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Epigenetics of suicidal behavior

R.N. Mustafin[1, 2] ✉, A.V. Kazantseva[3], R.F. Enikeeva[2, 3], Yu.D. Davydova[3], S.B. Malykh[4], V.V. Viktorov[1], E.K. Khusnutdinova[1, 2, 3]

[1] Bashkir State Medical University, Ufa, Russia
[2] Bashkir State University, Ufa, Russia
[3] Institute of Biochemistry and Genetics – Subdivision of the Ufa Federal Research Centre, RAS, Ufa, Russia
[4] Psychological Institute of the Russian Academy of Education, Moscow, Russia
✉ e-mail: ruji79@mail.ru

Suicide is the second leading cause of death among young people and therefore being a serious global problem worldwide. The study of genetic and epigenetic factors in the development of suicidal behavior plays an important role in the development of advanced methods of diagnosis and treatment of this pathology. The role of hereditary factors in the development of suicidal behavior is estimated at 30–55 %, with a pronounced comorbidity with other psychopathologies. The study of genetic liability to suicidal behavior is based on molecular-genetic methods including association and linkage analyses, chip gene expression arrays, and genome-wide association studies. Published data identified multiple genes including those involved in the functioning of serotonergic (*SLC6A4*, *TPH*, *5-HT1A*), hypothalamic-pituitary-adrenal systems (*FKBP5*) and polyamines (*SAT* and *OATL1*) associated with suicidal behavior. However, the diversity of interacting genetic loci complicates the interpretation of the development of a complex phenotype of pathology and prevents the association from being detected. To solve this problem and interpret the missing relationship between the environment and the genome, promising results were obtained from a study of epigenetic factors, which affected the expression of a number of candidate genes involved in brain functioning in suicidal behavior. The analysis of a brain obtained from suicide victims, representing a unique tool for the analysis of modified genomic processes, revealed a wide range of reprogramming patterns of DNA methylation in promoters of the genes of polyamine (*OAZ1*, *OAZ2*, *AMD1*, *ARG2*, *SKA2*), serotonergic (*SLC6A4*) and GABAergic (*GABRA1*) systems, HPA-axis (*GR*, *NR3C1*), tyrosine kinase (*TrkB*) receptors, brain-derived neurotrophic factor (*BDNF*). The role of histone modifications in distinct genes (*Cx30*, *Cx43*, *TrkB.T1*) and the expression of specific long non-coding RNAs and microRNAs in the development of suicidal behavior, which is promising for the development of diagnostic algorithms and target therapy, is discussed.
Key words: association; brain; methylation; non-coding RNAs; suicide; epigenetics.

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Эпигенетика суицидального поведения

Р.Н. Мустафин[1, 2] ✉, А.В. Казанцева[3], Р.Ф. Еникеева[2, 3], Ю.Д. Давыдова[3], С.Б. Малых[4], В.В. Викторов[1], Э.К. Хуснутдинова[1, 2, 3]

[1] Башкирский государственный медицинский университет, Уфа, Россия
[2] Башкирский государственный университет, Уфа, Россия
[3] Институт биохимии и генетики – обособленное структурное подразделение Уфимского федерального исследовательского центра Российской академии наук, Уфа, Россия
[4] Психологический институт Российской академии образования, Москва, Россия
✉ e-mail: ruji79@mail.ru

Самоубийства занимают второе место среди причин смерти среди молодежи, в связи с чем являются серьезной глобальной проблемой человечества. Для разработки перспективных методов диагностики и лечения данной патологии важное значение имеет исследование генетических и эпигенетических факторов в развитии суицидального поведения. Роль наследственных факторов в развитии суицидального поведения оценивается в 30–55 %, при этом характерна выраженная коморбидность с другими психическими расстройствами. Для исследования генетической предрасположенности к суициду используются молекулярно-генетические методы, включая контролируемые анализы ассоциаций и сцепления, микроматричные анализы экспрессии генов и полногеномный поиск ассоциаций. В литературе представлены данные об идентификации множества генов, в том числе связанных с изменениями функционирования серотонинергической (гены *SLC6A4*, *TPH*, *5-HT1A*), гипоталамо-гипофизарно-надпочечниковой систем (ген *FKBP5*) и полиаминов (гены *SAT* и *OATL1*), ассоциированных с развитием суицидального поведения. Однако разнообразие взаимодействующих генетических локусов усложняет интерпретацию развития сложного фенотипа патологии и не позволяет определить выраженную ассоциацию. Для разрешения данной проблемы и интерпретации недостающей связи между окружающей средой и геномом были получены многообещающие результаты при изучении эпигенетических факторов, роль которых при суицидальном поведении показана в изменении экспрессии

