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A REVIEW ON THE DEVELOPMENT OF MICRO RNA AND ITS REGULATORY ROLE ON DEPRESSION

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ABSTRACT

Depression is a psychiatric disorder accountable for high death, morbidity, destructive health behaviors, missing occupation efficiency, and enlarged health care consumption. The presence of miRNAs in brain tissues and the potential of postmortem brain samples to recognize the severity of depressive and peripheral tissues provide a promising approach for the wide regulatory use of miRNA. Because of the inherent restrictions associated with obtaining brain tissue in vivo, the use of postmortem brain tissue may confuse by an unlimited postmortem gap and prior medication exposure. Therefore, this review aims to assess the potential broad applications of micro-RNA and its current advancement in depression.

INTRODUCTION

Depression is a psychiatric disorder with an etiopathogenesis of genetic and environmental factors, which could perform at diverse levels and are accountable for high death, morbidity, destructive health behaviors, missing occupation efficiency, and enlarged health care consumption [9]. It groups into a pathologically stumpy frame of mind (hypothermia) and negative value about oneself; one's standing in the actual world [50].

Major depressive disorder is the most common psychiatric disorder, which causes suicide, incapacitating psychological problems, and increase the economic burden, which affects up to 120 million people with a high disability rate in the world [55]. Major depressive disorder groups into severe depression without psychotic symptoms, recurrent depression disorder (DD), moderate or severe degree depending on severity, the occurrence of psychiatric symptoms, and recurrence DDs and incident of gradual depression by the international classification of diseases and the diagnostic [8,17].

Different studies show a wide variety of factors like alteration to neural plasticity, structural plasticity, neurotransmitter systems, epigenetic and genetic susceptibility leads to depression disorder as serotonin or 5-hydroxytryptamine (5-HT) [11]. It is a monoamine neurotransmitter that forms from tryptophan in the neurons of raphe nuclei and controls many cognitive and physiological functions [26].

Lopez-Leon [56] conducts genetic case-control research on DDs in large-scale meta-analyses on 20 polymorphisms in 18 genes [49]. The polymorphic variants of genes associated with the monoamine theory of DD pathogenesis have little influence on the risk of developing depression. The meta-analysis of genome-wide association study by Psychiatric Genomics Consortium (PGC) demonstrates as none of the single nucleotide polymorphisms (SNPs), identities in earlier studies, achieve a genome-wide significance level and no locus consistently associated with [50].

The hypothesis of genetic moderation claims differences between individuals that derive from differences in the DNA sequence and promote individual variation in response to environmental conditions [5]. A strong interaction between genetic and coincidental factors usually associates with stressful actions and consequence psychiatric disorders. Environmental factors alter gene expression, possibly via epigenetic mechanisms, and affect the expression of disease [3].

The epigenetic regulations of gene function via DNA modifications, histone modifications, chromosome remodeling, RNA regulation, and long non-coding RNA (lncRNA) study epigenetic mechanisms with biochemical changes of nucleotides, but without altering the DNA sequence, and the associated histone proteins[9]. They affect gene expression by allowing transcription factors to gain access to gene regulatory elements through environmental factors that induce changes in the chromatin state and improve the exposure of genes to the impact of different transcription factors. As a result, increasing or decreasing gene expression keeping the original DNA sequence unchanged[51].

Micro RNAs are small non-coding RNAs with about 22 nucleotides and significant players in sorrow pathogenesis, which concern cell and sub-atomic pathways of different levels like angiogenesis, development, and differentiation[52]. They regulate post-transcriptional base pairing to target miRNAs and inhibit protein synthesis by repressing translation, inducing deadenylation, degradation of target mRNA. It influences the expression of over 60% protein-coding genes[37]. Two thousand five-handed find in humans and regulate 60% of human protein-coding regions [27]. Therefore, this review aims to assess the potential broad applications of micro-RNA (miRNA) and its current advancement in depression.

