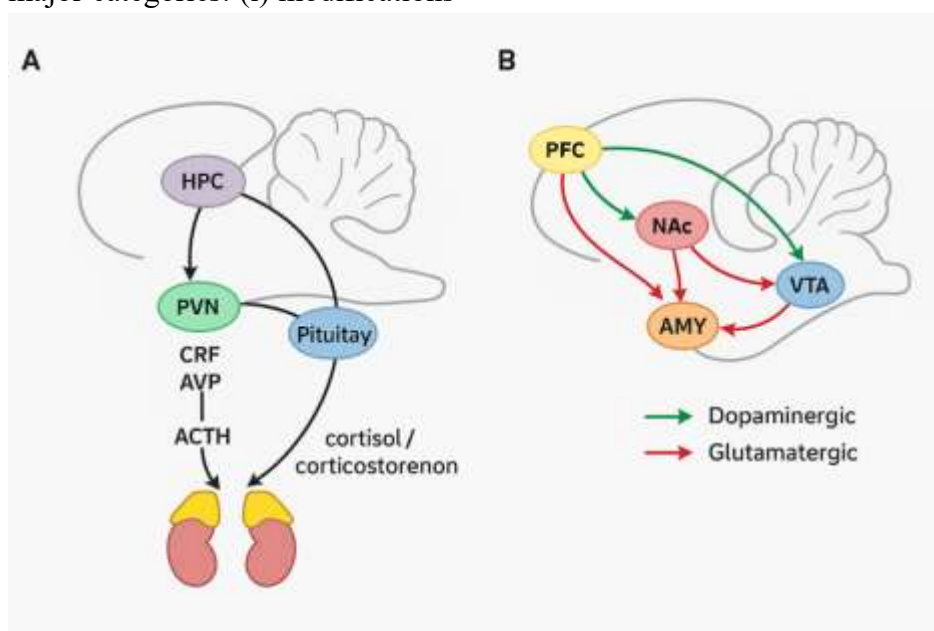


Figure 1:

Understanding how histone modifications modulate gene expression in depressive states not only offers insight into the molecular underpinnings of depression but also opens avenues for novel therapeutic strategies. Drugs targeting histone-modifying enzymes, such as histone deacetylase (HDAC) inhibitors, are being explored as potential antidepressant agents due to their ability to reverse maladaptive epigenetic marks (Covington et al., 2009).

This article reviews current knowledge on the epigenetic regulation of depression with a focus on histone marks, highlighting their role in stress susceptibility, antidepressant response, and potential as therapeutic targets.

2. BASICS OF EPIGENETIC MECHANISMS

Epigenetic regulation refers to heritable yet reversible changes in gene expression that occur without alterations in the DNA sequence. These modifications are crucial for normal development, cellular differentiation, and adaptive responses to environmental stimuli. Key epigenetic mechanisms include DNA methylation, non-coding RNAs, and histone modifications, all of which contribute to chromatin remodeling and transcriptional control (Jaenisch & Bird, 2003).

2.1. DNA Methylation

DNA methylation typically involves the addition of a methyl group to the 5' position of cytosine residues in CpG dinucleotides, often leading to transcriptional repression. It plays a crucial role in X-chromosome inactivation, genomic imprinting, and suppression of transposable elements. In psychiatric disorders such as depression, abnormal methylation patterns of genes like BDNF and NR3C1 have been linked to altered stress reactivity and neuroplasticity (Kundakovic & Champagne, 2015).

2.2. Non-coding RNAs

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and small interfering RNAs (siRNAs), regulate gene expression at the transcriptional and post-transcriptional levels. miRNAs, for example, can silence mRNA transcripts by targeting them for degradation or translational repression. Altered expression of ncRNAs has been observed in depressive patients and is thought to mediate neuroinflammatory responses and synaptic plasticity (Issler & Chen, 2015).

