

# Epigenetic Alterations in Depression and Treatment Perspectives

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**Abstract:** The global incidence of depression is progressively on the rise and tends to occur more in younger generations, however the pathogenesis of the disease is unclear. Meanwhile, epigenetics is a modification which produces heritable alterations in the DNA sequence, which ultimately manifest in phenotypic differences. It has been suggested that the onset and development of depression can be tentatively explained by the combination of epigenetic and environmental factors. This paper reviews epigenetic changes in depression in the context of environmental factors, including DNA methylation modifications, histone modifications, and non-coding RNA regulation. An epigenetic-based therapeutic outlook was also proposed in this paper, which initially elucidates the epigenetic mechanisms underlying the pathogenesis of depressions and provides a theoretical basis for the treatment of depression.

**Keywords:** Depression; Epigenetics; DNA methylation modifications; Histone modifications; Non-coding RNA regulation; Therapeutic perspectives

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## 1. Introduction

Major depression disorder (MDD) is a syndrome of depressed mood or lack of pleasure lasting at least two weeks, accompanied by abnormalities in cognitive and or physiological (weight, exercise, and sleep patterns) functioning<sup>[1]</sup>. Depression affects more than 300 million people worldwide, and its prevalence in China is close to 5% with a rapid increase in the last three decades 10-20%, and a gradual trend towards younger age groups. It is now believed that depression is the result of a combination of congenital genetic factors and acquired environmental factors<sup>[2]</sup>, such as the presence of polygenic disorders, and early childhood abuse which may cause the depressive episodes.

Epigenetics is the distinction between genes that express genetic information that is transmitted from mother to offspring without changes in the DNA of the cell nucleus caused by and ultimately reflected in the phenotype. The main regulatory mechanisms of epigenetics, include DNA methylation, histone modification, and non-coding RNA regulation<sup>[1]</sup>. In recent years, more researcher has proposed the pathogenesis of depression based on the epigenetic premise, where genetic and environmental factors interact with each other, leading to the development of depression.

This paper integrates both epigenetic and environmental factors to explain the pathogenesis of depression, subsequently propose possible treatment strategies. The research on the epigenetic mechanisms of depression in the future may provide new therapeutic targets for clinical treatment, thereby improve the diagnosis and cure rates of depression.

## **2. Analysis of epigenetic alterations in depression**

### **2.1. Depression and environmental factors**

Emotional trauma in early childhood is an important factor in the development of depression, as school bullying and stress can increase the risk of depression in adolescence and into adulthood. In addition, some researchers have found that high levels of social stress and prolonged exposure to hostile living conditions increase the risk of depression, concluding that a hostile environment plays a significant role in the development of depression.

### **2.2. Depression and epigenetic factors**

Environmental and genetic factors, complement each other in the pathogenesis of depression. For example, abuse due to a poor family environment may cause changes in certain genes in young children, such as the 5-hydroxytryptamine transporter protein SLC6A4, which can over-activate the hypothalamic-pituitary-adrenal (HPA) axis pathway of the autonomic nervous system, which subsequently can produce plastic changes in the brain. Such changes do not alter the patient's DNA sequence, but can directly contribute to the onset of depression. Currently, the epigenetic factors of depression are most notable for DNA methylation modifications and histone modifications.

#### **2.2.1. DNA methylations**

DNA methylation generally refers to the process of methyl group transfer from S-adenosylmethionine to the cytosine of CpG dinucleotides, catalyzed by DNA methyltransferase, which in turn forms 5-methylcytosine. The degree of methylation of 27,000 CpG islands in a genome of approximately 14,000 genes was analyzed in patients with pre-existing depression and normal subjects, and differences were observed between these two groups, for example the interleukin-6 (IL-6) concentrations in serum were greater in patients with pre-existing depression than in normal subjects, and the gene was also hypomethylated.

It has been suggested that the methylation status of brain-derived neurotrophic factor (BDNF) may be an important biomarker for the diagnosis of depression [3]. BDNF is an important gene in the development of human brain neurons, and as the methylation of BDNF increases, the corresponding amount of protein produced decreases, resulting in the delayed neuronal development, difficulty in survival, and difficulty in maintaining its function in the brain. In addition, immunoprecipitation sequencing of whole-genome methylated DNA from identical twins [4] revealed that the overall gene methylation level was much greater in twins with a history of depression than in normal twins, where the Coiled Coil Domain Containing 1 (CCDC-1) gene contained in proline and serine was significantly increased in twins with a history of depression, resulting in reduced expression of the corresponding protein.

The study of abnormally methylated DNA in the brain tissue of depressed patients is extremely important. Due to the scarcity of samples, the degree of methylation of the genes gamma-aminobutyric acid (GABA) B receptor 2 (GABBR2) and RUN and FYVE domain containing 3 (RUFY3) has been shown to be highly associated with the development of depression, which can subsequently affect the growth and development of neurons in the brain, except BDNF.