ряда кандидатных генов, вовлеченных в функционирование головного мозга. Уникальным объектом для прямого исследования изменения геномных процессов является головной мозг умерших от суицида людей, при изучении которого был выявлен широкий спектр репрограммирования паттернов ДНК-метилирования промоторов генов системы полиаминов (*OAZ1*, *OAZ2*, *AMD1*, *ARG2*, *SKA2*), серотонинергической (*SLC6A4*) и ГАМК-ергической (*GABRA1*) систем, глюкокортикоидных (*GR*, *NR3C1*) и тирозинкиназных (*TrkB*) рецепторов, нейротрофического фактора головного мозга (*BDNF*). Показана роль изменений модификации гистонов в области расположения специфических генов (*Cx30*, *Cx43*, *TrkB.T1*) и экспрессии специфических длинных некодирующих РНК и микроРНК в развитии суицидального поведения, что перспективно для разработки программ диагностических алгоритмов и таргетной терапии.
Ключевые слова: ассоциации; головной мозг; метилирование; некодирующие РНК; суицид; эпигенетика.

Introduction

Suicide represents violence against oneself with the serious intention to destroy life. Every 40 seconds in the world 1 individual dies from suicide (Roy, Dwivedi, 2017). According to the WHO, about 1 million individuals commit suicide every year (Cui et al., 2017), and the global prevalence of suicide is 11.4 per 100,000 individuals (Lutz et al., 2017). Suicidal behavior (SB) is a generic term used to denote risk, attempts and committed suicide (Bani-Fatemi et al., 2015). SB is the second cause of death among individuals of young age and takes the 10th place in all age groups worldwide (Roy, Dwivedi, 2017; Fanelli, Serretti, 2018). For example, a longitudinal study of adolescents aged 13–18 revealed that 12.1 % of American adolescents had suicidal thoughts, 4 % were planning suicides, and 4.1 % committed suicide (Nock et al., 2013). These observations together with the absence of appropriate preventive strategies make SB an essential public health problem (Roy, Dwivedi, 2017).

SB is a multifactorial pathology showing high comorbidity with mental illness (MI) and major psychopathologies, including major depressive disorder (MDD), bipolar disorder (Ludwig et al., 2017) and schizophrenia (Bani-Fatemi et al., 2015). For example, about 4 % of MDD patients die as a result of suicide (Serafini et al., 2012), and the youngest individuals with SB are diagnosed with mental illness (Nock et al., 2013). Certain environmental stimuli increase the genetic predisposition to SB in MDD patients (Roy, Dwivedi, 2018). However, it should be taken into account that SB is caused by complex risk factors, which are not universal for each individual (Turecki, 2014).

Over the past decades, a number of theories have been proposed explaining the mechanisms for the development of SB. According to one of the most influential theories proposed by Mann (Mann et al., 1999), individuals with a certain vulnerability ("diathesis") to SB would develop SB under the influence of psychological crises or mental disorders. According to the interpersonal theory of suicide proposed by Joiner (2005), the main factors of SB include suicidal desire (due to high levels of adherence and impaired affiliation) and the ability to perform suicide (the sum of genetic, epigenetic and environmental factors) (Ludwig et al., 2017). According to twin studies, SB showed heritability ranging from 21 to 50 %, while population studies suggested up to 55 % (Roy, Dwivedi, 2017). Molecular-genetic methods are used to study the genetic susceptibility to SB including controlled analyses of associations and linkages, micromatrix analyses of gene expression and genome-wide analyses of associations. An important role in SB development belongs to epigenetic factors, since they mediate environmental effects on the degree of phenotypic manifestation of genetic susceptibility to pathology (Tsai et al., 2011). The brain obtained from individuals who died from suicide represents a unique object for direct study of changes in genomic processes in SB (Almeida, Turecki, 2016).