2.3. Histone Modifications: An Overview

Histones are proteins around which DNA is wound to form nucleosomes—the basic unit of chromatin. Post-translational modifications (PTMs) of histone tails modulate chromatin structure and gene expression by either loosening (euchromatin) or tightening (heterochromatin) the DNA-histone interaction. These modifications include:

- **Acetylation:** Addition of acetyl groups to lysine residues by histone acetyltransferases (HATs) leads to relaxed chromatin and increased gene transcription. Histone deacetylases (HDACs) remove these groups, generally resulting in gene repression. Reduced histone acetylation has been linked to depression-like behavior in animal models (Tsankova et al., 2006).
- **Methylation:** Histone methylation can either activate or repress gene expression depending on the specific residue and number of methyl groups added. For instance, H3K4me3 is associated with gene activation, while H3K27me3 is a repressive mark. Dysregulated methylation patterns have been observed in brain regions of depressed individuals (Sun et al., 2015).



- **Phosphorylation:** Histone phosphorylation, often in response to cellular stress, is associated with DNA repair and chromatin condensation. For example, phosphorylation of H3S10 has been implicated in immediate-early gene activation during stress responses (Rossetto et al., 2012).
- **Ubiquitination:** Histone ubiquitination, especially of H2A and H2B, is involved in transcription elongation and DNA damage repair. Its role in depression remains under investigation but may contribute to synaptic gene regulation (Weake & Workman, 2008).
- **Sumoylation:** The addition of SUMO (Small Ubiquitin-like Modifier) proteins to histones can repress gene transcription by promoting heterochromatin formation. Although less studied, histone sumoylation is emerging as a regulatory mechanism in neuronal plasticity and stress adaptation (Cubañas-Potts & Matunis, 2013).

3. HISTONE MODIFICATIONS IN THE BRAIN: RELEVANCE TO MOOD DISORDERS

Epigenetic regulation through histone modifications plays a vital role in maintaining neuronal plasticity, memory formation, and emotional regulation—functions that are often disrupted in mood disorders such as depression. Stress, environmental stimuli, and pharmacological treatments can lead to dynamic changes in histone marks, especially within brain regions like the hippocampus, prefrontal cortex, and nucleus accumbens, which are implicated in the pathophysiology of depression (Nestler et al., 2016).

3.1. Histone Acetylation and Deacetylation in Depression

Histone acetylation, catalyzed by histone acetyltransferases (HATs), relaxes chromatin structure, facilitating gene transcription. In contrast, histone deacetylases (HDACs) remove acetyl groups, leading to chromatin condensation and gene repression. In rodent models of depression, chronic stress is associated with decreased histone acetylation at promoters of genes such as BDNF, contributing to reduced neuroplasticity (Tsankova et al., 2006) [2]. Conversely, HDAC inhibitors like sodium butyrate and SAHA (suberoylanilide hydroxamic acid) have shown antidepressant-like effects by restoring acetylation levels and enhancing expression of neuroprotective genes (Covington et al., 2009). These findings suggest that targeting histone acetylation may offer therapeutic potential in treating mood disorders.

3.2. Histone Methylation and Demethylation

Histone methylation can either activate or repress transcription depending on the specific lysine or arginine residue modified and the degree of methylation (mono-, di-, or tri-methylation). For example, H3K4me3 is associated with active gene expression, whereas H3K9me2 and H3K27me3 are linked to transcriptional repression. Studies have shown increased levels of repressive histone methylation marks (e.g., H3K27me3) in the prefrontal cortex of depressed patients and animal models (Sun et al., 2015). Enzymes such as G9a (a histone methyltransferase) and Jumonji-domain demethylases are known to mediate these changes and influence depressive-like behavior. Targeting these enzymes may help reverse maladaptive gene expression patterns in depression.

3.3. Chromatin Remodeling Complexes and Transcriptional Control

Chromatin remodeling complexes use ATP-dependent mechanisms to reposition or eject

nucleosomes, thereby regulating DNA accessibility. Complexes like SWI/SNF and NuRD (nucleosome remodeling and deacetylase) are involved in regulating transcription in response to environmental cues and stress. Altered activity of these complexes has been implicated in depression and other neuropsychiatric disorders (Kim et al., 2010). For example, components of the SWI/SNF complex interact with transcription factors such as CREB and NF- κ B, modulating the expression of genes involved in mood regulation, such as BDNF and FOS (Bharadwaj et al., 2014).