Micro-RNAs, generation: basic concepts

Production of adult miRNA is a multi-step process, starts with a primary transcription of genes by RNA enzyme II. These lead to long, capped, and polyadenylated primary miRNAs [21]. The primary

square transcripts measure processes by the ribonuclease (RNase) III Drosha. DGCR8 nuclear complicated into pin structure precursor miRNAs of 60–100 nucleotides that square measure afterward transported from the nucleus to the protoplasm by exportin-5, and more cleaved by the transferase accelerator mechanical mechanism into double-stranded miRNA[16].

miRNA are small segments of RNA [20]. containing 22–24 nucleotides. The molecular mechanisms are the basis for their transcription processing and maturation. The action summarizes in figure 1 below. Hundreds of diverse miRNA present, each miRNA able to control (reduce) the mRNA translation of hundreds of protein-coding genes, which themselves stand sites easy to get too many species of miRNA. As of these simple observations, a permutational complication of this new division of non-transcriptional regulation becomes clear [24].. Most species of miRNA induce changes in mRNA levels of around 0.5–2 fold: before degradation, they can interact with several mRNA molecules, and a single species of miRNA can control the translation of many genes, as shown in figure1 below.

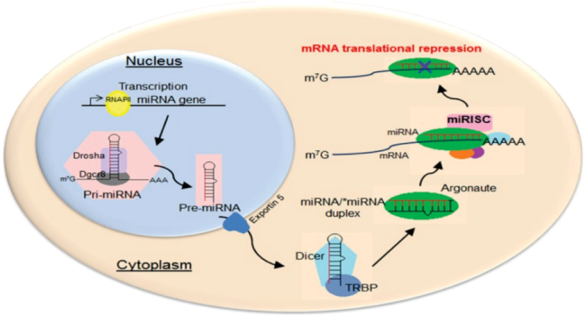

Figure 1. Micro-RNAs, generation: and maturation [29]

Micro-RNA Maturation and Its Function

Micro RNA biogenesis and function in animals begin in the nucleus. Transcription of NAPII produces a comparatively huge capped, polyadenylated transcript called pri miRNA and Pri-miRNA processed to produce OSHA. Dgcr8 processes into smaller stem-looped structures called precursor miRNAs by RNase III endonuclease [29]. With the help of Exportin 5, Pri- miRNA takes off the nucleus and moves into the cytosol and RNase III enzyme processing for a second time additionally. Mature miRNA and miRNA-induced silencing complex (miRISC) links and results in the seed's involvement-sequence of miRNA and complementary sequences in 3'-UTRs of mRNAs fallout post-transcriptional gene silencing from the Watson-Crick base-pairing [44]. The cleavage of primary miRNA (pri-miRNA) to generate mature miRNA produces and incorporates into the result or complicated RNA-induced silencing complex (RISC). Complementarity among mRNA and guide target determines which silencing mechanism would engage. Cleavage of target messenger RNA (mRNA) with consequent degradation or translation inhibits when negatively regulates the miRNA expression functions as a guide by base-pairing [47].

Gene transcription is capable of up-regulated by enhancers that are on the genomic cis-regulatory basis. The markers used to enhance genes such as H3K27ac are present in the miRNAs gene, and enhancers and some micro RNAs genes overlap. According to Hongyu [33]. report miRNAs such as miR-339, miR-26a-1, miR-3179, miR-24-1, and miR-24-2 verify the expression of the nearest genes. Protein-coding genes such as ITGA9, CTDSPL, VILL, PLCD1 enclosed miR- 26a-1 gene, and expression of miR- 26a-1 from HEK293 will direct to transcriptional commencement of VILL and ITGA9. When the seed regions of miRNAs remove or delete, the inauguration disrupts and suggests the deletion of the seed region of miRNA function relies on miRNA enhancer base paring and increasing expression of additional miRNA, miR-24-1 will increase expression to the nearest gene of FANC FBPI. Increased miR-24-1 will improve RNA polymerase II, p300/CBP, enhancer RNAs, all of which specify energetic regulatory functions.

Factors, consequences, and controlling mechanism depression

The cause for depression.

Factors associated with depression pathogenesis occur because of changes in the complex signaling networks, genetic factor contributors, interaction of susceptible genes, and stress environment[53].

