ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatry 2022 September 19; 12(9): 1115-1267

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

Contents

Monthly Volume 12 Number 9 September 19, 2022

World Journal of Psychiatry

Monthly Volume 12 Number 9 September 19, 2022

Contents

LETTER TO THE EDITOR

World Journal of Psychiatry

Monthly Volume 12 Number 9 September 19, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Giampaolo Perna, MD, PhD, Chairman, Professor, Department of Biomedical Sciences, Humanitas University, Milan 20090, Italy. giampaolo.perna@hunimed.eu

AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry* (*WJP*, *World J Psychiatry*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, *etc.*

INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJP* as 3.500; IF without journal self cites: 3.313; 5-year IF: 7.380; Journal Citation Indicator: 0.62; Ranking: 89 among 155 journals in psychiatry; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
September 19, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 September 19; 12(9): 1150-1168

DOI: 10.5498/wjp.v12.i9.1150

ISSN 2220-3206 (online)

REVIEW

Depressive disorder and antidepressants from an epigenetic point of view

Iris Šalamon Arčan, Katarina Kouter, Alja Videtič Paska

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Han J, China; Luo ZW, China

Received: March 25, 2022
Peer-review started: March 25, 2022
First decision: May 11, 2022
Revised: May 27, 2022
Accepted: August 6, 2022
Article in press: August 6, 2022
Published online: September 19, 2022

Iris Šalamon Arčan, Katarina Kouter, Alja Videtič Paska, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, Ljubljana SI-1000, Slovenia

Corresponding author: Alja Videtič Paska, PhD, Associate Professor, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, Vrazov Trg 2, Ljubljana SI-1000, Slovenia. alja.videtic@mf.uni-lj.si

Abstract

Depressive disorder is a complex, heterogeneous disease that affects approximately 280 million people worldwide. Environmental, genetic, and neurobiological factors contribute to the depressive state. Since the nervous system is susceptible to shifts in activity of epigenetic modifiers, these allow for significant plasticity and response to rapid changes in the environment. Among the most studied epigenetic modifications in depressive disorder is DNA methylation, with findings centered on the brain-derived neurotrophic factor gene, the glucocorticoid receptor gene, and the serotonin transporter gene. In order to identify biomarkers that would be useful in clinical settings, for diagnosis and for treatment response, further research on antidepressants and alterations they cause in the epigenetic landscape throughout the genome is needed. Studies on cornerstone antidepressants, such as selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, norepinephrine, and dopamine reuptake inhibitors and their effects on depressive disorder are available, but systematic conclusions on their effects are still hard to draw due to the highly heterogeneous nature of the studies. In addition, two novel drugs, ketamine and esketamine, are being investigated particularly in association with treatment of resistant depression, which is one of the hot topics of contemporary research and the field of precision psychiatry.

Key Words: Epigenetics; Depression; DNA methylation; Histone tail modification; microRNA; Antidepressants

Core Tip: Deeper knowledge on the biological background of depressive disorder could be achieved through understanding of epigenetic mechanisms that alter the response of cells to environmental stimuli. Antidepressants are of particular interest since it has been shown that they affect DNA methylation, histone modifications, and microRNA expression. As not all patients respond to prescribed antidepressants, it is of interest to discover specific biomarkers that could be used in a clinical setting.

Citation: Šalamon Arčan I, Kouter K, Videtič Paska A. Depressive disorder and antidepressants from an epigenetic point of view. *World J Psychiatry* 2022; 12(9): 1150-1168
URL: https://www.wjgnet.com/2220-3206/full/v12/i9/1150.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i9.1150

INTRODUCTION

Depressive disorder

Depressive disorder is a complex heterogeneous disease that affects more than 280 million people[1]. The principal form of depressive disorder is major depressive disorder (MDD). Symptoms of depressive disorder are persistent depressive mood, diminished ability to feel pleasure and rejoice, weight changing, disturbed sleep, loss of energy, lowered self-esteem, trouble with concentration, elevated emotional psychomotor activity in children and teenagers, psychomotor agitation or motor retardation, and self-injuring or suicidal ideation[2]. The suicidality phenotype includes ideation, suicide attempt, and death by suicide. MDD is, along with bipolar disorder, schizophrenia, and substance use disorder, one of the most common mental disorders in people who die by suicide[3]. Depression contributes to suicidality, and it increases mortality risk by 60%-80%[4]. According to the Diagnostic and Statistical Manual of Mental Disorder Diagnosis, MDD must exhibit five (or more) out of ten symptoms[2].

The prevalence of depression is higher for women (4.1%) than for men (2.7%)[5]. Sex differences are exhibited in multiple cells of the central nervous system (CNS), neurons, astrocytes, and microglia[6]. Emerging data is showing that besides hormones, epigenetic differences have considerable sexual dimorphism[7]. However, steroid hormone levels influence levels of DNA methyltransferases (DNMTs). For example, female rats had higher levels of DNMT3a and methyl CpG binding protein 2 (MeCP2) in the amygdala (an important center for modulating juvenile social play, aggression, and anxiety)[6] and the preoptic area[7]. As a result of a difference in DNMT3a, there is also a difference in the DNA methylation level[6].

Moreover, people aged 50 years and more have a 1.5 times higher risk for developing depression than younger people[5]. Modern lifestyle promotes independence of the environmental light/dark cycle, which leads to shifting in sleep-wake patterns. Circadian rhythm disruption is affected by the increase in nocturnal activity, decrease of sleep, and extended exposure to artificial light during the nighttime [8]. Limbic brain regions, monoamine neurotransmitters, and the hypothalamic-pituitary-adrenal (HPA) axis are under circadian regulation. It is thought that the perturbation of circadian rhythms contributes to the prevalence of depression and other mood disorders[9].

Depressive disorder is a result of the interplay of many different factors: Environmental, genetic, neurobiological, and cultural[10]. Known environmental risk factors for developing depressive disorder are poverty, negative experiences in the family (bad relationship, violence, divorce, child maltreatment), or other stressful life events. In the time after a stressful life event, the risk for depressive disorder is elevated but the effects of adversity can persist over time[4]. In depressive symptoms that persist over time, stable molecular adaptations in the brain, especially at the level of epigenetics, might be involved [11].

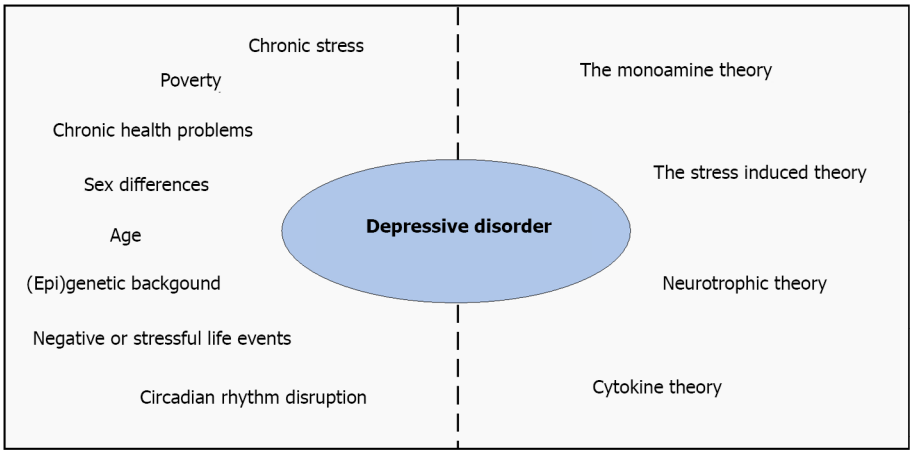
Genetic heritability for depressive disorder, estimated from twin studies, is around 35%–40%[10,12]. Genome-wide association studies have discovered multiple loci with small effects that contribute to MDD[13]. Pandya *et al*[14] collected results from neuroimaging, neuropsychiatric, and brain stimulation studies and showed similar results. In recent years, more and more studies are oriented towards epigenetics to understand new mechanisms and the way epigenetics is linked to a depressive state.

The nervous system is susceptible to shifts in the activity of epigenetic modifiers, which allow for significant plasticity and response to rapid changes in the environment[15]. Epigenetic mechanisms are dynamic. They are very important for early development of the organism as well as later in life, as a response to external factors[16].

From a biological perspective, there are four theories of depressive disorder: Monoamine theory, stress induced theory, neurotrophic theory, and cytokine theory (Figure 1).

Theories of depressive disorder

The monoamine theory of depressive disorder: Monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) are chemical messengers involved in the regulation of emotion, arousal, and



DOI: 10.5498/wjp.v12.i9.1150

Figure 1 Depressive disorder risk factors. Depressive disorders are influenced by various and often overlapping risk factors that form theories of depressive disorders.

certain types of memory. The monoamine hypothesis of depressive disorder proposes development of depressive disorder by signal dysfunction between neurons: A decreased level of neurotransmitters leads to the depressive state[2,17].

The stress induced theory of depressive disorder: Prenatal stress, early-life adversities, chronic stress, and stressful life events are all strong predictors of the onset of depressive disorder. The HPA axis, a neuroendocrine system, is responsible for adaptation to changing environments. Response to stress begins in the hypothalamus, with the secretion of corticotropin-releasing hormone, which affects the pituitary gland to release adrenocorticotropic hormone. Adrenocorticotropic hormone circulates in the blood and stimulates the release of glucocorticoid hormones (cortisol) in the adrenal cortex. Cortisol binds to glucocorticoid receptors in the brain, which are key regulators of the stress response. Cortisol with a negative loop inhibits the HPA axis. Dysregulation of the negative loop is associated with depressive disorder[2,17].

Neurotrophic theory of depressive disorder: Neurotrophic factors are peptides or small proteins that support the growth, survival, and differentiation of developing and mature neurons. Decreased neurotrophic support affects the development of depressive symptoms. Brain-derived neurotrophic factor (BDNF) is a very well examined neurotrophic factor. Many studies made on brain and blood showed decreased expression of *BDNF* in patients with depressive disorder. Also, decreased *BDNF* expression has been associated with epigenetic modifications of the *BDNF* gene[17].

Cytokine theory of depressive disorder: Cytokines are small secreting proteins important in cell signaling. Cytokines include chemokines, interferons, interleukins (IL), lymphokines, and tumor necrosis factors (TNF)[18]. The cytokine (or inflammation) theory of depressive disorder suggests that inflammation has a significant role in its pathophysiology. Patients with depressive disorder have increased inflammatory markers, IL-1β, IL-6, TNF-α, and C-reactive protein[19]. Depressive disorder is not a typical autoimmune disease, so the elevation of cytokines in patients with depressive disorder is lower than in autoimmune or infectious diseases[2].

There are several proposed theories by which the immune system (cytokines and immune cells) could affect depressive-like behavior[20]. For example, inflammation in peripheral tissue can signal the brain *via* the vagus nerve, cytokine transport systems, and a leaky blood-brain barrier caused by rising TNF-α, which leads to brain accessibility for other peripheral signals[19].

Cytokines in the brain elevate during chronic stress and depressive disorder, but besides peripheral cytokines they can also arise from the CNS. Cytokines IL-6 and TNF-α activate indoleamine-2,3-dioxygenase, which decreases tryptophan (a serotonin precursor) and consequently reduces serotonin. Moreover, indoleamine-2,3-dioxygenase is included in the kynurenine pathway. Metabolites from this pathway activate monoamine oxidase (MAO), which degrades serotonin, dopamine, and norepinephrine. Cytokines might also act directly on neurons, changing excitability, synaptic strength, and synaptic scaling. Furthermore, cytokine IL-1β can contribute to heightened activation of the HPA axis and lowering inflammatory response to stress. During chronic stress microglia (neural immune cells) enhance phagocytic activity and synaptic remodeling[20].

Microglia represent 10% of all brain cells[21]. During the development of the organism, microglia are extremely active. They significantly contribute to shaping and refining developing neural circuits by regulating neurogenesis, synaptogenesis, synaptic pruning, and behavior. Early life stress, which is strongly associated with depressive disorder and other mental disorders, can trigger microglia perturb-

ations and affect development through changed morphological and functional changes of microglia. For example, microglial phagocytic activity and neuronal-microglial signaling can disrupt neural circuits and alter the formation of behavior. Furthermore, aberrant functionality of maturing microglial cells can alter their developmental programs and have long-lasting consequences for their reactivity[22]. It is thought that innate immune memory is mediated through epigenetic reprogramming and can last *in vivo* for several months[23].