4. REGION-SPECIFIC HISTONE MODIFICATIONS IN DEPRESSION

Different brain regions implicated in mood regulation—such as the hippocampus, prefrontal cortex, nucleus accumbens, and amygdala—exhibit unique patterns of histone modifications in response to stress, antidepressant treatment, and environmental stimuli. These region-specific epigenetic alterations affect the expression of key genes involved in synaptic plasticity, neurogenesis, and emotional behavior, contributing to the pathophysiology of depression (Nestler et al., 2016).

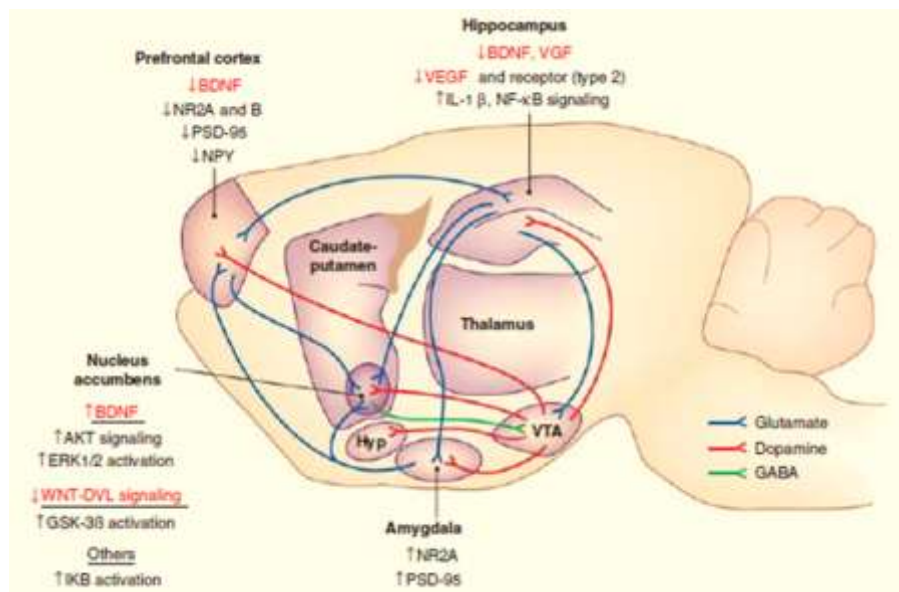


Figure 2: Circuitry with molecular adaptations overlaid onto different brain regions. Multiple brain regions are implicated in the pathophysiology of depression.

4.1. Hippocampus

The hippocampus is a critical site for stress response, neurogenesis, and memory formation. Chronic stress or depressive-like behavior in animal models is associated with decreased histone acetylation, especially at promoters of neurotrophic genes like BDNF, leading to reduced expression and impaired neuroplasticity (Tsankova et al., 2006). HDAC inhibitors have been shown to reverse this effect and restore hippocampal function, suggesting the therapeutic

relevance of enhancing histone acetylation in this region (Fuchikami et al., 2016).

4.2. Prefrontal Cortex

The prefrontal cortex (PFC) governs executive function, emotional regulation, and decision-making—all of which are impaired in depression. Repressive histone methylation marks, such as H3K27me₃, have been found to be elevated in the PFC of individuals with major depressive disorder (Sun et al., 2015) [4]. Reduced acetylation of

histones H3 and H4 in the PFC has also been observed in chronic stress models, correlating with downregulation of synaptic and plasticity-related genes (Covington et al., 2009).

4.3. Nucleus Accumbens

The nucleus accumbens (NAc), a key component of the brain's reward circuitry, is sensitive to stress-induced epigenetic changes. Chronic social defeat stress in rodents increases H3K9 dimethylation and decreases H3 acetylation at specific promoters in the NAc, leading to anhedonia-like behavior (Renthal et al., 2007). Antidepressants and HDAC inhibitors can normalize these histone marks and restore reward sensitivity, highlighting the NAc as a potential epigenetic target for mood disorders (Covington et al., 2009).