The role of genetic factors in the development of suicidal behavior

The scientific literature presents data on the associations of SB with more than 200 genes including genes associated with changes in the functioning of a number of neurobiological systems. These include genes of the serotonergic, noradrenergic and hypothalamic-pituitary-adrenal (HPA) systems (Lutz et al., 2017). According to functional studies, SB is characterized by decreased levels of serotonin metabolites and changes in the number of receptors and serotonin transporter levels in the brain (Chandley, Ordway, 2012). To date, numerous studies on genetic predisposition to SB have demonstrated association of SB risk with serotonergic system genes such as serotonin transporter (*SLC6A4*), tryptophan hydroxylase (*TPH*), and serotonin receptor 1A (*5-HT1A*) (Bach, Arango, 2012). In 2018, a meta-analysis of 45 studies was conducted, confirming the association of a low-expressing S allele in the serotonin transporter gene (*SLC6A4*) with an increased risk of developing SB (Fanelli, Serretti, 2018).

A number of authors have identified the involvement of the noradrenergic system in SB development. For example, a decreased number of noradrenergic neurons in the locus coeruleus, higher β2-adrenergic and lower α-adrenergic receptor binding in the cortex, reduced levels of noradrenaline metabolites in the cerebrospinal fluid were detected in SB patients (Mann, Currier, 2010). Therefore, impaired noradrenergic functioning promotes SB development. At the same time, antidepressants acting on the noradrenaline transporter, α2-adrenoreceptors and other stress-sensitive targets (glutamate transporter and receptors, GABA receptors) can reduce the risk of suicide (Chandley, Ordway, 2012).

A great importance in the phenotypic manifestation of SB belongs to stressful events in childhood, which mediate changes in the functioning of monoaminergic and HPA systems in ontogenesis (Mann, Currier, 2010). The important role of stress in SB development is confirmed by the involvement of HPA-axis genes in the development of this pathology. For

instance, an association of the C-allele *FKBP5* polymorph rs3800373 with SB was determined. The *FKBP5* gene encodes FK506 binding protein involved in the regulation of HPA-axis activity via its binding to glucocorticoid receptors (Fudalej et al., 2015). According to functional data, a lower level of corticotropin-releasing hormone receptor, one of the most important components of the HPA axis, was detected in the prefrontal cortex of individuals with completed suicide (Mann, Currier, 2010). The SB development is also influenced by changes in the genes of the polyamine system: *SAT* (spermidine/spermine N1-acetyltransferase) and *OATL1* (ornithine aminotransferase like-1) (Fiori et al., 2010). However, the involvement of many genes with a small effect was noted. A variety of interactions between the proteins encoded by these genes is also shown. In addition, heterogeneity in the clinical groups of patients with SB was shown in various studies. These problems indicate insufficient data on SB etiopathogenesis. To solve this problem, a number of recent studies were conducted demonstrating promising results by interpreting the missing link between the environment and the genome via epigenetic factors (Roy, Dwivedi, 2017).

The relationship of epigenetic factors with the expression of genes associated with suicidal behavior

The epigenome mediates the gene × environment interaction, including the effect of adverse life situations (Schneider et al., 2015). An epigenetic approach examines the effect of environmental stimuli such as stressors, life adversity, and various biological processes on the genome. Epigenetic factors include DNA methylation, histone modifications, RNA interference (RNAi) using non-coding RNA (ncRNA) and changes in the nucleus organization. These epigenetic modifications allow the genome to respond and adapt to internal and external factors through variations in gene expression (Bani-Fatemi et al., 2015).

According to epigenetic studies of SB, the pathogenesis of this disease is based on an impaired plasticity of the neuronal pathways with the brain's inability to provide an appropriate adaptive response to environmental stimuli. For instance, individuals with SB are characterized by changes in the expression of genes crucial for synaptic and structural plasticity (Dwivedi, 2018). A number of researchers have demonstrated the role of changes in the expression of genes of the cytokine system and polyamines in SB pathogenesis. In particular, a significantly higher level of expression of tumor necrosis factor alpha (TNF-α) and miR-19a-3n was observed in the prefrontal cortex of individuals with completed suicide compared to the control. This miRNA has a targeted effect on TNF-α (Wang et al., 2018). The role of epigenetic factors in the regulation of polyamine gene (*SAT1*) (spermidine/spermine N1-acetyltransferase) expression in the prefrontal cortex of individuals with completed suicide has been identified (Fiori, Turecki, 2011).