Altered pro-inflammatory cytokines

Inflammatory diseases that lead to psychiatric disorders, such as depression, inflammation of the central nervous system (CNS) caused by infection, caused the development of psychiatric symptoms full-blown syndromes such as depressive or manic episodes[31]. Activated microglia can create pro-inflammatory cytokines, which cause major depression [40]. Interferon affects the frontal lobe, anterior cingulate, serotonergic, glutamatergic, and dopaminergic activity. Growth inflammatory cytokines are essential elements in the pathogenesis of MDD [39].

Recurrent stress

Stress causes molecular and structural changes in the hippocampus associate with the down-regulation of specific synaptic proteins. The hippocampi know for their convenience in the glucocorticoid receptors' expression in neurons, astrocytes, and some neural stem cells[41]. A recent study reports stress response as it causes plenty of biological feedback to alter neuronal connectivity [2]. It promotes adaptation over time in resilient adults through the dendritic remodeling within the hippocampus, amygdala, and prefrontal cortex (PFC). But in susceptible individuals, the adaptive changes remain irreversible after the stress remove**s.** Hippocampus is part of the limbic system and connects nerve fibers with emotion-related brain regions. For instance, the prefrontal cortex and amygdala have a high level of glucocorticoid receptors and glutamate to control the HPA axis, as more susceptible to stress and depression[55].

Genetic influences

The abundant evidence from family, twin, and adoption studies that genetic factors play a significant role in the etiology of affective disorders[10].Various genetic mechanisms mainly concern the interaction of many genes that are not sufficient or strong enough to steer to a susceptibility to the disease. The influence of genes in major unipolar depression is less vibrant than for bipolar disorder, as shown in figure 2 below. Yet, population-based and hospital register-based twin studies have found a considerable heritability in depression [10].The variation in liability by non-genetic factors seems to be more pronounced in unipolar major depression than in bipolar disorders. The results of linkage analyses are less convincing for this disease [54], but it increasingly expects those genetic components to contaminate environmental measures and life events.

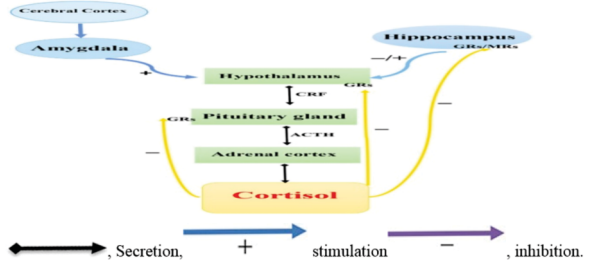

Fig.2.Vibrant schematic diagram of the hypothalamic-pituitary-adrenal axis [45].

CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone; GRs, glucocorticoid receptor; MRs mineralocorticoid receptors

Molecular mechanism of miRNA in depression

miRNA transcribe and encode in the nucleus as primary miRNA (Pre-miRNA). At the five- ends, long miRNA transcribes with a cap structure, and at the three- ends, the polyadenylation processes. Then miRNA processes into pre-miRNA in Drosha with microprocessor subunit DGCR8 [36].

In addition, pieces of evidence telling that a marginal of miRNA processes in a Drosha-DGCR8 independent way. The endoribonuclease Dicer clears the pre-miRNA in the cytoplasm, producing a short double-stranded miRNA duplex, which next processed in a mature miRNA. miRNA integrated into the RNA-induced silencing complex by the mechanism of the Argonaute family protein [46], and β-catenin protein acting involves a defensive role in stress situations and upstream miRNA synthesis during the control of the enzyme Dicer1. The presence of lower levels of Dicer1 because of stress exposure also connects with an improved vulnerability to stress [38].

Mature micro RNAs (miRNAs) generates with an enzyme Dicer 1 to regulate post-transcriptional gene expression in the brain and tissues and concerns with synaptic maturation and flexibility. The different somatic and germ-line mutations in the genes encoding enzymes involved in miRNA biogenesis, such as Drosha, DGCR8, Xpo5, Dicer1, and TRBP, identify malignant tumors [22]. An association between genes concerned in miRNAs' biogenesis and depression [28], and they investigated single-nuclear polymorphisms (SNPs) within a full panel of genes comprising Di George syndrome chromosomal region 8 (DGCR8), Argonaute1 (AGO1), and Gem associated Protein presents more in depressed patients, and less in non-patients controls, viewing to SNPs within DGCR8 (rs3757), and AGO1 (rs636832) links with an enlarged threat for depression.