Epigenetics

In the 1940s, Waddington named the environmental influence of the genome epigenetics. Epigenetic modifications alter gene expression without changing the DNA sequence. The three key types of epigenetic change that occur in cells are DNA methylation, histone posttranslational modifications, and non-coding RNAs. The first two regulate gene transcription through altered chromatin structure and DNA accessibility, while the latter one regulates already transcribed messenger RNA (mRNA)[10]. Studies of epigenetics have escalated in the last 20 years and are gaining importance in the field of psychiatry. Through epigenetic studies, further understanding of depressive disorder is being achieved, but there are still many questions left to answer (Figure 2).

DNA methylation: DNA methylation is a process in which a single methyl group is added on the 5C of the cytosine DNA base. Methyl groups are transferred from S-adenosyl-L-methionine to cytosine by DNMTs[17]. In mammals, there are three groups of DNMTs; DNMT1, DNMT2, and DNMT3. DNMT1 maintains DNA methylation, DNMT3a and DNMT3b carry out *de novo* DNA methylation, and DNMT3L modulates DNMT3a and DNMT3b. DNMT2 has no DNA methylation activity. Instead it catalyzes RNA methylation, specifically on transfer RNAs[24]. DNA methylation mainly occurs at cytosine-phosphate-guanine (CpG) dinucleotides. When those dinucleotides are repeated many times in DNA sequence, they are called CpG islands. CpG islands have an average length of 1000 bp, and they contain more than 50% guanines and cytosines. Approximately 40% of genes contain CpG islands in promoter regions. Methylation of a promoter results in the inability of transcription factors to bind properly to regulatory elements and repression of gene transcription[17]. However, in mammals DNA methylation also occurs at CpA, CpT, and CpC. Those non-CpG methylation sites are common in brain tissue and several other tissue types[25] but at a three times lower rate than CpG methylation[26]. Besides methylation in promoter regions, it can also occur in the gene body and in intergenic regions and affect gene transcription[27]. DNA methylation is a stable cell state, but it can be reversed. Demethylation occurs when 5-methylcytosines are oxidized back to cytosines *via* three cytosine derivate forms: 5-hydoxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[28].

Histone tail modification: The basic unit of chromatin is the nucleosome, which consists of negatively charged DNA and positively charged histone proteins. The nucleosome is an octamer, containing two copies of H2A, H2B, H3, and H4 proteins. Typically, a 147 bp long segment of DNA is wrapped around each nucleosome. H1 protein serves as a linker protein between the other histones that helps to condense nucleosomes even more[29]. Histone proteins have a long amino acid tail on their N-terminal end. In contrast with the core part of the histone protein, this extended part is very dynamic and is prone to chemical modifications[30]. To describe histone modifications we follow a standard nomenclature. First we write the name of the histone protein (H2A, H2B, H3, H4, or H1), then the modified amino acid residue (the name of amino acid and its site; for example, K4–lysine at site 4), and finally the type of modification (for example trimethylation–me3). An example of a final structure is H3K4me3. Specific proteins chemically modify histones and change chromatin conformation. Changes in conformation lead to the opening or closing of the chromatin, which allows or prevents transcription.

There are many different types of histone posttranslational modification, such as acetylation, methylation, phosphorylation, ubiquitination, *etc*, that can be modified differently and by different proteins called "writers" and "erasers." Furthermore, "readers" are proteins important for cross-talk between different epigenetic modifications. For example, DNA methylation and histone modifications mutually influence each other. There are many different reader domains that recognize histone modifications[31]. The most studied histone modifications are acetylation and methylation[29].

Histone acetyltransferases are proteins that transfer acetyl groups to lysine residues on the amino acid tail of histone proteins, while histone deacetylases (HDACs) are proteins that remove acetyl groups from the histone tails. Addition of a negative acetyl group loosens the tight bond between the negatively charged DNA and positively charged histones. This enables access of transcriptional machinery to the regulatory parts of DNA and consequently gene transcription[10].

Histone methylation is the adding of methyl groups to lysine and arginine residues on the histone tail. Histone methyltransferases add methyl groups to the histone tail, and histone demethylases remove methyl groups. Methylation of the histone tail can work in two ways. It can open chromatin or condense it. This depends on the position of the lysine/arginine residue in the histone tail and the number of methyl groups added to the amino acid[10].

MicroRNAs: Non-coding RNAs include many different RNAs: PIWI-interacting RNAs, small nucleolar RNAs, long non-coding RNAs and the most studied, microRNAs (miRNAs). MiRNAs are noncoding, 19–24 nt long RNAs that bind to mRNAs. A mature miRNA goes through biogenesis before it achieves

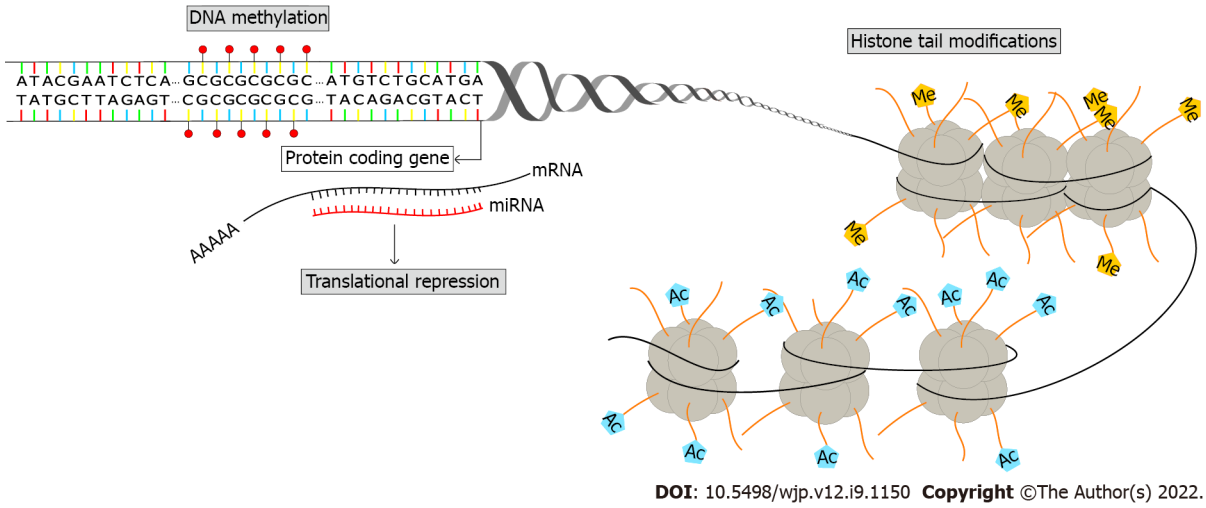


Figure 2 Epigenetic mechanisms. Epigenetic mechanisms include DNA methylation, noncoding RNA activity (such as microRNA), and posttranslational histone tail modifications. Ac: Histone acetylation; Me: Histone methylation; mRNA: Messenger RNA.

its final form. Briefly, it is transcribed as a 1 kb long primary RNA with a stem and loop structure. Primary miRNA is cleaved by Drosha ribonuclease III into a 60–100 bp long precursor miRNA. Precursor miRNA is then translocated from the nucleus into the cytoplasm where the endonuclease Dicer converts it into an unstable, double stranded small RNA. One strand of the duplex is degraded and the other, the mature miRNA, incorporates into the RNA-induced silencing complex along with Argonaut protein. Mature miRNA is complementary to one or more mRNAs. It binds to the 3′ untranslated region of the target mRNA and silences targeted mRNA or sends mRNA to degradation when binding is highly complementary[32].

EPIGENETICS AND DEPRESSIVE DISORDER

Biomarkers that could be associated with MDD are BDNF, the cortisol response, cytokines, and neuroimaging. However, due to the complex nature of depressive disorder a single biomarker is not sufficient for use in diagnosis or monitoring of the disorder. Therefore, it has been proposed to examine multiple biomarkers and use them for patient examination[33]. In genetic studies several polymorphisms associated with a depressive state were found in genes of the monoaminergic system (the gene that encodes for serotonin transporter, receptor genes for dopamine and serotonin, genes involved in signaling of noradrenaline and dopamine…), and genes involved in the functioning and regulation of the HPA axis[2] but did not reveal the role of the DNA sequence itself in the etiology of depressive disorder. Future epigenetics may present new findings, which could be included as possible biomarkers for MDD[33].

Epigenetic modifications were studied in the saliva and blood of the depressed patients, postmortem brain tissue of depressed patients who died by suicide, and rodent animal models (rats and mice). There are several ways to induce stress and a depressed state in animal models[34]. Chronic stress is induced with "bullying" by a bigger more aggressive mouse or witnessing another mouse being physically aggressed for several days[10]. Early life stress from humans can be evoked on animal models by maternal separation of offspring during early postnatal periods. Such induced stress in animals results in mimicking certain behavioral features of human depressive disorder. It has been shown that these methods evoke epigenetic changes, similar to those seen in humans[34].

Tables 1–4 show selected studies of epigenetic changes detected in samples of depressed patients and animal models. The most studied epigenetic modification is DNA methylation, and it has been rather extensively investigated in the *BDNF* gene, specifically exon I. In studies of depressive disorder induced by stress in the prenatal and early stages of life, methylation of glucocorticoid receptor gene (*NR3C1*) was the most analyzed. Lately, more studies are also considering histone 3 modifications among which are methylation of lysines 27, 9, and 4 and acetylation of lysine 14. Studies of miRNAs are diverse and are showing that a more standardized approach is needed.

DNA methylation studies (Table 1 and Table 4) were performed on blood, buccal swabs, or brain tissue of humans and brain tissue of animal models. As we can see from Table 1, there are a lot of studies investigating DNA methylation in the *BDNF* gene (different parts of the *BDNF* gene were tested; exon I, IV, IX, promoter region, whole gene). Most studies showed elevated DNA methylation in the *BDNF* gene in depressed patients. However, a few studies showed that DNA methylation is decreased.

Table 1 DNA methylation studies on depressed subjects, also associated with suicidality and life adversities

Gene (region)	Alteration	Subjects and collected tissue	Ref.
NR3C1 1-F and *FKBP5* intron 7 promoter	↑ DNA methylation at *NR3C1* 1-F, without significant differences at any of the measured individual CpG site in depressed patients. Association in salivary cortisol level and DNA methylation. ↑ DNA methylation in *NR3C1* 1-F at CpG 38 site in depressed patients, with early life adversity. No differences in *FKBP5* intron 7 promoter	33 depressed patients (24 females, 9 males), 34 controls (21 females, 13 males). Whole blood and saliva	Farrell *et al*[67], 2018
MAOA and *NR3C1* exon 1-F	↓ DNA methylation at *MAOA*'s first exon/intron junction; significantly ↓ at CpG 8 site from the intron region. ↑ DNA methylation at *NR3C1* 1-F's promoter and exon in individuals experienced early parental death; significant ↑ at CpG 35 and 10.11 (sites close to NGFI-A binding site)	82 (for *MAOA* gene) and 93 (for *NR3C1* 1-F gene) depressed females, victims of early-life adversity and 92 or 83 controls. Saliva	Melas *et al*[35], 2013
BDNF, *NR3C1*, and *FKBP5*	Significant alteration in DNA methylation at 9 sites in *BDNF* gene body, at 6 sites in *NR3C1* promoter region, and at 4 sites in *FKBP5* gene body, 3'UTR and promoter	94 maltreated and 96 non-traumatized children. Saliva	Weder *et al*[68], 2014
BDNF exon I	↓ DNA methylation; differences at loci 87, 88 and 92–94, located within the CpG island region on the promoter of the exon I	360 depressed patients (32 females, 328 males). Saliva	Song *et al*[69], 2014
BDNF promoter between –694 and –577 relative to the transcriptional start site (12 CpG sites). *SLC6A4* promoter adjacent to exon 1a between –479 and –350 relative to the transcriptional start site (10 CpG sites)	Depressed mood in 2nd trimester associated with ↓ DNA methylation at maternal *SLC6A4* promoter methylation status. ↓ DNA methylation at *SLC6A4* promoter in infants, from mothers with higher depressed mood during 2nd trimester. No difference in *BDNF* gene	82 female and male infants exposed to prenatal maternal stress–33 mothers treated with SRI and 49 mothers not treated with SRI. Blood	Devlin *et al*[70], 2010
NR3C1 exon 1-F and *BDNF* promoter IV	↑ DNA methylation within *NR3C1* 1-F gene (male infants). ↓ DNA methylation within *BDNF* promoter IV region (female and male infants)	20 female and male infants exposed to prenatal maternal stress and 37 controls. Buccal tissue	Braithwaite *et al*[71], 2015
NR3C1 exon 1-F	Depressed mood in 2nd trimester associated with ↑ DNA methylation of CpG 2 site (relative to translational start site) at *NR3C1* exon 1-F in infants. Depressed mood in 3^{d} trimester associated with ↑ DNA methylation of CpG 2 and CpG 3 site (relative to translational start site) at *NR3C1* exon 1-F in infants	46 depressed females (33 treated with SRI and 13 not medicated), 36 controls, and their infants. Blood	Oberlander *et al*[72], 2008
BDNF, *NR3C1*, *CRHBP*, *CRHR1*, *FKBP5* promoter	Hypermethylated *BDNF*, *NR3C1*, *CRHBP* and *FKBP5* promoter. mRNA down regulation of *BDNF, NR3C1, FKBP5* and *CRHBP* in MDD-suicidal ideation group	15 females and 9 males with MDD (14 with and 10 without suicidal ideation) and 20 controls (14 females and 6 males). PBMC	Roy *et al*[73], 2017
BDNF exon I promoter	↑ percentage of methylated reference values	207 female and male MDD patients and 278 controls. PBMC	Carlberg *et al*[58], 2014
BDNF exon I promoter	↑ at CpG 1, CpG 3 and CpG 5 site, ↓ BDNF serum level	49 female and male MDD patients and 57 controls. Blood	Schröter *et al*[74], 2020
BDNF exon I and IV promoter	↑ methylation at CpG site 3 of promoter IV	251 female and male MDD patients aged 65 > and 773 controls. Buccal tissue	Januar *et al*[75], 2015
BDNF exon IX	Changes in DNA methylation; ↑ at CpG site 217, ↓ at CpG site 327, and 362. ↓ BDNF level and mRNA levels	51 MDD patients (35 females and 16 males) and 62 controls (39 females and 23 males). Venous blood	Hsieh *et al*[60], 2019
BDNF upstream of exon I and IV	Changes in DNA methylation within CpG exon I promoter	20 MDD patients (12 females and 8 males) and 18 controls (8 females and 10 males). Blood	Fuchikami *et al*[76], 2011
MYO16 and *IDE*	↑ 5hmc in one CpG position of *MYO16* and two CpG positions of *IDE* in the PFC. ↑ gene expression of *MYO16*. ↓ gene expression of *IDE*	19 depressed male suicide victims and 19 controls. Brain tissue (PFC; inferior frontal gyrus)	Gross *et al*[77], 2017
$GABA_A$ receptor α1 subunit promoter	↑ DNA methylation of the CpG 2 and CpG 4 site (500 bp from transcriptional start site). ↑ DNMT-3B expression in FPC. ↓ expression of *DNMT1* mRNA and ↑ expression of *DNMT3b* mRNA in FPC. ↓ expression of *DNMT3b* and *DNMT1* mRNA in AMG	10 male suicide victims and 10 controls. Brain tissue (FPC, AMG)	Poulter *et al*[78], 2008

