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Is it possible to develop a vaccine against depression based on microRNA?

Abstract

It is difficult to create vaccinations to prevent mental diseases like depression because of their complex underlying mechanisms. In order to create an effective vaccine, the underlying causes of these diseases must be understood. In addition, it has been observed that microRNAs are crucial regulators of various cell functions, including proliferation, growth, differentiation, neoplastic transformation, and tissue regeneration. Their importance goes beyond posttranscriptional control of gene expression. In light of this, the study recommends employing microRNA in the production of live-attenuated vaccines to produce strong, long-lasting immunity against mental diseases.

Keywords: microRNA, mental health, depression, vaccination

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Raúl Isea
Fundación IDEA, Hoyo de la Puerta, Baruta, Venezuela

Correspondence: Raúl Isea, Fundación IDEA, Hoyo de la Puerta, Baruta, Venezuela, Email raul.ise@gmail.com

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Introduction

Major depressive disorder (MDD) is a frequent illness that has a significant influence on psychosocial functioning and quality of life. It is responsible for emotional shifts, sadness, and cognitive impairment. MDD pathophysiology is complicated, with different theories including the monoamine hypothesis, the hypothalamic-pituitary-adrenal (HPA) axis, neuroplasticity and neurogenesis, epigenetics, and inflammation.[1] Depression, according to the monoamine theory, is produced primarily by a decrease in monoamine neurotransmitters, whereas the HPA axis can stimulate glucocorticoid and cortisol release, leading to depression.[2,3]

According to research by Mandelli et al.,[4] stress is a well-studied etiologic factor in the emergence of depression and other mental disorders. Neglect and abuse throughout childhood raise the likelihood of adult depression.[5] People's responses to stressors in the future are influenced by long-term alterations in the brain and peripheral stress regulation systems caused by past stressors. According to recent research, miRNA activity may be crucial for long-term alterations linked to the etiology and management of depression.[6]

Breen et al.,[7] identified a gene on chromosome 3p25–26 that seems to be shared by multiple family members who experience depression. This suggests a new risk factor for severe recurrent depression: 3p25-26. Breen et al.,[7] have reported the first instance of a depression-related genome-wide significant locus with independent genome-wide significant replication. Bupropion, mirtazapine, trazodone, nefazodone, vilazodone, and vortioxetine are antidepressants that have been developed thus far. These medications have distinct mechanisms of action. Significant depression, anxiety, addiction, and chronic pain are all treated with antidepressants.[8] Iripramine and trazodone are especially useful in treating generalized anxiety disorder (GAD).[9]

Furthermore, antidepressants called monoamine oxidase inhibitors (MAOIs) are used to treat depression by halting the breakdown of neurotransmitters. According to Van den Eynde et al.,[10] some examples are phenalgine, tranylcypromine, and isocarboxazid. However, because of drug-drug and drug-food interactions, they are frequently the last option. To be clear, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), atypical antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin/norepinephrine reuptake inhibitors (SNRIs) are just a few of the antidepressants that are used to treat bipolar depression.[11] Both postsynaptic noradrenergic neurons and presynaptic serotonergic neurons are affected by these medications. Receptors are stimulated by the release of serotonin and norepinephrine, which are then reabsorbed by the serotonin transporter (SERT) and the norepinephrine transporter (NET), respectively.

What has Covid-19 shown us about microRNAs?

As revealed in the COVID-19 scenario, strategies based on microRNAs (miRNAs) have recently been found to be successful as a therapeutic approach.[12] Recall that posttranscriptional regulation of gene expression is governed by short, single-stranded RNAs called miRNAs. They were discovered in 1933[13] and have since grown into a variety of roles. miRNAs regulate cellular processes and cell-to-cell communication, making them potential biomarkers and therapeutic agents for diseases. They are less immunogenic and have fewer toxic side effects than gene therapy and protein-based drugs.