Early-life adversity (ELA) in childhood as a stress-related component represents an important risk factor for developing SB in adults, even if much time will have passed since exposure to stress. ELA includes child abuse, neglect, loss of parents, low socioeconomic status. Although only negative effects of ELA are often assumed, it is important to note that stress effects are not deterministic and can cause conflicting effects in adulthood, and in some cases can even result in increased stress sensitivity. However, most studies focus on the negative effects of ELA. As a result of a number of studies, it was concluded that ELA long-term effects might be due to changes in the epigenetic landscape due to impaired DNA methylation, post-translational modification of histones and the expression of non-coding RNA (Burns et al., 2018). The study of DNA methylation demonstrated an increased methylation of 97 % of 1000 differentially methylated regions, including functional categories of genes highly expressed in the brain (*APLP2*, *BDNF*, *HTR1A*, *NUAK1*, *PHACTR3*, *MSMP*, *SLC6A4*, *SYN2*, and *SYNE*), in the cerebral cortex of individuals with completed suicide compared to the control group (Schneider et al., 2015).

Changes in DNA methylation and histone modification

Nowadays the majority of studies on the role of epigenetic factors in SB development are focused on resistant markers, such as DNA methylation and histone modifications. DNA methylation is a dynamic process that occurs throughout ontogenesis, even in postmitotic cells, such as neurons. Traditionally, DNA methylation is defined as the addition of a methyl group to the fifth carbon of the cytosine base (5mC) in CpG islands of gene promoters in mammalian genomes, which is functionally related to gene silencing. Unlike 5mC, hydroxymethylated DNA (5hmC) often found in the genes has a global positive effect on gene expression. TET 2/3 enzymes play a role in the formation of 5hmC (ten-eleven translocation of methylcytosine dioxygenases 2 and 3). This process is described in neural cells. The brain is characterized by a high level of methylation of cytosine outside the CG dinucleotides, the so-called CH-methylation, especially characteristic of the first year of life (Burns et al., 2018).

A number of studies have been carried out on the association of changes in epigenetic factors with SB development in individuals who have experienced severe stress in childhood. In this context the effect of changes in stress response systems, mainly the HPA axis, which is programmed under the influence of environmental factors in early childhood, is actively analyzed. Changes in the HPA axis are associated with an increased risk of suicide (Turecki, 2014). Evidence of a significant role of environmental factors in active demethylation in childhood includes methylation differences in exon 1C of the glucocorticoid receptor (*GR*) gene in the brain of individuals with completed suicide with ELA history (Turecki, 2014). SB patients who experienced early-life stress demonstrated hypermethylation in two CpG islands in the promoter region of the neuron-specific glucocorticoid receptor gene (*NR3C1*), which resulted in suppression of gene expression in the brain of individuals with completed suicide compared to the control (McGowan et al., 2009). Serotonergic system genes, in particular, the serotonin transporter gene (*5-HTT*), are also regulated by individual reaction to stress. Namely, the important role of stress mediating the association between modifications in the promoter region of the *5-HTT* gene and the risk of developing SB was suggested to be caused by changes in *5-HTT* gene methylation (Jimenez-Trevino et al., 2017).

Recently, the expression and methylation of polyamine system genes have been actively studied. Stress-mediated impairments in various components of the polyamine system were found in cortical and subcortical structures in individuals with SB with marked changes in the epigenetic regulation of gene expression (Turecki, 2014). The genome-wide DNA methylation studies demonstrated significant site-specific differences in the methylation patterns of the promoter regions of the polyamine system genes including *OAZ1* (ornithine decarboxylase antienzyme 1), *OAZ2* (ornithine decarboxylase antizyme 2), *AMD1* (S-adenosylmethionine decarboxylase 2), *ARG2* (arginase 2) (Gross et al., 2013), and *SKA2* (spindle and kinetochore associated complex subunit 2) (Guintivano et al., 2014; Pandey et al., 2016; Olie, Gourtet, 2017) in the brain of individuals with completed suicide compared to the control. The methylation pattern of the *SKA2* gene is specific to SB and can be used as a biomarker for determining suicidal risk (Sadeh et al., 2016).