SLC6A4 promoter	↑ mean methylation level	28 MDD patients (20 females and 8 males) and 29 controls (21 females and 8 males). Blood	Iga *et al*[79], 2016
NR3C1 exon 1 promoter	↑ methylation at CpG 30 and 32 site. ↓ expression of total *NR3C1* mRNA and *NR3C1*-1F mRNA in suicide victims without childhood abuse and control group	12 suicide victims with traumatic childhood experience, 12 suicide victims without traumatic childhood experience, and 12 controls. Brain tissue (HPC)	McGowan *et al* [80], 2009

↓: Decreased expression; ↑: Increased expression; AMG: Amygdala; *BDNF*: Brain derived neurotrophic factor; bp: Base pair; CpG: Cytosine-phosphate-guanine; *CRHBP*: Corticotropin releasing hormone binding protein; *CRHR1*: Corticotropin releasing hormone receptor 1; *DNMT3B*: DNA methyltransferase 3; *FKBP5*: FK506 binding protein 5; FPC: Frontopolar cortex; $GABA_A$: γ-aminobutyric acid; H3K14ac: Acetylation of lysine 14 on histone 3; *HDAC2*: Histone deacetylase 2; HPC: Hippocampus; *IDE*: Insulin-degrading enzyme; MDD: Major depressive disorder; *MAOA*: Monoamine oxidase A; mRNA: Messenger RNA; *MYO16*: Myoxin XVI; NGFI-A: Nerve growth factor-induced protein A; *NR3C1*: Nuclear receptor subfamily 3 group C member 1; PFC: Prefrontal cortex; PBMC: Peripheral blood mononuclear cells; *SLC6A4*: Solute carrier family 6 member 4; SRI: Serotonin reuptake inhibitor antidepressant; UTR: Untranslated region; 5hmc: 5-hydroxymethylcytosine.

Table 2 Histone tail modifications studies on depressed suicide victims

Gene (region)/histone tail modification	Alteration	Subjects and collected tissue	Ref.
BDNF, H3K9/14ac, H3K27me2	↓ H3K9/14ac, ↑ HDAC2, ↑ HDAC3, ↑ H3K27me2, ↓ BDNF in HPC and NAc. ↑ Sin3a in HPC	14 suicide victims (5 females and 9 males) without psychiatric diagnosis and 8 controls (3 females and 5 males). Brain tissue (HPC, NAc, and FCx; BA10)	Misztak *et al*[53], 2020
H3K4me3	↑ In H3K4me3 at promoter of *SYN2*. ↑ expression *SYN2b*; no changes in *SYN2a* expression	7 females and 11 males with MDD suicide victims and 14 controls (3 females and 12 males). Brain tissue (PFC; BA10)	Cruceanu *et al*[81], 2013
H3K14ac	↑ H3K14ac. ↓ *HDAC2* mRNA expression	8 depressed females and males. Brain tissue (NAc)	Covington *et al*[11], 2009

↓: Decreased expression; ↑: Increased expression; BA10: Brodmann area 10; *BDNF*: Brain derived neurotrophic factor; FCx: Frontal cortex; H3K14ac: Acetylation of lysine 14 on histone 3; H3K9/14ac: Acetylation of lysine 9/14 on histone 3; H3K27me2: Dimethylation of lysine 27 on histone 3; H3K4me3: Trimethylation of lysine 4 on histone 3; HDAC2: Histone deacetylase 2; HDAC3: Histone deacetylase 3; HPC: Hippocampus; MDD: Major depressive disorder; mRNA: Messenger RNA; NAc: Nucleus accumbens; Sin3a: SIN3 transcription regulator family member A; PFC: Prefrontal cortex; *SYN2*: Synapsin II; *SYN2b*: Synapsin IIb; *SYN2a*: Synapsin IIa.

The main conclusion is that alteration in *BDNF* methylation is associated with a depressive state.

The gene *NR3C1* is included in many studies of early life adversities (childhood abuse, parental loss, exposure to maternal depression during pregnancy and after birth). Results show an association between increased methylation of the exon 1-F of the *NR3C1* gene, decreased total *NR3C1* mRNA, and early life adversities[35]. *NR3C1* encodes for the glucocorticoid receptor and is responsible for the effects of cortisol on peripheral tissues. It is self-regulated by a negative feedback loop within the HPA axis [36]. The glucocorticoid receptor can work as a transcription factor that binds to glucocorticoid receptor elements in the promoters of glucocorticoid responsive genes or as a regulator of other transcription factors[37].

In terms of the histone modification data presented in Table 2 and Table 4, H3K27me and H3K14ac are the most studied. The majority of the studies are carried out on animal models and a few on postmortem brain tissue. Studies include information of whole tissue histone modifications and not of single genes. From studies on animal models (Table 4), we can see that the histone tail modifications change over time and are different regarding tissue type.

Many studies in the last 15 years took into consideration miRNAs as important contributors either to the depressive state or as a biomarker of the depressive state. Studies examining humans (Table 3) are in correlation with studies performed on rodents (Table 4). For example, miR-218 and miR-511 are both downregulated in the prefrontal cortex of depressed subjects who died by suicide and in rodent models (mice or rat). On the other hand, miR-16 and miR-376b were oppositely regulated in humans *vs* animal models. This might be due to different tissues tested. There are several more miRNAs regulated in the same direction in human *vs* animal (rodent) models[38]. Upregulation of miR-139-5p is seen in blood-derived exosomes from MDD patients and in brain tissue from chronically depressed mice. Upregulation of miR-323-3p is seen in lateral habenula and Brodmann area 24 in depressed subjects. Consistently, there is also upregulation of miR-323-3p in the brains of rats exposed to prenatal stress. MiR-155 is downregulated in peripheral blood mononuclear cells of depressed subjects and serum of mice exposed to restraint stress. Furthermore, blood-derived exosomes with increased levels of miR-

Table 3 MicroRNA expression studies on depressed suicide victims

miRNAs	Alteration	Subjects and collected tissue	Ref.
miR-218	↓ miR-218 and ↑ *DCC* in PFC	11 male suicide victims with MDD and 12 male controls. Brain tissue (PFC; BA44)	Torres-Berrío *et al*[82], 2017
↓ miR-142-5p, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR-20b, miR-376a*, miR-190, miR-155, miR-660, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p. ↓ by 30% or more: miR-211, miR-511, miR-424, miR-369-3p, miR-597, miR-496, miR-517c, miR-184, miR-34a, miR-34b-5p, miR-24-1*, miR-594, miR-34c-5p, miR-17*, miR-545, miR-565	Globally ↓ miRNAs expression by 17% on average in depressed subjects. miR-148b targets *DNMT3B*, protein level was upregulated in depressed subjects. miR-34a targets *BCL2*, protein level was downregulated in depressed subjects	18 suicide victims (2 females and 16 males) with depression and 17 male control subjects. Brain tissue (PFC; BA9)	Smalheiser *et al*[83], 2012
miR-1202	↓ miR-1202, and ↑ *GRM4* mRNA expression in BA44	25 suicide victims (2 females and 23 males) with MDD and 29 control subjects (4 females and 25 males). Brain tissue (PFC; BA44). 32 subjects with MDD (24 females and 10 males) and 18 control subjects (8 females and 10 males). Blood	Lopez *et al* [84], 2014
miR-30e	↑ miR-30e, ↓ ZDHHC21 protein	16 suicide victims (7 females and 9 males) with MDD and 16 controls (6 females and 10 males). Brain tissue (PFC; BA9)	Gorinski *et al*[85], 2019
miR-19a-3p	↑ miR-19a-3p (might be involved in the modulation of TNF-α signaling)	12 depressed patients with severe suicidal ideation, 12 control subjects. PBMC	Wang *et al* [86], 2018
More than 10 miRNAs	↑ miR-17-5p, miR-20b-5p, miR-106a-5p, miR-330-3p, miR-541-3p, miR-582-5p, miR-890, miR-99b-3p, miR-550-5p, miR-1179. ↓ miR-409-5p, let-7g-3p, miR-1197	9 depressed suicide victims (3 females and 6 males) and 11 control subjects (2 females and 9 males). Brain tissue (*locus coeruleus*)	Roy *et al* [37], 2017
miR-326	↓ miR-326, ↑ UCN1	5 male suicide victims with MDD and 8 male controls. Edinger-Westphal nucleus	Aschrafi *et al*[87], 2016
10 miRNAs tested	↑ miR-34c-5p, miR-139-5p, miR-195, miR-320c. ↓ *SAT1* and *SMOX* mRNA	15 male suicide victims with MDD and 16 male control subjects. Brain tissue (BA44)	Lopez *et al* [88], 2014
miR-204-5p, miR-320b, miR-323a-3p, miR-331-3p	↑ miR-204-5p, miR-320b, miR-323a-3p, miR-331-3p in ACC and lateral habenula. miR-323a-3p influences the expression of *ERBB4*. Decreased expression in ACC and lateral habenula	39 suicide victims with MDD (13 females and 26 males) and 41 control subjects (10 females and 31 males) for ACC region. 24 suicide victims with MDD (10 females and 14 males), 13 control subjects (5 females and 8 males) for lateral habenula. Brain tissue (ACC and lateral habenula)	Fiori *et al* [89], 2021
171 miRNA differently expressed	↑ 117 miRNAs. ↓ 54 miRNAs	22 (10 females and 12 males) MDD subjects (10 died by suicide, 12 died from cause other than suicide) and 25 control subjects (10 females and 15 males). Brain tissue (ACC)	Yoshino *et al* [90], 2020
miR-128-3p	↑ miR-128-3p. ↓ WNT5B, DVL1 and LEF1	20 MDD (10 females and 10 males) subjects and 22 control subjects (9 females and 13 males). Brain tissue (AMG)	Roy *et al* [91], 2020
miR-16	↓ miR-16	36 MDD (21 females and 15 males) subjects and 30 controls (17 females and 13 males). CSF	Song *et al* [92], 2015

↓: Decreased expression; ↑: Increased expression; ACC: Dorsal anterior cingulate cortex; AMG: Amygdala; BA44: Brodmann area 44; BA9: Brodmann area 9; *BCL2*: B-cell lymphoma 2; CSF: Cerebrospinal fluid; *DCC*: Developmental netrin-1 guidance cue receptor; *DNMT3B*: Gene coding for DNA methyltransferase 3; DVL1: Dishevelled segment polarity 1; *GRM4*: Gene coding for metabotropic glutamate receptor 4; LEF1: Lymphoid enhancer binding factor 1; MDD: Major depressive disorder; miR: MicroRNA; mRNA: Messenger RNA; PBMC: Peripheral blood mononuclear cells; PFC: Prefrontal cortex; *SAT1*: Gene coding for spermidine/spermine N1 -acetyltransferase 1; *SMOX*: Gene coding for spermine oxidase; TNFα: Tumor necrosis factor; UCN1: Urocortin; WNT5B: Wingless-related integration site, member 5B.