4.4. Amygdala

The amygdala is central to fear processing and emotional memory. Stress and early-life adversity

can alter histone modifications in the amygdala, such as reduced H3 acetylation and altered methylation patterns, which affect the expression of genes involved in stress responsiveness and emotional behavior (Bilang-Bleuel et al., 2005). These epigenetic changes are thought to underlie hyperactivity of the amygdala observed in depression and anxiety disorders.

5. ENVIRONMENTAL AND STRESS-INDUCED EPIGENETIC ALTERATIONS

Environmental exposures—especially during critical developmental windows—can cause enduring epigenetic changes that influence vulnerability to depression. These include alterations in histone modifications, DNA methylation, and non-coding RNA expression in brain regions involved in stress regulation and emotional behavior. Importantly, these epigenetic responses to environmental stressors mediate gene-environment interactions that shape the risk for mood disorders (Turecki & Meaney, 2016).

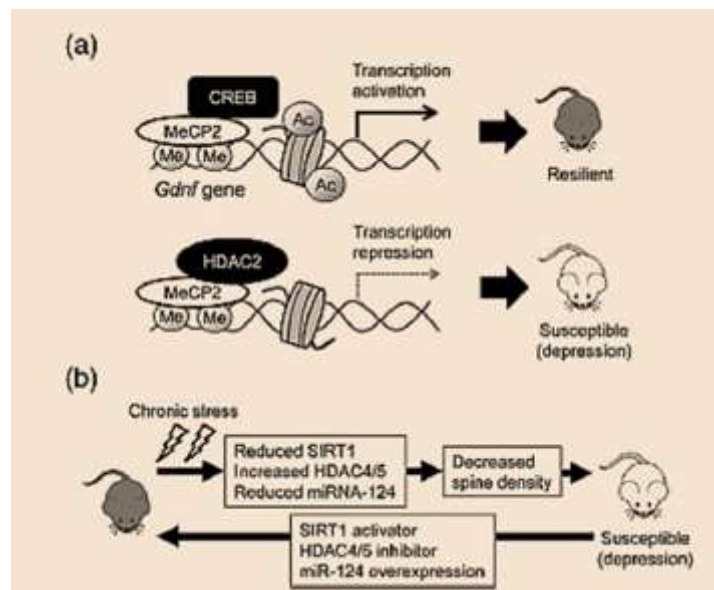


Figure 3: Epigenetic mechanisms of chronic stress-induced neuronal plasticity and depression.

5.1 Early-Life Stress

Early-life stress (ELS), such as neglect, abuse, or institutionalization, is associated with long-lasting

changes in the epigenetic regulation of stress-related genes. For instance, decreased histone acetylation and increased DNA methylation at the glucocorticoid receptor (NR3C1) gene promoter in

the hippocampus have been observed following ELS, leading to altered hypothalamic-pituitary-adrenal (HPA) axis regulation and increased depression risk in adulthood (McGowan et al., 2009). Animal models confirm that maternal care affects histone acetylation at BDNF and GR gene loci, shaping stress responsiveness throughout life (Weaver et al., 2004).

5.2 Chronic Social Defeat Stress

Chronic social defeat stress (CSDS) is a well-established animal model of depression that mimics social stress exposure in humans. CSDS leads to increased repressive histone methylation (e.g., H3K9me2) and decreased histone acetylation in the nucleus accumbens and prefrontal cortex, suppressing genes involved in reward processing and emotional regulation (Covington et al., 2009). Interestingly, antidepressant treatment can reverse these epigenetic marks, highlighting their plasticity and therapeutic potential (Vialou et al., 2013).

5.3 Maternal Separation and Trauma

Maternal separation during early development alters histone modifications in brain regions regulating emotion and stress. Rodent studies show reduced acetylation and increased methylation at BDNF and CRH promoters following early trauma, contributing to anxiety- and depression-like behaviors in adulthood (Roth et al., 2009). These alterations may persist into adulthood, suggesting that early trauma programs long-term gene expression patterns through epigenetic pathways.