A large number of studies on the epigenetic regulation of SB were focused on changes in methylation in the gene encoding neurotrophic brain-derived factor (*BDNF*) (Kang et al., 2018). Moreover, SB patients were characterized by a significant increase in DNA methylation in the promoter and non-coding exon 4 of the *BDNF* gene, while a hypermethylation was observed in promoter IV of this gene (Keller et al., 2010, 2011). Noteworthy, the association of the hypermethylated *BDNF* gene with SB risk was observed independently of the presence of potential covariates or a particular genotype (Kim et al., 2014). Moreover, distinct changes in *BDNF* expression are also considered to be a risk factor for developing SB in the elderly (Kim et al., 2014). Considering the data obtained, it is suggested to use the methylation pattern of the *BDNF* gene as a marker of a history of suicidal attempts, as well as to predict the possible inefficacy in SB therapy (Kang et al., 2013). Since the effect of BDNF is present due to its binding to the tropomyosin tyrosine kinase receptor TrkB-T1, several authors have reported a decrease in the expression of the *TrkB-T1* gene, which is caused by higher methylation in the promoter and the 3′-untranslated regions (UTR) of this gene in the frontal lobe in patients with completed suicide (Ernst et al., 2009b; Maussion et al., 2014).

Some studies have shown a possible role of modified expression of such genes as *MPP4* (membrane palmitoylated protein 4), nucleoporin (*NUP133*), a member of the TRE2/BuB2/CDC16 family of domains (*TBC1D16*), the alpha1 subunit of the gamma-aminobutyric acid receptor (*GABRA1*) in SB development. In particular, a total decrease in methylation in the 5′-UTR of the *MPP4* gene and in intron 3 of the *TBC1D16* gene together with increased methylation in exon 1 of the *NUP133* gene was observed in patients with bipolar disorder and comorbid SB compared to the control group (Jeremian et al., 2017). In addition, hypermethylation of CpG islands in the promoter of the *GABRA1* gene was associated with changes in mRNA expression of the DNA methyltransferase gene (*DNMT*) in the brain of individuals with completed suicide (Poulter et al., 2008).

Histone modifications also make a significant contribution to the regulation of expression in SB. Data were obtained on the suppression of gene expression of connexins 30 and 43 (*Cx30* and *Cx43*) in the brain of individuals with completed suicide due to histone methylation (Nagy et al., 2017). Namely, changes in astrocyte interaction occurring due to the channels formed mainly by connexins 30 and 43 are largely regulated by histone modifications in the *Cx30* and *Cx43* genes. The role of histone modifications in the regulation of tropomyosin tyrosine kinase receptor (*TrkB.T1*) (Ernst et al., 2009a) and ornithine decarboxylase antienzyme genes (*OAZ*), which is involved in the synthesis of polyamines, was reported (Fiori et al., 2012). In the former study, a decrease in *TrkB.T1* gene expression was observed due to methylation in the third histone (H3K27) (Ernst et al., 2009a). The latter case, in contrast, reported activated *OAZ* gene expression due to enhanced levels of H3K4me3, a marker of transcriptionally active chromatin (Fiori et al., 2012).

The role of long non-coding RNAs

Long non-coding RNA (lncRNA) represents RNA molecules longer than 200 bp with low protein-coding potential. The lncRNAs are classified mainly on the basis of their interaction with known genes. For example, lncRNAs can be antisense, sense, overlapping, intronic, and intergenic transcripts. LncRNAs are characterized by tissue-specific expression and mediate important biological functions by regulating the functioning of protein-coding genes. It was found that the lncRNA genes formed various isoforms with different functions manifesting *in-cis* and *in-trans* regulatory mechanisms. Therefore, one lncRNA gene can control the functioning of several distal target genes (Zhou et al., 2018). It is important to note that transposable elements (TEs) represent the sources of over 41 % of the functional lncRNA domains (Johnson, Guigo, 2014) and are considered to be stress-sensitive elements (Wheeler, 2013), which in site-specific transposition activate the stress response genes (Feng et al., 2013). Moreover, TEs can serve directly as sources of dsRNA genes, whose transcripts regulate the differentiation of stem cells (Lu et al., 2014). This observation is caused by a significant role of lncRNA in human brain functioning and is determined by lncRNA activity in the hippocampus (simultaneously with TEs expression) during neurogenesis. For example, *lncRNA2393* expression promotes the maturation of neural stem cells in the dentate gyrus (Deng et al., 2017).