139-5p collected from depressed subjects, evoked depressive-like behavior when administered intravenously in mice[38].

However, from all the data currently available, it is hard to pinpoint particular miRNAs that could be used as biomarkers for depressive disorder. Studies presented in Table 4 show lack of overlap between

Table 4 Epigenetic (DNA methylation, histone tail modifications, and microRNAs) studies on animal models of depressive disorder

Epigenetic modification	Gene (region)/histone tail modification/miRNA	Alteration	Organism and collected tissue	Ref.
DNA methylation	*Crf* promoter of exon 1 and intronic region between exon 1 and exon 2 (relative to exon 1 start site)	Overall ↑ DNA methylation, and specific ↑ in CpG –147 and CpG –101 site of the *Crf* gene in stressed female rats in the PVN. No changes in male rats. ↓ DNA methylation in CpG –15 (male and female rats), ↓ DNA methylation in CpG –226, CpG –55 and ↑ in CpG +485 and CpG +494 (male rats) and ↓ DNA methylation in CpG –95 site (female rats) in BNST. ↑ DNA methylation in CpG –232 and CpG –226 (male rats), ↓ CpG –226 and CpG +535 (female) in the CeA	Male and female Wistar-R Amsterdam rats; sacrificed 2 h after stress. Brain tissue (PVN, BNST, CeA)	Sterrenburg *et al* [93], 2011
DNA methylation	*Crf* promoter (relative to exon 1 start site)	Chronic social stress induced ↑ DNA methylation in *Crf* promoter region at CpG site –226 and ↓ DNA methylation level in intronic region of the gene *Crf* in the PVN. Long term effect of social defeat in mice susceptible to social defeat: ↑ in *Crf* mRNA levels in PVN and ↓ DNA methylation level at CpG –226, –101, –95, and –79	Chronically stressed adult mice C57BL/6. Brain tissue (PVN)	Elliott *et al*[94], 2010
DNA methylation and histone tail modification	*Gdnf*	↑ DNA methylation at CpG site 2. ↓ H3ac in NAc of BALB mice and C57BL/6 mice. C57BL/6 mice had higher H3ac and higher *Gdnf* expression	BALB/c mice with maladaptive response to stressful stimuli and stress resilient strain C57BL/6. Brain tissue (NAc)	Uchida *et al*[95], 2011
Histone tail modification	H3K14ac	↓ H3K14ac 1 h after final stress. ↑ H3K14ac 24 h and 10 d after final stress. ↓ *Hdac2* mRNA expression 24 h and 15 d after final stress in NAc	Chronically social defeated adult male mice C57BL/6J. Brain tissue (NAc).	Covington *et al* [11], 2009
Histone tail modification	H3K14ac	H3K14ac ↑ after 24 h and ↓ at longer time in HPC. H3K14ac ↑ after 1 h and 24 h, no changes 10 d and longer in AMG	Chronically social defeated adult male mice C57/BL6J. Brain tissue (HPC and AMG)	Covington *et al* [96], 2011
Histone tail modification	*Bdnf* exon IV, H3ac, H4ac	↓ exon IV *Bdnf* mRNA. ↓ H3ac and H4ac. ↑ MeCP2 levels. ↑ *Hdac* mRNA	Rats (early life adversity induced by maternal separation). Brain tissue (HPC)	Seo *et al*[97], 2016
Histone tail modification	*Bdnf* III and IV promoter, H3K27me2	↑ H3K27me2 at promoter *Bdnf* III and IV. ↓ total *Bdnf* mRNA. No change at H3K9me2	Chronic social defeat stress mice. Brain tissue (HPC)	Tsankova *et al* [62], 2006
Histone tail modification	H3K9me2	↑ H3K9me2 in HPC and mPFC. ↓ *Bdnf* expression in HPC and mPFC	Wistar rats exposed to maternal separation and chronic unpredicted mild stress. Brain tissue (HPC and mPFC)	Jiang *et al*[98], 2021
Histone tail modification	H3K4me3, H3K9me3, H3K27me3	Acute restrain stress: ↑ in H3K9me3 in CA1 and DG; no changes in CA3; ↓ in H3K27me3 in DG and CA1; not significantly altered in CA3. No significant changes for H3K4me3. Subchronic 7-d restraint stress: The basal level of H3K9me3 on day 7 increased in DG, CA1 and CA3. ↓ in H3K9me3 in CA1, CA3 and DG. ↓ in H3K27me3 in DG	Adult male Sprague–Dawley rats (acute stress/7 d restraint stress). Brain tissue (HPC parts: DG, CA1, CA3)	Hunter *et al*[99], 2009
miRNA	miR Let-7a-1, miR-9, miR-25a/b	↑ miR Let-7a-1, miR-9, miR-25a/b after acute stress in FCx. No changes in HPC	Male CD1 mice with induced acute or repeated stress. Brain tissue (FCx and HPC)	Rinaldi *et al* [100], 2010
miRNA	miR-218	↓ miR-218 and ↑ *DCC* in PFC	Chronically social defeated adult male mice C57BL/6. Brain tissue (mPFC)	Torres-Berrío *et al*[82], 2017
miRNA	miR-16	↑ miR-16. ↓ *Bdnf* mRNA	Sprague-Dawley rats exposed to maternal deprivation. Brain tissue (HPC)	Bai *et al*[101], 2012
miRNA	342 miRNAs differently expressed (response to gestational stress) and 336 miRNAs differently	↑ 147 miRNAs and ↓ 195 miRNAs in FCx of female rats. ↑ 205 miRNAs and ↓ 131 miRNAs in offspring	Stress induced through pregnant female Long-Evans rats. Offspring	Zucchi *et al*[102], 2013

	expressed in offspring (response to prenatal stress)		(decapitated 1 to 5 h after parturition). Brain tissue (FCx)	
miRNA	AMG: 10 miRNAs under acute stress and 28 after chronic stress; HPC CA1: 16 after acute stress and 22 after chronic stress	The overlap: ↑ miR Let-7a-1 in AMG affected by acute and chronic stress. ↑ miR-376b and miR-208, ↓ miR-9 in HPC by acute and chronic stress. Other changes are unique to acute/chronic stress or brain region analyzed	Adult male rats with induced acute or chronic stress. Brain tissue (AMG, HPC CA1 region)	Meerson *et al* [103], 2010
miRNA	miR-124a, miR-18a, miR-511	↑ miR-124a, miR-18a in PFC and HPC persistently. ↓ miR-511 in PFC (in adult rats experienced CUMS)	Adolescent male Wistar rats were stressed with CUMS. Brain tissue (PFC and HPC)	Xu *et al*[104], 2019

↓: Decreased expression; ↑: Increased expression; AMG: Amygdala; *Bdnf*, brain derived neurotrophic factor; BNST: Bed nucleus of the stria terminalis; CeA: Central amygdala; CpG: Cytosine-phosphate-guanine; *Crf*: Corticotropin releasing factor; CUMS: Chronic unpredictable mild stress; *DCC*: Gene coding developmental netrin-1 guidance cue receptor; DG: Dentate gyrus; FCx: Frontal cortex; *Gdnf*: Glial cell-derived neurotrophic factor; HDAC: Histone deacetylase; H3ac: Acetylation of histone 3; H4ac: Acetylation of histone 4; H3K14ac: Acetylation of lysine 14 on histone 3; H3K9me2: Dimethylation of lysine 9 on histone 3; H3K9me3: Trimethylation of lysine 9 on histone 3; H3K27me2: Dimethylation of lysine 27 on histone 3; H3K27me3: Trimethylation of lysine 27 on histone 3; H3K4me3: Trimethylation of lysine 4 on histone 3; *Hdac2*: Histone deacetylase 2; HPC: Hippocampus; HPC CA1: Hippocampal CA1 region; HPC CA3: Hippocampal CA3 region; MeCP2: Methyl CpG binding protein 2; mPFC: Medial prefrontal cortex; miR: Micro RNA; miRNA: Micro RNA; mRNA: Messenger RNA; NAc: Nucleus accumbens; PFC: Prefrontal cortex; PVN: Hypothalamic paraventricular nucleus.

studies; there are several different tissues used, and the number of miRNAs interrogated vary from whole RNome studies to single miRNA studies. Although many limitations exist in the miRNA research, current results are promising enough to persist with the search for miRNAs or even miRNA networks that could serve as biomarkers.

Due to variation in study design, comparisons between the obtained results are limited. In particular, criteria for subject inclusion are very diverse (inclusion of one/two sexes, age, ethnic background, and so on), and studies are frequently underpowered. In addition, the background of the depressive state is not the same for all depressed patients. Some studies analyze the consequences of early life adversity, others include patients with depressive disorder at older age or depressed patients without a known cause. When working with animal models the study design is more standardized and controlled, while the trigger of depressed state is selected based on the interest of the study.

POSSIBLE TREATMENTS OF DEPRESSIVE DISORDER

There are pharmacological and nonpharmacological (psychotherapy, lifestyle interventions, and neuromodulatory treatment) ways of treating depressive disorder. For pharmacological treatment, there are many different antidepressants available, and they are a cornerstone for treating depressive disorder [39]. The main drug classes of antidepressants are selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, noradrenergic and specific serotonergic agents, tricyclic antidepressants, MAO inhibitors, and melatonin modulators (agomelatine)[40]. However, there is no universally effective treatment for all depressed patients[39].

People suffering from depressive disorder can recover in a year or not recover in more than 20 years. Furthermore, depressive episodes recur in almost half of recovered patients[5]. Even though there are many different antidepressants available and many different treatment options, 34%–46% of MDD patients still do not respond effectively to one or more antidepressant treatments (*i.e.* fail to achieve remission). That is why there is still a great need for new antidepressants for curing treatment-resistant depression[41]. Among novel drugs, ketamine and eskatemine are being extensively used. Also, the HDAC inhibitors (HDACis) are being tested on animal models as one possibility of treatment.

Selective serotonin inhibitors

SSRIs are the most commonly prescribed antidepressants and are used as the first treatment step for depressive disorder. Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter that modulates mood, reward, learning, and memory. Deficiency in serotonin release is not associated with serotonin biosynthesis. The serotonin deficit is more likely due to less serotonin neuron firing and less serotonin release. However, SSRIs block the reabsorption of serotonin into presynaptic neuron cell and with that improve message transmission between cells[40].

Fluoxetine was the first SSRI to be developed and is the most used antidepressant for children and adolescents. Many different SSRIs have now been developed that vary in binding affinity; some are more specific to serotonin than others. It became clear that using the available antidepressants targeting specific monoamines also have side effects. Those side effects come from neurotransmitters binding to different receptors. For example, when serotonin binds to the 5HT1A receptor, there is an antide-

pressant and anxiolytic effect; when it binds to 5HT2A/C receptor, there is an effect on sexual dysfunction. Multimodal antidepressants directly target specific serotonin receptors and inhibit reuptake of serotonin. Vilazodone is an example of a multimodal antidepressant, which targets a specific receptor (5HT1A). Still, vilazodone is not as superior as it was expected to be compared to other antidepressants[40,42]. Vortioxetine is more promising since it shows superior efficacy compared to the other antidepressants in trials. Vortioxetine is an agonist of 5HT1A, (partial) antagonist of other receptors, and a potent serotonin reuptake inhibitor. Besides the antidepressant effect, it also improves cognitive function[40,42].

Ketamine

Novel treatments that target outside of the monoaminergic system are ketamine [targeting the glutamate system through N-methyl-aspartate (NMDA) receptor antagonism] and agomelatin (a melatonin receptor agonist)[40]. Agomelatin is a melatonin agonist and a selective serotonin antagonist. For antidepressant effect, both actions are necessary. Agomelatin showed good antidepressant effect for people with seasonal affective disorder[43].