5.4 Gene-Environment Interaction

Epigenetic mechanisms mediate how environmental stressors interact with genetic predispositions to influence mental health

outcomes. For example, polymorphisms in the SLC6A4 serotonin transporter gene interact with early-life adversity to influence histone marks and transcriptional activity in stress-related circuits (Caspi et al., 2010). These findings support the concept that epigenetic "priming" of gene expression patterns may underlie individual differences in resilience or vulnerability to depression.

6. HISTONE MODIFICATIONS AND ANTIDEPRESSANT RESPONSE

Emerging evidence indicates that the therapeutic effects of antidepressants involve, at least in part, epigenetic mechanisms such as histone modifications. These changes influence the expression of genes related to neuroplasticity, stress resilience, and mood regulation. Both conventional and novel treatments, including selective serotonin reuptake inhibitors (SSRIs), histone deacetylase (HDAC) inhibitors, and certain natural products, modulate histone marks to exert their effects (Nestler et al., 2016).

6.1 SSRIs and Epigenetic Regulation

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and sertraline, are known to induce histone acetylation and modulate chromatin structure, particularly in the hippocampus and prefrontal cortex. Chronic fluoxetine treatment increases acetylation at histone H3 in promoters of neuroplasticity-related genes like BDNF and CREB, facilitating their expression and promoting synaptic plasticity and neurogenesis (Tsankova et al., 2006). This epigenetic modulation may underlie the delayed onset of antidepressant efficacy.

6.2 HDAC Inhibitors as Potential Antidepressants

Histone deacetylase (HDAC) inhibitors have demonstrated antidepressant-like effects in preclinical models. Compounds such as sodium butyrate, valproic acid, and SAHA enhance global histone acetylation, reverse stress-induced gene repression, and promote expression of genes involved in neuronal survival and mood regulation (Covington et al., 2009). HDAC inhibition in the nucleus accumbens and hippocampus enhances BDNF expression and improves behavioral outcomes in animal models of depression, making them promising candidates for novel antidepressant therapies (Fuchikami et al., 2016).

6.3 Natural Products and Phytochemicals Affecting Histone Marks

Several phytochemicals have been shown to influence histone modifications and exhibit antidepressant properties. Curcumin (from turmeric) increases histone acetylation and BDNF expression, potentially through inhibition of HDACs and modulation of HAT activity (Kulkarni et al., 2008). Resveratrol, a polyphenol found in grapes, also promotes histone acetylation and exhibits neuroprotective and antidepressant-like effects via the CREB-BDNF pathway (Liu et al., 2014). These natural compounds highlight the potential of dietary and botanical agents in epigenetic-based mood regulation.

7. CLINICAL IMPLICATIONS AND FUTURE THERAPEUTIC TARGETS

Histone modifications are increasingly recognized as dynamic and reversible regulators of gene expression in neuropsychiatric disorders, including depression. Their modulation offers exciting opportunities for clinical applications such as biomarker development, personalized medicine, and novel antidepressant strategies. However, translating these findings into effective

clinical therapies remains a significant challenge (Peedicayil & Grayson, 2018).

7.1 Biomarker Potential of Histone Modifications

Histone marks, especially acetylation and methylation patterns, show promise as biomarkers for diagnosis, prognosis, and treatment response in depression. Peripheral blood mononuclear cells (PBMCs) and postmortem brain samples from depressed individuals often show altered histone acetylation and methylation at key regulatory genes like BDNF, SLC6A4, and NR3C1 (Tsankova et al., 2007; Labonté et al., 2013). Monitoring these changes could aid in early detection and personalized treatment plans.

7.2 Drug Discovery Targeting Epigenetic Enzymes

The development of drugs targeting histone-modifying enzymes—such as histone deacetylases (HDACs), histone acetyltransferases (HATs), and histone methyltransferases—has gained momentum. HDAC inhibitors (e.g., valproate, vorinostat) have shown antidepressant-like effects in preclinical models and are currently being evaluated in clinical trials (Yoon et al., 2021). Targeting specific isoforms (e.g., HDAC2, HDAC5) may enhance efficacy and reduce off-target effects.