#### **2.2.2. Histone modifications**

Histone modification generally refers to the process of methylation, acetylation, phosphorylation, adenylation, ubiquitination, ADP-ribosylation, and other modifications of histones by the action of related enzymes [5]. Histone modifications have been most intensively studied for histone acetylation and histone methylation.

Histone methylation often occurs at lysine and arginine terminal residues, and this covalent modification causes gene activation, extension, or repression. In two models of depression, social failure and isolation, H3K9/K27 methylation alterations were observed on the promoters of many genes <sup>[6]</sup>, in which the alterations were reversible <sup>[7]</sup>, where the degree of methylation can be reversed by treatment. This suggests that the degree of histone methylation is a factor in determining the onset and remission of depression.

Compared to histone methylation, histone acetylation occurs more rapidly and have greater effect. Histone acetyltransferases and histone deacetylases play an important role in the process of histone acetylation, and the coordination of these two enzymes maintains the normal expression of the genes. In patients with acute depression, histone deacetylases 2 and 5 tend to be upregulated, meaning that the ability of these enzymes to silence gene expression is further increased. The change in gene acetylation levels is not permanent, and histone deacetylase levels return to normal levels once the patient's symptoms have subsided. This point may allow for follow-up studies of histone deacetylase as a diagnostic marker for depression.

### **2.2.3. Non-coding RNA regulations**

Compared to DNA methylation modifications and histone modifications, research on non-coding RNA regulation is currently limited. MiRNAs are important members of non-coding RNAs and generally consist of 21-24 nucleotides <sup>[6]</sup>, and aberrant expression of miRNAs is closely associated with the development of depression. In tissue taken from the prefrontal cortex of the brains of suicidal patients with depression, a miRNA that regulates glutamate receptors, miR-1202 were significantly downregulated. However, this trend was also reversible, where the miRNA-1202 levels tend to rise and return to normal level following the treatment with antidepressants.

## **3. Treatment prospects and outlook**

### **3.1. Histone deacetylase inhibitors**

Histone deacetylase inhibitors are a class of compounds that inhibit the activity of histone deacetylases <sup>[8]</sup>. Most histone deacetylase inhibitors have a pharmacophore consisting of a three-dimensional elemental structure, including a cap, a linker, and a chelator.

Current research suggests that histone deacetylase inhibitors can generally exert antidepressant effects in three ways <sup>[8]</sup>; (1) Histone deacetylases can play a role in reducing oxidative and inflammatory damage caused by stress, by modulating the inflammation-related pathways, such as c-Jun N-terminal kinase (JNK), which can reduce the concentration of chemokines and pro-inflammatory cytokines which are present in higher concentrations in depressed patients compared to normal subjects; (2) Blocked glutamate transmission can also lead to depression. Histone deacetylase inhibitors can act on the 5-HT pathway to improve the glutamate transmission and alleviate depressive symptoms; (3) The administration of histone deacetylase inhibitors can upregulate the expression of genes related to neuronal development in the brain, such as BDNF, which has a neuroprotective effect.

### **3.2. Norepinephrine Selective Reuptake Inhibitors**

Norepinephrine Selective Reuptake Inhibitors usually work by binding to a norepinephrine transporter to block the extracellular norepinephrine reuptake <sup>[9]</sup>. There is evidence that serum norepinephrine levels correlate with the onset of depression <sup>[10]</sup>, and in normal subjects, serum norepinephrine levels are much higher, compared to depressed patients. Currently, reboxetine is the first Norepinephrine Selective Reuptake Inhibitors to be used for the treatment of depression.

### **3.3. Outlook**

As one of the most important psychiatric disorders that threaten the normal life of human beings, therefore, it is particularly important to study the pathogenesis of depression. Epigenetic inheritance is not the same as Mendelian inheritance, where it brings reversible changes, and the integration of environmental factors and epigenetics can broaden the thinking and research horizons for the development of depression, as well as contribute to the study of the pathogenesis of more psychiatric disorders. Although epigenetics-based treatment for depression is still in its infancy, it can to a certain extent filled the clinical gap brought by the unclear pathogenesis. There is a great potential for future research in this direction.

### **4. Conclusion**

The onset of depression may due to an overactive of HPA axis caused by early childhood abuse or adverse life circumstances, resulting in alterations in some areas of the brain. Such epigenetic alterations are usually caused by DNA methylations, histone modifications, and non-coding RNA regulation, which are usually reversible. The degree of methylation of BDNF, histone methylation or acetylation, and miRNA-1202 concentration levels can be used as a diagnostic marker of depression for follow-up studies.

For the treatment of depression, histone deacetylase inhibitors have become a popular treatment for depression in recent years, with the ability to reduce the concentration of inflammation-related factors in the body, improve glutamate transmission, and protect the nerves, and these are the drugs that are currently being used in clinical practice.

At present, the lack of clinical research materials such as brain tissue and peripheral blood, as well as the different research methods, has made the epigenetic study of depression still in its early stages. In addition, some of the newer depression treatments lack clinical data or have been reported to have high rates of loss of self-control or side effects, which need to be further investigated.

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The authors declare no conflict of interest.

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