Ketamine is used in many clinical studies for treatment-resistant patients who fail to respond to SSRIs. Ketamine showed good results, with a response rate between 40% and 90%[43]. Intravenous infusion of ketamine produces a rapid and prolonged effect within a few hours of administration. It is accompanied by psychotomimetic effects, which subside within 2 h. The effect of a single intravenous insertion lasts 2–14 d, and it has an anti-suicide effect[41]. Ketamine is restricted for routine clinical use due to its side effects: Dissociative effects, changes in sensory perception, intravenous administration, and risk of abuse[44].

Ketamine is a mixture of two enantiomers, S-ketamine and R-ketamine. In the past few years, esketamine (S-ketamine) has been studied as a better option than ketamine because of its easier administration. Esketamine can be inserted intranasally and is therefore easier for at home administration. Recently, researchers investigated R-ketamine. Preclinical and clinical studies on intravenously infused R-ketamine elicit a fast and sustained antidepressant state, without psychotic symptoms[45].

Ketamine's action: Ketamine affects the glutamate system. Glutamate is an excitatory neurotransmitter and is involved in neurodevelopment, neurocognitive (memory learning) function, and neuroplasticity (neurogenesis, neuronal growth and remodeling, maintenance, and synaptic plasticity). Dysregulation of neuroplasticity can contribute to MDD and other neuropsychiatric conditions. The majority of neurons use glutamate as a neurotransmitter. Two types of glutamate receptors (ionotropic or metabotropic glutamate receptors) are categorized into four major classes: α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptors, NMDA receptors (NMDAR), kainate receptors, and metabotropic glutamate receptors[46]. NMDARs are located at the postsynaptic and presynaptic side of glutamatergic synapses in the CNS[47]. In postmortem brains of MDD patients, many studies have revealed alteration in NMDAR. Several changes were discovered, such as NMDAR dysfunction (reduced glutamate recognition and allosteric regulation) and altered expression of NMDAR subunits. The latter might be manifested by altered glutamatergic input and abnormal glutamate neurotransmission[46].

There are several mechanisms of ketamine action, which may act complementarily. Ketamine can bind to NMDAR on presynaptic or postsynaptic glutamatergic neuron and on GABAergic interneurons. Binding leads to blockade and inhibition of NMDAR. For the antidepressant effects of ketamine, cascades of actions happen: γ-aminobutyric acid decrease, glutamate release, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors activation, BDNF release, tropomyosin receptor kinase B activation, and mammalian target of rapamycin complex 1 activation. The result is an acute change in synaptic plasticity and sustained strengthening of excitatory synapses[44]. The process of synaptogenesis is activated and further probably affects cognition, mood, and thought patterns[48].

HDACis

Decreased acetylation is associated with a depressive state and because of that, HDACs (as erasers of acetylation) might become a novel treatment target[10]. HDACs, "erasers" of histone acetylation, are classified into two categories: The zinc-dependent and nicotinamide-adenine-dinucleotide–dependent sirtuins (Table 5)[49].

HDACs I, II, and IV are expressed in the brain, primarily in neurons. Class I and II regulate histone deacetylation at most genes, and class III deacetylates nuclear and cytoplasmic substrates beside histones[50]. The balance between histone acetyltransferases and HDAC activity determines the (de)condensation status of the chromatin and gene transcription[10].

HDACis are potent to specific classes of HDACs. The United States Food and Drug Administration has approved a few HDACis [vorinostat (SAHA), belinostat, panobinostat, and romidepsin] for treatment of some types of cancers. Many preclinical studies on mice showed an antidepressant effect of HDACis by reversing the acetylated state. Moreover, HDACis also promote neuronal rewiring and recovery of motor functions after traumatic brain injury. Use in clinical practice is limited due to severe side effects including thrombocytopenia and neutropenia[51].

Table 5 Histone deacetylase classification and localization

HDAC category	HDAC class	HDAC type	Localization
Zinc-dependent HDACs	Class I	HDACs 1, 2, 3, 8	Localized in nucleus
	Class II	HDACs 4, 5, 7, 9, 10	Pass between nucleus and cytoplasm
		HDAC6	Localized in the cytoplasm
	Class IV	HDAC11	
NAD-dependent SIRTs	Class III	SIRTs 1, 2, 6 and 7	Localized in the nucleus
		SIRTs 3, 4 and 5	Localized in the mitochondria

HDACs: Histone deacetylases; NAD-dependent sirtuins: Nicotinamide-adenine-dinucleotide–dependent sirtuins; SIRTs: Sirtuins.

DEPRESSIVE DISORDER ASSOCIATED GENES AND CLASSICAL ANTIDEPRESSANT DRUGS

How different antidepressants affect depressive symptoms can be measured by a subject's phenotype (behavior for animals and psychiatric evaluation for humans). Epigenetic alterations might become one of the tools to check how well specific subjects respond to the antidepressant[52].

BDNF and depressive disorder

One of the most studied genes of depressive disorder is *BDNF*. BDNF is one of the most important neurotrophins. The human *BDNF* gene contains nine exons (I–IX), each regulated by its own promoter. All the different transcripts are translated into an identical BDNF protein[53]. It is highly expressed in the CNS[54] and plays an important role in proper brain development and functioning, including neuronal proliferation, migration, differentiation, and survival[53]. BDNF binds to p75 neurotrophin receptor (p75NTR) and tropomyosin receptor kinase B[54]. In many studies, exon I and IV showed alteration in expression levels in depressed subjects. Splice variant tropomyosin receptor kinase B.T1 is an astrocytic variant and has gained a lot of interest in the study of the depressive state[10]. Two single nucleotide polymorphisms, Val66Met and *BE5.2*, of *BDNF* reduce BDNF release. In addition, studies show significant effects of epigenetic changes on the depressive state[53]. Treatment with SSRIs and HDACi antidepressants increases levels of BDNF in peripheral tissues. If BDNF does not increase early after administration, this predicts non-response to antidepressants[55].

BDNF and antidepressants: Human studies: The studies on DNA methylation and antidepressant effect in general include a rather low number of subjects but several different antidepressants.

Two studies analyzed H3K27me3 modification, and both reported decreased H3K27me3 in patients with MDD. Chen *et al*[56] performed a study on Caucasians (French Canadian origin, 9 control subjects, 11 MDD subjects without a history of antidepressant use, and 7 MDD subjects who used antidepressants). All MDD subjects died due to suicide. Several different antidepressants were administered: Fluoxetine (n = 1), venlafaxine (n = 2), clomipramine (n = 1), amitriptyline (n = 1), citalopram (n = 1), and doxepin (n = 1). Analysis of the epigenetic modification H3K27me3 in brain tissue from Brodmann area 10 between the control group and the non-medicated MDD group showed no differences. Subjects with a history of antidepressant use showed an increase in *BDNF* IV expression but not *BDNF* I, II, and III expression and a decreased level of H3K27me3 at the *BDNF* IV promoter[56].

Lopez *et al*[57] investigated 25 MDD patients (13 females and 12 males) whose blood levels of total BDNF and H3K27me3 were measured before antidepressant treatment and after 8 wk of citalopram administration. After treatment, there was an elevation of peripheral *BDNF* mRNA in patients responsive to antidepressant treatment and a decrease in H3K27me3 level at promoter IV of the *BDNF* gene[57].

An increase of *BDNF* DNA methylation level after antidepressant administration was shown in three studies. Carlberg *et al*[58] (2014) studied *BDNF* methylation on peripheral blood mononuclear cells of 207 MDD patients and 278 control subjects from Vienna, Austria. From 207 MDD patients, 140 subjects were treated with antidepressant medication and 25 subjects were not. There was an alteration in DNA methylation at the *BDNF* exon I promoter. After antidepressant administration, there was an increase in methylation in MDD patients compared with patients without antidepressant medication and healthy controls[58].

D'Addario *et al*[59] reported that there was an increase in DNA methylation at the *BDNF* promoter in 41 MDD patients with stable pharmacological treatment in comparison to 44 healthy control subjects. In addition, there was a significant reduction in expressed *BDNF* from peripheral blood mononuclear cells in MDD patients than in the control group. Patients who took only SSRIs or selective serotonin and norepinephrine reuptake inhibitors had a higher methylation level of the *BDNF* promoter than patients

who received antidepressants and mood stabilizers[59].

In a study by Wang *et al*[16], 85 Chinese Han patients with MDD (females and males) were treated with escitalopram. Blood samples were tested for DNA methylation in the *BDNF* region. DNA methylation before treatment was significantly lower than after 8 wk of treatment. A difference was seen between remitted and non-remitted patients. Patients with remission had higher DNA methylation than non-remitters[16].

Two studies included analysis of patients who responded and those who did not. In both, higher methylation level was an important contributor to treatment response. Hsieh *et al*[60] included 39 patients with MDD (females and males) and 62 healthy controls (females and males). Higher methylation levels were detected at CpG site 217 and lower methylation level at CpG sites 327 and 362 in the *BDNF* exon IX promoter in MDD patients compared to controls. After drug administration (SSRIs; fluoxetine, paroxetine, and escitalopram), 25 patients who responded to SSRIs had a higher methylation level at CpG sites 24 and 324 than patients who did not respond (n = 11). Methylation analysis results also showed consistent results of BDNF protein level and mRNA level in peripheral blood[60].

A study by Tadić *et al*[52] (2014) included 46 MDD patients (females and males) with different monoaminergic antidepressants prescribed: Escitalopram (n = 5), fluoxetine (n = 2), sertraline (n = 6), venlafaxine (n = 19), duloxetine (n = 2), mirtazapine (n = 6), amitriptyline (n = 1), clomipramine (n = 3), trimipramine (n = 1), or tranylcypromine (n = 1). Although different antidepressants were used, the main observation of the study was the response or non-response to the antidepressant treatment. From 13 CpG sites checked for methylation status on blood samples within the *BDNF* IV promoter, one stood out; antidepressant non-responders had lower methylation at CpG position –87 (relative to the first nucleotide of exon IV). There were no other DNA methylation changes after treatment[52].

Animal studies: In animal models, it has been shown that histone tail modifications significantly affect gene expression and that they are changed after antidepressant administration.

In the study by Park *et al*[34], male Sprague-Dawley rat pups were separated from mothers during early life. Maternal separation evoked a decrease of exon I mRNA *Bdnf*, H3 acetylation (ac) levels and an increase in *Dnmt1* and *Dnmt3a* mRNA level in the hippocampus. After 3 wk of escitalopram administration in adult rats subjected to maternal separation, the result was an increase in BDNF protein, exon I mRNA, levels of H3ac, and a decrease in *Mecp2*, *Dnmt1*, and *Dnmt3a* mRNA levels[34].

Xu *et al*[61] showed that mice stressed in the adolescent period show epigenetic changes also in adult life. Stress in tested male C57BL/6J mice were induced by confrontation of aggressor mice CD1. The expression level of total *Bdnf* and *Bdnf* IV mRNA were decreased in the medial prefrontal cortex (the same results were observed in the hippocampus). *Bdnf* I and VI mRNA levels changed over time in the medial prefrontal cortex. Adult mice had upregulated H3K9me2 in a region downstream of the promoter of the gene *Bdnf* IV, but there were no differences in H3K4me3, H3K9ac, and H3K4ac. Tranylcypromine administration reversed this change and increased levels of H3K4me3. Tranylcypromine is a non-selective MAO inhibitors[61].

Tsankova *et al*[62] showed decreased expression of *Bdnf* III and IV, which manifested in the total level of *Bdnf* mRNA in the hippocampus in chronically defeated BL6/C57 mice. Changes in *Bdnf* III and IV expression persisted a month after cessation of the chronic defeat stress. On the promoter of *Bdnf* III and *Bdnf* IV there was an increase of H3K27me2 but not H3K9me2. Chronic imipramine (a tricyclic antidepressants) administration reversed changes of *Bdnf* expression but did not reverse H3K27me2 to the base level. After chronic social defeat stress and imipramine administration, H3 was hyperacetylated (H3K9/14ac) at the promoter *Bdnf* III and IV, which affected mRNA expression. Furthermore, H3K4me2 was similarly enriched in the *Bdnf* III promoter and correlated with transcriptional activation. There were no changes in H4ac. There was a decrease in *Hdac5* mRNA level but only on chronically stressed mice treated with chronic imipramine. Acute imipramine did not influence *Hdac* level[62].

Solute carrier family 6 member 4 and depressive disorder

Solute carrier family 6 member 4 (*SLC6A4*) is a gene that codes for serotonin transporter. The protein's name comes from the name of the monoamine neurotransmitter serotonin (5-HT) that binds to it. The gene *SLC6A4* was associated with the protein later. Serotonin transporter is an integral membrane protein that transports serotonin from synapse to presynaptic neurons. Besides involvement in regulation of the serotonergic system, *SLC6A4* also acts as an important element of stress susceptibility. Serotonin transporter linked promoter region polymorphism at gene *SLC6A4* has 2 variants, a short allele and a long allele. The short allele results in lower gene transcription and is therefore associated with a depressive state[63]. In addition, there are also several epigenetic studies explaining its dysfunction. Some studies have shown how treatment with classical antidepressants affects epigenetic changes of the *SLC6A4* gene. Therefore, *SLC6A4* is a key target for antidepressant treatment research.