7.3 Challenges in Clinical Translation

Despite promising preclinical data, clinical translation faces major hurdles. These include:

- Lack of specificity of current epigenetic drugs
- Potential for widespread genomic effects and off-target toxicity



- Limited understanding of region- and cell-type-specific histone dynamics in the human brain (Duman et al., 2016).

8. LIMITATIONS OF CURRENT RESEARCH

Despite significant progress in understanding histone modifications in depression, current research faces several limitations that hinder the translation of epigenetic findings into clinical practice. These include methodological constraints, the gap between animal and human studies, and concerns about the long-term safety of epigenetic-based therapies.

8.1 Methodological Constraints

One major challenge lies in the complexity of measuring histone modifications with high spatial and temporal resolution. Techniques like chromatin immunoprecipitation (ChIP) are limited by tissue accessibility, especially in living humans, and often lack cell-type specificity (Shulha et al., 2013). Additionally, variability in experimental protocols and antibody specificity can affect reproducibility and comparability across studies (Bock et al., 2016).

8.2 Animal Models vs. Human Applicability

Much of what is known about epigenetic regulation in depression comes from animal models, which, while informative, may not fully capture the complexity of human mood disorders. Rodents do not exhibit the full spectrum of depressive symptoms seen in humans, and stress paradigms like maternal separation or chronic social defeat may not accurately model the chronic, multifactorial nature of human depression (Nestler & Hyman, 2010). Furthermore, the brain structure and epigenetic landscapes differ across

species, limiting direct translatability (Hyman, 2012).

8.3 Long-Term Effects and Safety of Epigenetic Drugs

The long-term safety of epigenetic drugs, such as HDAC inhibitors, remains a significant concern. These agents can broadly alter gene expression across the genome, raising the risk of unintended effects, including oncogenesis or neurotoxicity (Grayson et al., 2010). Additionally, chronic manipulation of chromatin states may disrupt natural gene-environment interactions and neural plasticity, leading to unknown neurodevelopmental or cognitive consequences.

9. FUTURE DIRECTIONS

Future research in depression epigenetics is poised to revolutionize therapeutic strategies through precision medicine, targeted epigenome editing, and comprehensive longitudinal studies. Precision medicine aims to tailor treatments based on individual genetic and epigenetic profiles, enhancing the prediction of treatment responses and disease trajectories. Integrating multi-omics data—including genomics, epigenomics, transcriptomics, and proteomics—facilitates the identification of epigenetic biomarkers that may serve as diagnostic tools or therapeutic targets, thereby improving personalized care for patients with depression. Emerging technologies like CRISPR-dCas9-based epigenome editing offer the potential to modulate gene expression without altering the underlying DNA sequence. By targeting specific histone modifications or DNA methylation patterns, these tools can reversibly activate or repress genes implicated in depression. Preclinical studies have demonstrated the feasibility of using such approaches to modulate gene expression in neural circuits associated with mood regulation, highlighting



their therapeutic potential. Longitudinal studies are crucial for understanding the temporal dynamics of epigenetic changes in depression. Tracking epigenetic modifications over time in patient populations can reveal how environmental factors, treatment interventions, and disease progression influence the epigenome. Such studies can identify persistent epigenetic alterations that contribute to the chronicity of depression and may uncover reversible changes that serve as biomarkers for treatment efficacy.

10. CONCLUSION

In conclusion, the growing understanding of histone modifications and their role in depression highlights the intricate relationship between genetic, epigenetic, and environmental factors in the pathophysiology of mood disorders. Epigenetic changes, particularly in histone acetylation, methylation, and chromatin remodeling, influence the expression of genes involved in neuroplasticity and stress response, offering new insights into the molecular basis of depression. Integrating epigenetic research into psychiatry opens up novel avenues for personalized treatment approaches and the identification of reliable biomarkers for diagnosis and treatment response. The potential for epigenetically-targeted therapies, such as HDAC inhibitors and epigenome editing tools, provides hope for more effective and tailored interventions for patients who are resistant to conventional antidepressants. As research advances, the integration of epigenetics into psychiatric practice offers the promise of transformative strategies for treating depression and other neuropsychiatric disorders.

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CONFLICTS OF INTERESTS

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

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