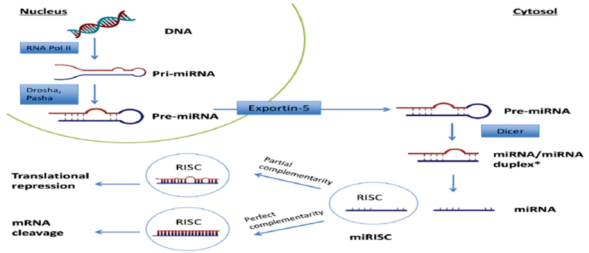

Figure.3 Molecular mechanism of miRNA in depression [25].

In the nucleus RNA- polymerase, II transcribes micro RNA from the miRNA gene. Similarly, Drosha (an RNase III enzyme) processed pri-miRNA and its cofactor, pasha, into 60-110 nucleotides pre-miRNA heparins and exported to the cytoplasm through the help of exportin-5 via nuclear pore. RNase activity of Dicer is cleaved pri-miRNA interested in passing, 22-nucleotide miRNA/miRNA duplex midway and duplex many onto AGO2. RISC guides the antisense strand of the miRNA to complement it with the target messenger RNA (mRNA) sequence, forming a double-stranded helix. mRNA binds with perfect complementarity encounter endonucleolytic cleavage.

miRNA biogenesis and the role in depression

The synthesis of miRNA takes place both in the nucleus and in the cytoplasm. First, a gene coding for miRNA transcribes by polymerase II within cell nuclei providing primary miRNA (pri-miRNAs). Then, it will cleave by Drosharibonuclease III (DROSHA), microprocessor complex subunits, and Di George syndrome critical region 8 (DGCR8) into precursor miRNAs (pre-miRNAs). Dicer and TAR RNA-binding protein (TRBP) to form double-stranded miRNA: miRNA complex, about 22nucleotides which can fit the RNA induced silencing complex (RISC), a complex like Argonaute that makes mature miRNA [43] .described in figure 3 below. The argonaute protein with PIWI and PAZ domain, the PIWI, cleaves the complementary strand within the complex. As a result, the guide strand makes complementary with the target mRNA, typically binds to the 3 untranslated region (UTR) of the target mRNA, and another strand called passenger removes with the help of the PAZ domain [15].

miRNA blocks the translation of miRNA into proteins by cutting the complementary target mRNA leading to degradation and inhibiting translation by removing the ribosomal subunits [4].

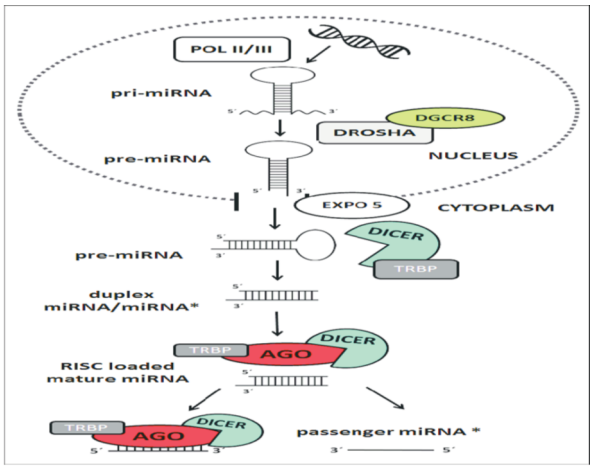

Figure3. General miRNA biogenesis pathway[14]

Mostly, bulk miRNAs are intergenic and processed from introns and a few exons of protein-coding genes. The rest are intergenic, transcribed autonomously of a crowd gene, and regulated by their promoters [14]. Occasionally miRNAs transcribes as one long transcript called clusters, miRNA biogenesis groups into canonical and non-canonical pathways.