***SLC6A4* and antidepressants:** Human studies: There is a difference in the response to antidepressants seen when analyzing DNA methylation in *SLC6A4* gene. Two studies reported higher methylation status after antidepressant administration and one lower methylation status.

Booij *et al*[64] included in their study 33 MDD patients (females and males). MDD patients who were taking SSRIs had higher methylation levels at CpG 11 and 12 within the regulatory region upstream of the promoter of the *SLC6A4* than patients who did not use antidepressants (n = 36). Research was done

on whole blood samples. There was no association between mRNA expression and DNA methylation [64]. In the study of Okada *et al*[65], peripheral blood was taken from 50 Japanese MDD patients (females and males) before and after antidepressant treatment. Different antidepressants (paroxetine, fluvoxamine, milnacipran) were used in this study. There were no differences in DNA methylation of *SLC6A4* exon I promoter between the healthy control group (n = 50) and patients without antidepressant administration. There was a significant increase in methylation at the CpG 3 site after 6 wk of antidepressant treatment[65].

Domschke *et al*[66] included 61 Caucasian MDD patients who were tested for changes in DNA methylation from blood cells. Administration of escitalopram was evaluated 6 wk after treatment. There was lower average methylation in the transcriptional control region upstream of exon 1A of *SLC6A4* gene. The CpG 2 site specifically stood out from these results[66].

CONCLUSION

Depressive disorder is affected by dysregulation of many different genes, each contributing a small effect. All hypotheses of depressive disorder involve a variety of changes that can occur in a depressive state. These are a consequence of gene variations or epigenetic changes that affect DNA transcription and/or mRNA translation resulting in imbalanced protein levels regulating the processes in the CNS. With the development of technologies and new knowledge, epigenetic research has become accessible for investigation in the field of psychiatry. Among candidate genes particular interest was placed on *BDNF, NR3C1,* and *SLC6A4*, as their roles in CNS regulation have been identified in association with response to external stress stimuli and mood regulation. Although the research has been fairly extensive, we still cannot identify a reliable biomarker or a set of them, either proteomic or (epi)genetic, to be used in a clinical setting.

However, in many studies scientists discuss the importance of epigenetic factors (DNA methylation and histone modifications) as playing a key role in predicting antidepressant response. The aggregation of subthreshold levels of the epigenetic changes in several different genes might show alterations caused by a depressive state. It appears that to date we have uncovered a few pieces of the jigsaw puzzle but that more studies are needed for understanding this complex disorder. For example, it has been determined that classical antidepressants change the epigenome, and it has been proposed that this effect might be an important contributor to treatment. These results have triggered further investigation of drugs targeting epigenetic modifiers (HDACs, histone methyltransferases). HDACis seem to be promising drugs, but there are no HDACis used for depression treatment.

Further research in clinical settings will be important to determine which epigenetic markers are informative for treatment response prediction and which markers actually change as a response to treatment. Although the field of pharmacoepigenetics is only starting to develop, we can already identify some potential genes that we can expect to become biomarkers with clinical value. With rapid technological advancement, enabling determination of markers from multi-omic data with the use of artificial intelligence and carefully designed studies in the growing field of psychiatry, we could expect to obtain relevant biomarkers that could be used by clinicians as meaningful guidance in addition to clinical interviews in the future. With the development of the field of pharmacoepigenetics, it will be possible to move towards personalized treatments, where combinations of genetic and environmental factors will need to be incorporated in treatment selection.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. John Hancock for critical appraisal and scientific English editing of the manuscript.

FOOTNOTES

Author contributions: Videtič Paska A and Šalamon Arčan I organized and planned the manuscript; Šalamon Arčan I wrote the first draft of the manuscript; Kouter K and Videtič Paska A reviewed and edited the manuscript; All authors approved the final version of the manuscript.

Supported by Slovenina Reserach Agency, Young Researcher Grant to IŠ, No. P1-0390.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Slovenia

ORCID number: Iris Šalamon Arčan 0000-0002-7483-306X; Katarina Kouter 0000-0002-1051-959X; Alja Videtič Paska 0000-0002-1182-5417.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **WHO**. Depression 2021. [cited 10 January 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
2 **Shadrina M**, Bondarenko EA, Slominsky PA. Genetics Factors in Major Depression Disease. *Front Psychiatry* 2018; **9**: 334 [PMID: 30083112 DOI: 10.3389/fpsyt.2018.00334]
3 **Turecki G**, Brent DA, Gunnell D, O'Connor RC, Oquendo MA, Pirkis J, Stanley BH. Suicide and suicide risk. *Nat Rev Dis Primers* 2019; **5**: 74 [PMID: 31649257 DOI: 10.1038/s41572-019-0121-0]
4 **Dunn EC**, Wang MJ, Perlis RH. A Summary of Recent Updates on the Genetic Determinants of Depression. In: McIntyre RS, editor Major Depressive Disorder: Manley P; 2020: 1-27
5 **Dattani S**, Ritchie H, Roser M. Mental Health. Our World in Data 2021. [cited 10 January 2022]. Available from: https://ourworldindata.org/mental-health
6 **Jessen HM**, Auger AP. Sex differences in epigenetic mechanisms may underlie risk and resilience for mental health disorders. *Epigenetics* 2011; **6**: 857-861 [PMID: 21617370 DOI: 10.4161/epi.6.7.16517]
7 **Han J**, Fan Y, Zhou K, Blomgren K, Harris RA. Uncovering sex differences of rodent microglia. *J Neuroinflammation* 2021; **18**: 74 [PMID: 33731174 DOI: 10.1186/s12974-021-02124-z]
8 **Salgado-Delgado R**, Tapia Osorio A, Saderi N, Escobar C. Disruption of circadian rhythms: a crucial factor in the etiology of depression. *Depress Res Treat* 2011; **2011**: 839743 [PMID: 21845223 DOI: 10.1155/2011/839743]
9 **Walker WH 2nd**, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. *Transl Psychiatry* 2020; **10**: 28 [PMID: 32066704 DOI: 10.1038/s41398-020-0694-0]
10 **Peña CJ**, Nestler EJ. Progress in Epigenetics of Depression. *Prog Mol Biol Transl Sci* 2018; **157**: 41-66 [PMID: 29933956 DOI: 10.1016/bs.pmbts.2017.12.011]
11 **Covington HE 3rd**, Maze I, LaPlant QC, Vialou VF, Ohnishi YN, Berton O, Fass DM, Renthal W, Rush AJ 3rd, Wu EY, Ghose S, Krishnan V, Russo SJ, Tamminga C, Haggarty SJ, Nestler EJ. Antidepressant actions of histone deacetylase inhibitors. *J Neurosci* 2009; **29**: 11451-11460 [PMID: 19759294 DOI: 10.1523/JNEUROSCI.1758-09.2009]
12 **Rice F**, Harold G, Thapar A. The genetic aetiology of childhood depression: a review. *J Child Psychol Psychiatry* 2002; **43**: 65-79 [PMID: 11848337 DOI: 10.1111/1469-7610.00004]
13 **Penner-Goeke S**, Binder EB. Epigenetics and depression. *Dialogues Clin Neurosci* 2019; **21**: 397-405 [PMID: 31949407 DOI: 10.31887/DCNS.2019.21.4/ebinder]
14 **Pandya M**, Altinay M, Malone DA Jr, Anand A. Where in the brain is depression? *Curr Psychiatry Rep* 2012; **14**: 634-642 [PMID: 23055003 DOI: 10.1007/s11920-012-0322-7]
15 **MacDonald JL**, Roskams AJ. Epigenetic regulation of nervous system development by DNA methylation and histone deacetylation. *Prog Neurobiol* 2009; **88**: 170-183 [PMID: 19554713 DOI: 10.1016/j.pneurobio.2009.04.002]
16 **Wang P**, Zhang C, Lv Q, Bao C, Sun H, Ma G, Fang Y, Yi Z, Cai W. Association of DNA methylation in BDNF with escitalopram treatment response in depressed Chinese Han patients. *Eur J Clin Pharmacol* 2018; **74**: 1011-1020 [PMID: 29748862 DOI: 10.1007/s00228-018-2463-z]
17 **Wang KZ**, Dada OO, Bani-Fatemi A, Tasmim S, Monda M, Graff A, De Luca V. Epigenetics of Major Depressive Disorder. *Major Depre Dis* 2020; 29-37 [DOI: 10.1016/b978-0-323-58131-8.00002-1]
18 **Himmerich H**, Patsalos O, Lichtblau N, Ibrahim MAA, Dalton B. Cytokine Research in Depression: Principles, Challenges, and Open Questions. *Front Psychiatry* 2019; **10**: 30 [PMID: 30792669 DOI: 10.3389/fpsyt.2019.00030]
19 **Majd M**, Saunders EFH, Engeland CG. Inflammation and the dimensions of depression: A review. *Front Neuroendocrinol* 2020; **56**: 100800 [PMID: 31654681 DOI: 10.1016/j.yfrne.2019.100800]
20 **Chan KL**, Cathomas F, Russo SJ. Central and Peripheral Inflammation Link Metabolic Syndrome and Major Depressive Disorder. *Physiology (Bethesda)* 2019; **34**: 123-133 [PMID: 30724127 DOI: 10.1152/physiol.00047.2018]
21 **Wang HT**, Huang FL, Hu ZL, Zhang WJ, Qiao XQ, Huang YQ, Dai RP, Li F, Li CQ. Early-Life Social Isolation-Induced Depressive-Like Behavior in Rats Results in Microglial Activation and Neuronal Histone Methylation that Are Mitigated by Minocycline. *Neurotox Res* 2017; **31**: 505-520 [PMID: 28092020 DOI: 10.1007/s12640-016-9696-3]
22 **Catale C**, Gironda S, Lo Iacono L, Carola V. Microglial Function in the Effects of Early-Life Stress on Brain and Behavioral Development. *J Clin Med* 2020; **9** [PMID: 32046333 DOI: 10.3390/jcm9020468]
23 **Wendeln AC**, Degenhardt K, Kaurani L, Gertig M, Ulas T, Jain G, Wagner J, Häsler LM, Wild K, Skodras A, Blank T, Staszewski O, Datta M, Centeno TP, Capece V, Islam MR, Kerimoglu C, Staufenbiel M, Schultze JL, Beyer M, Prinz M, Jucker M, Fischer A, Neher JJ. Innate immune memory in the brain shapes neurological disease hallmarks. *Nature* 2018; **556**: 332-338 [PMID: 29643512 DOI: 10.1038/s41586-018-0023-4]

24 **Duan Z**, Lu J. DNA Methyltransferases in Depression: An Update. *Front Psychiatry* 2020; **11**: 538683 [PMID: 33101076 DOI: 10.3389/fpsyt.2020.538683]

25 **Zhou J**, Li M, Wang X, He Y, Xia Y, Sweeney JA, Kopp RF, Liu C, Chen C. Drug Response-Related DNA Methylation Changes in Schizophrenia, Bipolar Disorder, and Major Depressive Disorder. *Front Neurosci* 2021; **15**: 674273 [PMID: 34054421 DOI: 10.3389/fnins.2021.674273]

26 **Guo JU**, Su Y, Shin JH, Shin J, Li H, Xie B, Zhong C, Hu S, Le T, Fan G, Zhu H, Chang Q, Gao Y, Ming GL, Song H. Distribution, recognition and regulation of non-CpG methylation in the adult mammalian brain. *Nat Neurosci* 2014; **17**: 215-222 [PMID: 24362762 DOI: 10.1038/nn.3607]

27 **Chen D**, Meng L, Pei F, Zheng Y, Leng J. A review of DNA methylation in depression. *J Clin Neurosci* 2017; **43**: 39-46 [PMID: 28645747 DOI: 10.1016/j.jocn.2017.05.022]

28 **Rodríguez-Aguilera JR**, Ecsedi S, Goldsmith C, Cros MP, Domínguez-López M, Guerrero-Celis N, Pérez-Cabeza de Vaca R, Chemin I, Recillas-Targa F, Chagoya de Sánchez V, Hernández-Vargas H. Genome-wide 5-hydroxymethylcytosine (5hmC) emerges at early stage of *in vitro* differentiation of a putative hepatocyte progenitor. *Sci Rep* 2020; **10**: 7822 [PMID: 32385352 DOI: 10.1038/s41598-020-64700-2]