More than 14,000 lncRNA genes have been identified in the human genome, at least 67 % of the mature transcripts of which consist of TE sequences, while many of them consist entirely of TE (Kapusta, Feschotte, 2014). TEs represent important sources of epigenetic regulation (Mustafin, Khusnutdinova, 2017), thus providing their study as a promising direction for identifying the mechanisms of SB development. A differential expression of six lncRNAs (*TCONS_00019174*, *ENST00000566208*, *NONHSAG045500*, *ENST00000517573*, *NONHSAT034045*, and *NONHSAT142707*) was observed in peripheral blood leukocytes of patients with SB and MDD (Cui et al., 2017), while 23 different lncRNAs were differentially expressed in the brains of individuals with completed suicide (Zhou et al., 2018) compared to the control group. Protein-encoding genes localized distally from lncRNAs identified in these studies are involved in the organization of the cytoskeleton and plasmatic membrane, cell adhesion, DNA binding and regulation of dendrite development (Zhou

et al., 2018). In another study, the association of *LOC285758* lncRNA expression with SB development was determined. This lncRNA represents an antisense transcript of the region flanking the intragenic CpG island of the *MARCKS* gene (myristoylated alanine-rich C-kinase substrate), of which expression is suppressed during prolonged lithium administration (Punzi et al., 2014).

The role of miRNAs

Recently, a great importance in the study of SB development has been attached to the role of small ncRNAs controlling gene expression. The miRNAs switching highly significant regulators of neuronal plasticity and higher nervous activity are the most studied to date (Dwivedi, 2018). For a number of miRNAs, a relationship with brain functioning was determined. For example, miR-16 affects the expression of *SERT*, miR-18a and miR-124a bind to the 3′-UTR of the *GR* gene, and miR-34a controls the effects of lithium and valproate by interacting with *GRM7*. The miR-96 and miR-510 were demonstrated to inhibit translation of *5-HT1B* and *5-HT3E* receptor subunits, while miR-124-1 is involved in serotonin-induced synaptic transmission via regulating *CREB* (cAMP response element-binding protein). In addition, it was shown that miR-30a-5p and miR-195 target the 3′-UTR of the *BDNF* gene in different brain regions (miR-30a in the third layer of the pyramidal neurons of the prefrontal cortex). The expression of miR-134 and miR-183, which target the splicing factor *SC35*, is enhanced by acute stress, miR-280 and miR-289 regulate the synthesis of synaptic proteins by binding to the *CaMKIIa* sites, miR-134 inhibits the translation of *Limk1* in the dendrites of the hippocampus; miR-137 regulates the proliferation of neuronal stem cells by affecting the transcription factor Sox2 (Serafini et al., 2012).

Studies of changes in miRNA expression in SB allowed us to detect significant variations in the level of their expression in the prefrontal cortex of individuals with completed suicide compared to healthy donors. At the same time, a significant decrease in the expression of 21 different miRNAs involved in the regulation of cell growth and differentiation was shown. The targets for these miRNAs include transcription factors (in particular, E2F1, E2F6, BACH1, SP1, HOXA5, and RUNX1) and other nuclear proteins. At the same time, the *VEGFA* gene associated with developing depression in both human and animals appears to be a target for four different miRNAs (miR-20b, 20a, 34a, 34b*) (Smalheiser et al., 2012). Differential expression of thirteen different miRNAs was detected in the brain of individuals with completed suicide. Among these miRNAs, an enhanced expression was detected in 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, and miR-1179. A reduced expression was determined in miR-409-50, let-7g-3p, and miR-1197. The analysis of the integrated gene regulatory network based on target genes of these miRNAs revealed various associations with mental disorders, including MDD and affective ones. These psychopathologies are assumed to be the most important risk factors for SB. The mapping of cellular pathways mediated by miRNA activity identified a total modification in the cellular signaling causing SB development (Roy et al., 2017).

Because changes in the metabolic pathways of polyamine system enzymes are involved in SB development, miRNAs interacting with the *SAT1* and *SMOX* genes were examined. The relationship between miRNAs and polyamine gene expression in SB was reported and the mechanism of post-transcriptional suppression of *SAT1* and *SMOX* gene activity was demonstrated. Individuals with completed suicide were characterized by a significant increase in the brain levels of miR-34c-5p, miR-139-5p, miR-195, and miR-320c, which target the 3′-UTRs of the *SAT1* and *SMOX* genes (Lopez et al., 2014). An enhanced expression of Hsa-miR-185 and Hsa-miR-491-3p causing suppression of the *TrkB-T1* gene was determined in the prefrontal cerebral cortex of individuals with completed suicide. A target binding site in 3′-UTR of the *TrkB-T1* gene was identified for Hsa-miR-185 (Maussion et al., 2012). Recently, considerable attention was focused on the identification of miRNAs associated with ELA in the context of SB development. ELA affects the activity of various miRNAs genes during brain development. For example, differences in the expression of miR-9, miR-29a, miR-124, and miR-132 were observed in the prefrontal cortex of rats aged 14 days when separated from the mother. The expression of miR-124 and miR-132 was suppressed at the 60th day of postnatal development, which indicates stable changes in miRNAs caused by ELA. At the same time, GR activation inhibits miR-132 expression, which suppresses expression of the *BDNF* gene previously associated with SB (Dwivedi, 2018).