Role of miRNA in regulating genes critical in stress response

miRNA expression upon exposure to environmental stressors leads to altered neuronal morphology and problems with neural circuitry. A study on adult male rats subject to acute and chronic stress reveals an altered expression of miR-134, miR-17-5p, and miR-124 in hippocampal and the central nucleus of the amygdala. It established brain or stress-related functions during regulating dendritic spine development and control of neuronal development and differentiation. miR-134 is mainly remarkable, which has a prominent role in synaptic plasticity and long-term memory formation[32].

Glucocorticoids regulate the HPA axis through a negative feedback mechanism. While binding to soluble GRs in the pituitary and the hypothalamus inhibit the release of corticotrophin-releasing factor and adreno-corticotropic hormone[16].miR-124a and miR-18a bind to 3 UTR of the GR gene to down-regulate its expression. The overexpression of miR-18a attenuate glucocorticoid-induced leucine zipper, a gene induced by stress-like levels of glucocorticoid, and the miR-18a-mediated downregulation of GR translation also showed increased expression of stress exposure [16].

The regulatory role of miRNAs

Among the six miRNAs(hsa-miR-146a-5p, hsa-miR-146b-5p, hsa-miR-221-3p, hsa-miR-24-3p, and hsa-miR-26a-5p) down-regulates and hsa-miR-151-3p found to be altered by another serotonin selective reuptake inhibitor (SSRI) called paroxetine in human lymphoblastoid cell lines (LCLs). While hsa-miR-221 is one of the microRNA down-regulated following chronic paroxetine exposure of LCLs[17]. The down-regulated miRNA especially, miR-125a-5p in plasma of MDD patients after treatment, suggests that antidepressant medication lowers the level of this miRNA to values closer to those found in healthy people.

The regulatory role of miRNAs in the post-mortem

A study on the PFC of suicide victims with depression reveals that 21 miRNAs significantly down-regulated, and most of each involves

growth and differentiation [48]. It deciphers that miR-101, hsa-miR-137, and hsa-miR-148brelates to depression [6]., miR-132, and miR-182 also over-expresses in depression patients those decrease BDNF level in neuronal cell model showing the involvement of these miRNAs in depression whose expression in the brain is to be the part of miRNA therapeutics[6].

The regulatory role of miRNAs in Brain Tissue

miRNA-128 encoded by two distinct genes (R3HDM1 and ARPP21). This locus regulates genes for apoptosis in brain tissue, cholesterol metabolism, and the antitumor effects [1]. miR-124, derived from three independent genes (miR-124-1 known as miR-124a, miR-124-2, and miR-124-3) that regulate adult neurogenesis, promote neuronal differentiation, and contribute to synaptic plasticity in-Vivo is the most abundant miRNA in the brain[30].

Hyeon [34]. demonstrate miR-124, which targets protein jagged-1 (Jag-1), Sry-type tall versatility bunch box 9, and DLX2 is the foremost plenteous miRNA within the brain. Its overexpression both in vivo and in vitro recommends that miR-124 plays a role in neural fate specification.

Modifications in cerebrospinal fluid (CSF) reflect the change of miRNA in brain tissue. Because of the inherent restrictions associated with obtaining brain tissue in vivo, using post-mortem brain tissue may confuse with unlimited post-mortem gap and prior medication exposure. Peripheral blood may not fully reflect gene expression levels in the brain. But because of the close relationship between the brain and CSF, the application of CSF-derived indicators represents an alternative method for detecting CNS [55].

The regulatory role of miRNAs and Polycystic Kidney Disease

According to Bergmann's [7] report, polycystic kidney diseases (PKDs) are kidney failure. Polycystic kidney diseases (PKDs) characterize various groups of kidney disorders and differentiate in the epithelial cell. Autosomal recessive PKD (ARPKD) is the most common type of PKD in children, that kidney- cysts are prominent as a component of the phenotypes of several clinical syndromes through linked anomalies. Although, in adults autosomal, dominant leading (ADPKD) is the most familiar type of kidney disease.

miR-17 promotes the proliferation of cyst epithelial and reduces the ADPKD gene's amount from figure 4 below. miR-21 inhibits apoptosis and increases the endurance of cyst epithelial cells. miR-200 reduces the Pkd1 gene amount and inhibits epithelial to mesenchymal transition (EMT). Failure of miR-200 could affect limited-EMT and improved Pkd1 amount, which together could intensify cyst growth [7].