29 **Sun H**, Kennedy PJ, Nestler EJ. Epigenetics of the depressed brain: role of histone acetylation and methylation. *Neuropsychopharmacology* 2013; **38**: 124-137 [PMID: 22692567 DOI: 10.1038/npp.2012.73]

30 **Munshi A**, Shafi G, Aliya N, Jyothy A. Histone modifications dictate specific biological readouts. *J Genet Genomics* 2009; **36**: 75-88 [PMID: 19232306 DOI: 10.1016/S1673-8527(08)60094-6]

31 **Sadakierska-Chudy A**, Filip M. A comprehensive view of the epigenetic landscape. Part II: Histone post-translational modification, nucleosome level, and chromatin regulation by ncRNAs. *Neurotox Res* 2015; **27**: 172-197 [PMID: 25516120 DOI: 10.1007/s12640-014-9508-6]

32 **Allen L**, Dwivedi Y. MicroRNA mediators of early life stress vulnerability to depression and suicidal behavior. *Mol Psychiatry* 2020; **25**: 308-320 [PMID: 31740756 DOI: 10.1038/s41380-019-0597-8]

33 **Hacimusalar Y**, Eşel E. Suggested Biomarkers for Major Depressive Disorder. *Noro Psikiyatr Ars* 2018; **55**: 280-290 [PMID: 30224877 DOI: 10.5152/npa.2017.19482]

34 **Park SW**, Seo MK, Lee JG, Hien LT, Kim YH. Effects of maternal separation and antidepressant drug on epigenetic regulation of the brain-derived neurotrophic factor exon I promoter in the adult rat hippocampus. *Psychiatry Clin Neurosci* 2018; **72**: 255-265 [PMID: 28990703 DOI: 10.1111/pcn.12609]

35 **Melas PA**, Wei Y, Wong CC, Sjöholm LK, Åberg E, Mill J, Schalling M, Forsell Y, Lavebratt C. Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities. *Int J Neuropsychopharmacol* 2013; **16**: 1513-1528 [PMID: 23449091 DOI: 10.1017/S1461145713000102]

36 **Bakusic J**, Vrieze E, Ghosh M, Bekaert B, Claes S, Godderis L. Increased methylation of NR3C1 and SLC6A4 is associated with blunted cortisol reactivity to stress in major depression. *Neurobiol Stress* 2020; **13**: 100272 [PMID: 33344725 DOI: 10.1016/j.ynstr.2020.100272]

37 **Roy B**, Wang Q, Palkovits M, Faludi G, Dwivedi Y. Altered miRNA expression network in locus coeruleus of depressed suicide subjects. *Sci Rep* 2017; **7**: 4387 [PMID: 28663595 DOI: 10.1038/s41598-017-04300-9]

38 **Żurawek D**, Turecki G. The miRNome of Depression. *Int J Mol Sci* 2021; **22** [PMID: 34768740 DOI: 10.3390/ijms222111312]

39 **Greer TL**, Joseph JK. Pharmacological and Nonpharmacological Treatment Effects on Functional Outcomes in Major Depressive Disorder. In: McIntyre RS, editor Major Depressive Disorder: Manley P; 2020: 131-146

40 **Rosenblat JD**, McIntyre RS. Pharmacological Treatment of Major Depressive Disorder. In: McIntyre RS, editor Major Depressive Disorder: Manley P; 2020: 103-119

41 **Hillhouse TM**, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp Clin Psychopharmacol* 2015; **23**: 1-21 [PMID: 25643025 DOI: 10.1037/a0038550]

42 **Cipriani A**, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults With Major Depressive Disorder: A Systematic Review and Network Meta-Analysis. *Focus (Am Psychiatr Publ)* 2018; **16**: 420-429 [PMID: 32021580 DOI: 10.1176/appi.focus.16407]

43 **Swainson J**, Thomas RK, Archer S, Chrenek C, MacKay MA, Baker G, Dursun S, Klassen LJ, Chokka P, Demas ML. Esketamine for treatment resistant depression. *Expert Rev Neurother* 2019; **19**: 899-911 [PMID: 31282772 DOI: 10.1080/14737175.2019.1640604]

44 **Zanos P**, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry* 2018; **23**: 801-811 [PMID: 29532791 DOI: 10.1038/mp.2017.255]

45 **Wei Y**, Chang L, Hashimoto K. A historical review of antidepressant effects of ketamine and its enantiomers. *Pharmacol Biochem Behav* 2020; **190**: 172870 [PMID: 32035078 DOI: 10.1016/j.pbb.2020.172870]

46 **Amidfar M**, Woelfer M, Réus GZ, Quevedo J, Walter M, Kim YK. The role of NMDA receptor in neurobiology and treatment of major depressive disorder: Evidence from translational research. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **94**: 109668 [PMID: 31207274 DOI: 10.1016/j.pnpbp.2019.109668]

47 **Baez MV**, Cercato MC, Jerusalinsky DA. NMDA Receptor Subunits Change after Synaptic Plasticity Induction and Learning and Memory Acquisition. *Neural Plast* 2018; **2018**: 5093048 [PMID: 29706992 DOI: 10.1155/2018/5093048]

48 **Liu RJ**, Fuchikami M, Dwyer JM, Lepack AE, Duman RS, Aghajanian GK. GSK-3 inhibition potentiates the synaptogenic and antidepressant-like effects of subthreshold doses of ketamine. *Neuropsychopharmacology* 2013; **38**: 2268-2277 [PMID: 23680942 DOI: 10.1038/npp.2013.128]

49 **Volmar CH**, Wahlestedt C. Histone deacetylases (HDACs) and brain function. *Neuroepigenetics* 2015; **1**: 20-27 [DOI: 10.1016/j.nepig.2014.10.002]

50 **Vialou V**, Feng J, Robison AJ, Nestler EJ. Epigenetic mechanisms of depression and antidepressant action. *Annu Rev Pharmacol Toxicol* 2013; **53**: 59-87 [PMID: 23020296 DOI: 10.1146/annurev-pharmtox-010611-134540]

51 **Park HS**, Kim J, Ahn SH, Ryu HY. Epigenetic Targeting of Histone Deacetylases in Diagnostics and Treatment of Depression. *Int J Mol Sci* 2021; **22** [PMID: 34065586 DOI: 10.3390/ijms22105398]

52 **Tadić A**, Müller-Engling L, Schlicht KF, Kotsiari A, Dreimüller N, Kleimann A, Bleich S, Lieb K, Frieling H. Methylation of the promoter of brain-derived neurotrophic factor exon IV and antidepressant response in major depression. *Mol Psychiatry* 2014; **19**: 281-283 [PMID: 23670489 DOI: 10.1038/mp.2013.58]

53 **Misztak P**, Pańczyszyn-Trzewik P, Nowak G, Sowa-Kućma M. Epigenetic marks and their relationship with BDNF in the brain of suicide victims. *PLoS One* 2020; **15**: e0239335 [PMID: 32970734 DOI: 10.1371/journal.pone.0239335]

54 **Hing B**, Sathyaputri L, Potash JB. A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. *Am J Med Genet B Neuropsychiatr Genet* 2018; **177**: 143-167 [PMID: 29243873 DOI: 10.1002/ajmg.b.32616]

55 **Hack LM**, Fries GR, Eyre HA, Bousman CA, Singh AB, Quevedo J, John VP, Baune BT, Dunlop BW. Moving pharmacoepigenetics tools for depression toward clinical use. *J Affect Disord* 2019; **249**: 336-346 [PMID: 30802699 DOI: 10.1016/j.jad.2019.02.009]

56 **Chen ES**, Ernst C, Turecki G. The epigenetic effects of antidepressant treatment on human prefrontal cortex BDNF expression. *Int J Neuropsychopharmacol* 2011; **14**: 427-429 [PMID: 21134314 DOI: 10.1017/S1461145710001422]

57 **Lopez JP**, Mamdani F, Labonte B, Beaulieu MM, Yang JP, Berlim MT, Ernst C, Turecki G. Epigenetic regulation of BDNF expression according to antidepressant response. *Mol Psychiatry* 2013; **18**: 398-399 [PMID: 22547115 DOI: 10.1038/mp.2012.38]

58 **Carlberg L**, Scheibelreiter J, Hassler MR, Schloegelhofer M, Schmoeger M, Ludwig B, Kasper S, Aschauer H, Egger G, Schosser A. Brain-derived neurotrophic factor (BDNF)-epigenetic regulation in unipolar and bipolar affective disorder. *J Affect Disord* 2014; **168**: 399-406 [PMID: 25106037 DOI: 10.1016/j.jad.2014.07.022]

59 **D'Addario C**, Dell'Osso B, Galimberti D, Palazzo MC, Benatti B, Di Francesco A, Scarpini E, Altamura AC, Maccarrone M. Epigenetic modulation of BDNF gene in patients with major depressive disorder. *Biol Psychiatry* 2013; **73**: e6-e7 [PMID: 22901293 DOI: 10.1016/j.biopsych.2012.07.009]

60 **Hsieh MT**, Lin CC, Lee CT, Huang TL. Abnormal Brain-Derived Neurotrophic Factor Exon IX Promoter Methylation, Protein, and mRNA Levels in Patients with Major Depressive Disorder. *J Clin Med* 2019; **8** [PMID: 31027379 DOI: 10.3390/jcm8050568]

61 **Xu H**, Wang J, Zhang K, Zhao M, Ellenbroek B, Shao F, Wang W. Effects of adolescent social stress and antidepressant treatment on cognitive inflexibility and Bdnf epigenetic modifications in the mPFC of adult mice. *Psychoneuroendocrinology* 2018; **88**: 92-101 [PMID: 29195162 DOI: 10.1016/j.psyneuen.2017.11.013]

62 **Tsankova NM**, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci* 2006; **9**: 519-525 [PMID: 16501568 DOI: 10.1038/nn1659]

63 **Mendonça MS**, Mangiavacchi PM, De Sousa PF, Crippa JAS, Mendes AV, Loureiro SR, Martín-Santos R, Quirino CR, Kanashiro MM, Rios AFL. Epigenetic variation at the SLC6A4 gene promoter in mother-child pairs with major depressive disorder. *J Affect Disord* 2019; **245**: 716-723 [PMID: 30447571 DOI: 10.1016/j.jad.2018.10.369]

64 **Booij L**, Szyf M, Carballedo A, Frey EM, Morris D, Dymov S, Vaisheva F, Ly V, Fahey C, Meaney J, Gill M, Frodl T. DNA methylation of the serotonin transporter gene in peripheral cells and stress-related changes in hippocampal volume: a study in depressed patients and healthy controls. *PLoS One* 2015; **10**: e0119061 [PMID: 25781010 DOI: 10.1371/journal.pone.0119061]

65 **Okada S**, Morinobu S, Fuchikami M, Segawa M, Yokomaku K, Kataoka T, Okamoto Y, Yamawaki S, Inoue T, Kusumi I, Koyama T, Tsuchiyama K, Terao T, Kokubo Y, Mimura M. The potential of SLC6A4 gene methylation analysis for the diagnosis and treatment of major depression. *J Psychiatr Res* 2014; **53**: 47-53 [PMID: 24657235 DOI: 10.1016/j.jpsychires.2014.02.002]

66 **Domschke K**, Tidow N, Schwarte K, Deckert J, Lesch KP, Arolt V, Zwanzger P, Baune BT. Serotonin transporter gene hypomethylation predicts impaired antidepressant treatment response. *Int J Neuropsychopharmacol* 2014; **17**: 1167-1176 [PMID: 24679990 DOI: 10.1017/S146114571400039X]

67 **Farrell C**, Doolin K, O' Leary N, Jairaj C, Roddy D, Tozzi L, Morris D, Harkin A, Frodl T, Nemoda Z, Szyf M, Booij L, O'Keane V. DNA methylation differences at the glucocorticoid receptor gene in depression are related to functional alterations in hypothalamic-pituitary-adrenal axis activity and to early life emotional abuse. *Psychiatry Res* 2018; **265**: 341-348 [PMID: 29793048 DOI: 10.1016/j.psychres.2018.04.064]

68 **Weder N**, Zhang H, Jensen K, Yang BZ, Simen A, Jackowski A, Lipschitz D, Douglas-Palumberi H, Ge M, Perepletchikova F, O'Loughlin K, Hudziak JJ, Gelernter J, Kaufman J. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 417-24.e5 [PMID: 24655651 DOI: 10.1016/j.jaac.2013.12.025]