Prospects for epigenetic studies of suicidal behavior

According to the stress diathesis model, suicide is positioned as a result of interactions between environmental stressors and susceptibility to SB, regardless of the present mental disorder. The genetic and epigenetic changes detected in the brain of individuals with completed suicide provide a basis for the possible neurobiological screening of SB patients to prevent suicide (van Heeringen, Mann, 2014). Among epigenetic factors, the study of lncRNAs suggested the mechanisms of action of certain pharmaceuticals used in SB therapy. For example, long-term use of lithium used for SB treatment suppresses the expression of the *MARCKS* gene, the expression of the antisense lncRNA of which is associated with SB (Punzi et al., 2014). These results promote further research of lncRNAs, which makes it possible to develop effective methods for SB prevention and therapy. Analysis of lncRNAs differentially expressed in SB (*TCONS_00019174*, *ENST00000566208*, *NONHSAG045500*, *ENST00000517573*, *NONHSAT034045*, and *NONHSAT142707*) has been proposed as a potential diagnostic and therapeutic SB biomarker for the prevention of suicidal attempts in MDD patients (Cui et al., 2017). The changes in miRNA expression identified in the brain of individuals with completed suicide can represent the basis for both clarifying SB pathogenesis and developing a targeted SB therapy (Maussion et al., 2012; Smalheiser et al., 2012; Roy, Dwivedi, 2017).

The analysis of the methylation pattern of *BDNF* (Kang et al., 2013; Kim et al., 2014) and the *SKA2* genes (Sadeh et al., 2016) made it possible to propose them as epigenetic biomarkers of SB. For SB therapy it was suggested to use the histone

deacetylase inhibitor tetrapeptide FK228, which is able to enhance transcription of the *Rap1* and *ERK1/2* genes known to be reduced in the hippocampus of SB individuals. Rap-1 (Ras-proximate-1) is a short nucleotide triphosphate binding protein expressed in neurons of the cerebral cortex involved in dendrites branching and growth. A significant decrease in Rap-1 mRNA expression was detected in the prefrontal cortex and hippocampus of depressed individuals and those with completed suicide compared to the control group. Reduced brain activity of Rap-1 was characteristic of individuals with completed suicide (Emanuele, 2007).

Nowadays, genome editing technologies allow the functional importance of specific epigenetic modifications and gene regulation to be studied directly and the disturbed epigenetic landscape to be remodeled due to the reversibility of epigenetic modifications. One of the most successful methods for epigenetic editing is CRISPR-Cas9, which allows specific changes to be introduced to DNA methylation (Vojta et al., 2016).

Conclusion

The study of the role of epigenetic factors in the development of suicidal behavior is a modern and promising method for determining reversible changes in the brain of patients. The association of specific expression of genes that play a role in the development of suicidal behavior with specific changes in DNA methylation, modifications of histone and levels of non-coding RNA has been proved. The results obtained indicate the prospects for the development of targeted therapy methods for this serious and socially significant pathology using epigenetic factors. The most successful objects of epigenetic exposure are non-coding RNAs, the use of which has already been started in clinical practice. In addition, it can be assumed that the correction of patients' lifestyles and psychotherapy with the study of the role of changes in the epigenetic regulation of the brain can be an effective treatment for suicidal behavior. This conclusion is due to the fact that epigenetic factors are modulated by environmental, especially stressful, influences.

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ORCID ID

R.N. Mustafin orcid.org/0000-0002-4091-382X
A.V. Kazantseva orcid.org/0000-0002-3744-8058
R.F. Enikeeva orcid.org/0000-0002-4301-5283
Yu.D. Davydova orcid.org/0000-0003-3508-4710
S.B. Malykh orcid.org/0000-0002-3786-7447
E.K. Khusnutdinova orcid.org/0000-0003-2987-3334

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