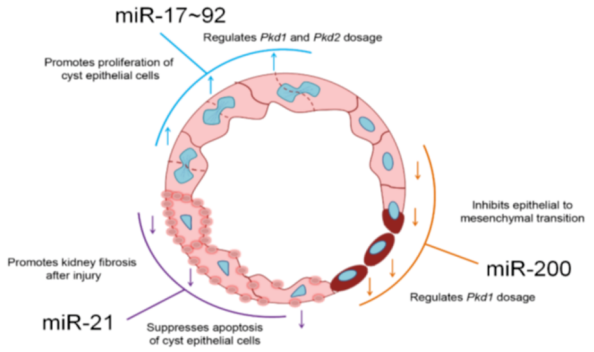

Figure 4. Potential mechanisms by which miRNAs regulate cyst growth [29]

Gene editing technologies, the Future hope for psychiatry disorders including depression

Using various treating psychiatric disorders, to date, face challenges of notoriously hard to treat, hard time committing, and slow-acting, and besides the heritable property of these disorders complicates the effectiveness that needs a novel technology that addresses all the symptoms of psychiatric disorders [23]. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) compose guide RNA and cas proteins. Cas9 possessing the highest degree of DNA sequence specificity and programmability, ease of design, cheapness, and efficiency to target and cut out an undesirable mutation gave it more attention [23].

Scientists have looked for ways to manipulate and design DNA. Gene-editing tools have been approximately for some time [35]. Yet, it wasn't awaiting the start of an economical, simple, and successful genome-engineering method known as CRISPR-Cas9 [12]. CRISPR triggered a revolution, and some reports can direct CRISPR to choose the exact mark along with an individual's DNA and have the molecular cutters create cuts in the gene sequence [13].

Scientists can direct CRISPR to select a specific spot with an individual's DNA and molecular scissors to make cuts within the gene sequence. Therapeutically relevant changes can then insert [18]. Using CRISPR systems releases a debate on legal and ethical implications of CRISPR technology [19].

CONCLUSION

Depression is a psychiatric disorder with an etiopathogenesis of genetic and environmental factors, which could perform at diverse levels and are accountable for high death, morbidity, destructive health behaviors, missing occupation efficiency, and enlarged health care consumption. A wide variety of factors like alteration to neural plasticity, structural plasticity, neurotransmitter systems, epigenetic and genetic susceptibility leads to depression disorder as serotonin or 5-hydroxytryptamine (5-HT). The epigenetic regulations of gene function via nucleic acid and long non-coding RNA (lncRNA) modifications regulate post-transcriptional base pairing to target mRNA and inhibit protein synthesis. It influences the expression of over 60% of all the protein-coding genes. Cleavage of target messenger RNA (mRNA) with consequent degradation or translation inhibits when negatively regulates the miRNA expression functions as a guide by base-pairing.

miRNA integrated into the RNA-induced silencing complex by the mechanism of the Argonaute family protein, and β-catenin protein acting involves a defensive role in stress situation and the upstream miRNA synthesis during the control of the enzyme Dicer1.Mature miRNAs generated with an enzyme Dicer 1 regulate post-transcriptional gene expression in the brain and tissues. miRNA expression upon exposure to environmental stressors leads to altered neuronal morphology and problems with neural circuitry.

CRISPR composes of guide RNA and cas proteins, cas9possessing the highest degree of DNA sequence specificity and programmability, ease of design, cheapness, and efficiency target and cut out an undesirable mutation expects to be ideal. Because of a close relationship between the brain and CSF, the application of CSF-derived indicators represents an alternative method for detecting the central nervous system.

Declarations

Ethics Approval And Consent To Take Part

Not applicable

Consent for Publication

Not applicable

Data Availability

Not applicable

Competing Interests

The authors declare that they have no competing interests

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Authors' Contributions

All authors read and approved the final manuscript.

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