69 **Song Y**, Miyaki K, Suzuki T, Sasaki Y, Tsutsumi A, Kawakami N, Shimazu A, Takahashi M, Inoue A, Kan C, Kurioka S, Shimbo T. Altered DNA methylation status of human brain derived neurotrophis factor gene could be useful as biomarker of depression. *Am J Med Genet B Neuropsychiatr Genet* 2014; **165B**: 357-364 [PMID: 24801253 DOI: 10.1002/ajmg.b.32238]

70 **Devlin AM**, Brain U, Austin J, Oberlander TF. Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. *PLoS One* 2010; **5**: e12201 [PMID: 20808944 DOI: 10.1371/journal.pone.0012201]

71 **Braithwaite EC**, Kundakovic M, Ramchandani PG, Murphy SE, Champagne FA. Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. *Epigenetics* 2015; **10**: 408-417 [PMID: 25875334 DOI: 10.1080/15592294.2015.1039221]

72 **Oberlander TF**, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics* 2008; **3**: 97-106 [PMID: 18536531 DOI: 10.4161/epi.3.2.6034]

73 **Roy B**, Shelton RC, Dwivedi Y. DNA methylation and expression of stress related genes in PBMC of MDD patients with

and without serious suicidal ideation. *J Psychiatr Res* 2017; **89**: 115-124 [PMID: 28246044 DOI: 10.1016/j.jpsychires.2017.02.005]

74 **Schröter K**, Brum M, Brunkhorst-Kanaan N, Tole F, Ziegler C, Domschke K, Reif A, Kittel-Schneider S. Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* 2020; **270**: 169-181 [PMID: 30929061 DOI: 10.1007/s00406-019-01007-y]

75 **Januar V**, Ancelin ML, Ritchie K, Saffery R, Ryan J. BDNF promoter methylation and genetic variation in late-life depression. *Transl Psychiatry* 2015; **5**: e619 [PMID: 26285129 DOI: 10.1038/tp.2015.114]

76 **Fuchikami M**, Morinobu S, Segawa M, Okamoto Y, Yamawaki S, Ozaki N, Inoue T, Kusumi I, Koyama T, Tsuchiyama K, Terao T. DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression. *PLoS One* 2011; **6**: e23881 [PMID: 21912609 DOI: 10.1371/journal.pone.0023881]

77 **Gross JA**, Pacis A, Chen GG, Drupals M, Lutz PE, Barreiro LB, Turecki G. Gene-body 5-hydroxymethylation is associated with gene expression changes in the prefrontal cortex of depressed individuals. *Transl Psychiatry* 2017; **7**: e1119 [PMID: 28485726 DOI: 10.1038/tp.2017.93]

78 **Poulter MO**, Du L, Weaver ICG, Palkovits M, Faludi G, Merali Z, Szyf M, Anisman H. GABAA receptor promoter hypermethylation in suicide brain: implications for the involvement of epigenetic processes. *Biol Psychiatry* 2008; **64**: 645-652 [PMID: 18639864 DOI: 10.1016/j.biopsych.2008.05.028]

79 **Iga J**, Watanabe SY, Numata S, Umehara H, Nishi A, Kinoshita M, Inoshita M, Shimodera S, Fujita H, Ohmori T. Association study of polymorphism in the serotonin transporter gene promoter, methylation profiles, and expression in patients with major depressive disorder. *Hum Psychopharmacol* 2016; **31**: 193-199 [PMID: 27005686 DOI: 10.1002/hup.2527]

80 **McGowan PO**, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009; **12**: 342-348 [PMID: 19234457 DOI: 10.1038/nn.2270]

81 **Cruceanu C**, Alda M, Nagy C, Freemantle E, Rouleau GA, Turecki G. H3K4 tri-methylation in synapsin genes leads to different expression patterns in bipolar disorder and major depression. *Int J Neuropsychopharmacol* 2013; **16**: 289-299 [PMID: 22571925 DOI: 10.1017/S1461145712000363]

82 **Torres-Berrío A**, Lopez JP, Bagot RC, Nouel D, Dal Bo G, Cuesta S, Zhu L, Manitt C, Eng C, Cooper HM, Storch KF, Turecki G, Nestler EJ, Flores C. DCC Confers Susceptibility to Depression-like Behaviors in Humans and Mice and Is Regulated by miR-218. *Biol Psychiatry* 2017; **81**: 306-315 [PMID: 27773352 DOI: 10.1016/j.biopsych.2016.08.017]

83 **Smalheiser NR**, Lugli G, Rizavi HS, Torvik VI, Turecki G, Dwivedi Y. MicroRNA expression is down-regulated and reorganized in prefrontal cortex of depressed suicide subjects. *PLoS One* 2012; **7**: e33201 [PMID: 22427989 DOI: 10.1371/journal.pone.0033201]

84 **Lopez JP**, Lim R, Cruceanu C, Crapper L, Fasano C, Labonte B, Maussion G, Yang JP, Yerko V, Vigneault E, El Mestikawy S, Mechawar N, Pavlidis P, Turecki G. miR-1202 is a primate-specific and brain-enriched microRNA involved in major depression and antidepressant treatment. *Nat Med* 2014; **20**: 764-768 [PMID: 24908571 DOI: 10.1038/nm.3582]

85 **Gorinski N**, Bijata M, Prasad S, Wirth A, Abdel Galil D, Zeug A, Bazovkina D, Kondaurova E, Kulikova E, Ilchibaeva T, Zareba-Koziol M, Papaleo F, Scheggia D, Kochlamazashvili G, Dityatev A, Smyth I, Krzystyniak A, Wlodarczyk J, Richter DW, Strekalova T, Sigrist S, Bang C, Hobuß L, Fiedler J, Thum T, Naumenko VS, Pandey G, Ponimaskin E. Attenuated palmitoylation of serotonin receptor 5-HT1A affects receptor function and contributes to depression-like behaviors. *Nat Commun* 2019; **10**: 3924 [PMID: 31477731 DOI: 10.1038/s41467-019-11876-5]

86 **Wang Q**, Roy B, Turecki G, Shelton RC, Dwivedi Y. Role of Complex Epigenetic Switching in Tumor Necrosis Factor-α Upregulation in the Prefrontal Cortex of Suicide Subjects. *Am J Psychiatry* 2018; **175**: 262-274 [PMID: 29361849 DOI: 10.1176/appi.ajp.2017.16070759]

87 **Aschrafi A**, Verheijen JM, Gordebeke PM, Olde Loohuis NF, Menting K, Jager A, Palkovits M, Geenen B, Kos A, Martens GJ, Glennon JC, Kaplan BB, Gaszner B, Kozicz T. MicroRNA-326 acts as a molecular switch in the regulation of midbrain urocortin 1 expression. *J Psychiatry Neurosci* 2016; **41**: 342-353 [PMID: 27045550 DOI: 10.1503/jpn.150154]

88 **Lopez JP**, Fiori LM, Gross JA, Labonte B, Yerko V, Mechawar N, Turecki G. Regulatory role of miRNAs in polyamine gene expression in the prefrontal cortex of depressed suicide completers. *Int J Neuropsychopharmacol* 2014; **17**: 23-32 [PMID: 24025154 DOI: 10.1017/S1461145713000941]

89 **Fiori LM**, Kos A, Lin R, Théroux JF, Lopez JP, Kühne C, Eggert C, Holzapfel M, Huettl RE, Mechawar N, Belzung C, Ibrahim EC, Chen A, Turecki G. miR-323a regulates ERBB4 and is involved in depression. *Mol Psychiatry* 2021; **26**: 4191-4204 [PMID: 33219358 DOI: 10.1038/s41380-020-00953-7]

90 **Yoshino Y**, Roy B, Dwivedi Y. Altered miRNA landscape of the anterior cingulate cortex is associated with potential loss of key neuronal functions in depressed brain. *Eur Neuropsychopharmacol* 2020; **40**: 70-84 [PMID: 32600964 DOI: 10.1016/j.euroneuro.2020.06.004]

91 **Roy B**, Dunbar M, Agrawal J, Allen L, Dwivedi Y. Amygdala-Based Altered miRNome and Epigenetic Contribution of miR-128-3p in Conferring Susceptibility to Depression-Like Behavior *via* Wnt Signaling. *Int J Neuropsychopharmacol* 2020; **23**: 165-177 [PMID: 32173733 DOI: 10.1093/ijnp/pyz071]

92 **Song MF**, Dong JZ, Wang YW, He J, Ju X, Zhang L, Zhang YH, Shi JF, Lv YY. CSF miR-16 is decreased in major depression patients and its neutralization in rats induces depression-like behaviors *via* a serotonin transmitter system. *J Affect Disord* 2015; **178**: 25-31 [PMID: 25779937 DOI: 10.1016/j.jad.2015.02.022]

93 **Sterrenburg L**, Gaszner B, Boerrigter J, Santbergen L, Bramini M, Elliott E, Chen A, Peeters BW, Roubos EW, Kozicz T. Chronic stress induces sex-specific alterations in methylation and expression of corticotropin-releasing factor gene in the rat. *PLoS One* 2011; **6**: e28128 [PMID: 22132228 DOI: 10.1371/journal.pone.0028128]

94 **Elliott E**, Ezra-Nevo G, Regev L, Neufeld-Cohen A, Chen A. Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. *Nat Neurosci* 2010; **13**: 1351-1353 [PMID: 20890295 DOI: 10.1038/nn.2642]

95 **Uchida S**, Hara K, Kobayashi A, Otsuki K, Yamagata H, Hobara T, Suzuki T, Miyata N, Watanabe Y. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. *Neuron* 2011; **69**: 359-372 [PMID: 21262472 DOI: 10.1016/j.neuron.2010.12.023]

96 **Covington HE 3rd**, Vialou VF, LaPlant Q, Ohnishi YN, Nestler EJ. Hippocampal-dependent antidepressant-like activity of histone deacetylase inhibition. *Neurosci Lett* 2011; **493**: 122-126 [PMID: 21335060 DOI: 10.1016/j.neulet.2011.02.022]

97 **Seo MK**, Ly NN, Lee CH, Cho HY, Choi CM, Nhu LH, Lee JG, Lee BJ, Kim GM, Yoon BJ, Park SW, Kim YH. Early life stress increases stress vulnerability through BDNF gene epigenetic changes in the rat hippocampus. *Neuropharmacology* 2016; **105**: 388-397 [PMID: 26877199 DOI: 10.1016/j.neuropharm.2016.02.009]

98 **Jiang Z**, Zhu Z, Zhao M, Wang W, Li H, Liu D, Pan F. H3K9me2 regulation of BDNF expression in the hippocampus and medial prefrontal cortex is involved in the depressive-like phenotype induced by maternal separation in male rats. *Psychopharmacology (Berl)* 2021; **238**: 2801-2813 [PMID: 34328517 DOI: 10.1007/s00213-021-05896-7]

99 **Hunter RG**, McCarthy KJ, Milne TA, Pfaff DW, McEwen BS. Regulation of hippocampal H3 histone methylation by acute and chronic stress. *Proc Natl Acad Sci U S A* 2009; **106**: 20912-20917 [PMID: 19934035 DOI: 10.1073/pnas.0911143106]

100 **Rinaldi A**, Vincenti S, De Vito F, Bozzoni I, Oliverio A, Presutti C, Fragapane P, Mele A. Stress induces region specific alterations in microRNAs expression in mice. *Behav Brain Res* 2010; **208**: 265-269 [PMID: 19913057 DOI: 10.1016/j.bbr.2009.11.012]

101 **Bai M**, Zhu X, Zhang Y, Zhang S, Zhang L, Xue L, Yi J, Yao S, Zhang X. Abnormal hippocampal BDNF and miR-16 expression is associated with depression-like behaviors induced by stress during early life. *PLoS One* 2012; **7**: e46921 [PMID: 23056528 DOI: 10.1371/journal.pone.0046921]

102 **Zucchi FC**, Yao Y, Ward ID, Ilnytskyy Y, Olson DM, Benzies K, Kovalchuk I, Kovalchuk O, Metz GA. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. *PLoS One* 2013; **8**: e56967 [PMID: 23451123 DOI: 10.1371/journal.pone.0056967]

103 **Meerson A**, Cacheaux L, Goosens KA, Sapolsky RM, Soreq H, Kaufer D. Changes in brain MicroRNAs contribute to cholinergic stress reactions. *J Mol Neurosci* 2010; **40**: 47-55 [PMID: 19711202 DOI: 10.1007/s12031-009-9252-1]

104 **Xu J**, Wang R, Liu Y, Wang W, Liu D, Jiang H, Pan F. Short- and long-term alterations of FKBP5-GR and specific microRNAs in the prefrontal cortex and hippocampus of male rats induced by adolescent stress contribute to depression susceptibility. *Psychoneuroendocrinology* 2019; **101**: 204-215 [PMID: 30469088 DOI: 10.1016/j.psyneuen.2018.11.008]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com