Short noncoding RNA molecules, or miRNAs, have recently been linked to mental illness.[14] Because miRNAs function as a switch to silence specific gene groups and dampen gene expression by reducing the amount of mRNA transcripts of particular targets, they are essential for development and cellular differentiation. miRNAs have been found to have major regulatory roles in cell processes like proliferation, differentiation, growth, neoplastic transformation, and tissue regeneration.[15] They also play a significant role in the posttranscriptional regulation of gene expression. Moreover, miRNAs do not translate into proteins or oligopeptides, they are known as "noncoding RNAs".[16]

New findings show that specific miRNAs have been altered at different levels in patients suffering from psychiatric disorders, including mental health disorders (MDD). For example, a review of 23 studies evaluating miRNAs in the peripheral tissues of patients with MDD found that there were differences between cases and controls in 178 distinct miRNAs.[17] These studies did not, however, consistently find changes in these miRNAs, which emphasizes the need for more rigorous research with bigger sample sizes, standardized procedures, and stricter diagnostic standards.

Remember that RNA polymerase II (Pol II) transcribes miRNA genes and that approximately 40% of miRNA genes are located in intron regions.[18] Transcription occurs in the nucleus to produce pro- and pre-miRNAs. After that, the nucleus processes these RNAs to create molecules with 70–100 nucleotides and hairpin-like structures.

Xu et al.,[19] reported that antidepressant medication can affect the levels of microRNA expression, with 28 miRNAs showing upregulation and 2 miRNAs showing downregulation after a 12-week treatment. As a result, these miRNAs can serve as biomarkers for the diagnosis of depression and to track the efficacy of therapy in patients.[19] As a result, miRNAs are crucial therapeutic targets and antidepressant medication mediators.

In fact, long-term use of serotonergic antidepressants decreases the expression of the 5-HT1A receptor and the serotonin transporter (SERT), which are both controlled by miR-135.[20] Targeted by miR-1202, miR-1202 can modify glutamatergic and serotoninergic synaptic transmission. Treatment for chronic depression, but not acute depression, can raise levels of miRNA expression, which is a key mediator of antidepressant effects and a mechanism linked to a delayed onset of therapy.

What steps should we take to develop a microRNA-based depression vaccine?

In neuronal synaptic signaling, neurotransmitters are integrated into presynaptic neurons, bundled into vesicles, and transported to post-synaptic neurons through the synaptic cleft.[21] This process is facilitated by miRNAs. These neurotransmitters are transported by mRNA-encoded receptors that are present in postsynaptic neurons.[22] The regulation of synaptosomal-associated protein-25 (SNAP-25) by MiR-153 facilitates the arrival of neurotransmitters and calcium-initiated vesicles in the synaptic cleft. In zebrafish, control expression of miR-153 has an antagonistic effect on the synaptic vesicle cycle, whereas overexpression suppresses it at the neuromuscular junction.

Hassan et al.[23]'s research demonstrates the critical role miRNAs play in innate and adaptive immune responses, controlling the growth, activation, survival, and proliferation of T and B cells. Acute inflammatory responses and pathogen recognition are significantly regulated by miRNAs, including miR-155, miR-146, and miR-223.[24] Additionally, they participate in adaptive immune responses that entail the activation of T and B cells as well as clonal expansion, which produce antibodies and cytotoxic effector responses. A number of human diseases, such as cancer and inflammatory disorders, have been linked to aberrant expression of miRs, which has also been linked to depression and suicidal ideation. As a negative feedback regulator of the TLR/NF-B pathway, miR-146a causes macrophages to express more miR-155 and miR-146 in response to lipopolysaccharide (LPS) stimulation.[25]

The last part of the work involves proposing an idea centered around developing an attenuated vaccine with microRNA that is similar to the results observed during the development of the COVID-19 pandemic.

MicroRNA-attenuated virus vaccines

Fay et al.,[26] argue that smallpox has been eradicated as a result of vaccinations' success in reducing viral infections. Live-attenuated vaccines may be less immunogenic and carry safety risks, even though they increase immunity.[27] Using miRNAs, live-attenuated vaccinations against DNA and positive and negative sense RNA viruses have been developed, enabling virus-specific attenuation.[26]

Any vaccination technique that uses live attenuation increases the risk that viral replication will be reduced to the point where the immune system is severely compromised, leaving the body with inadequate protection against recurrent infection. It is essential to ascertain the types of innate and adaptive immune responses against viruses that miRNA has suppressed.

Long-lasting immunity against viruses can be obtained through live-attenuated vaccinations, but these should be avoided because of their pathogenicity and tendency to revert to wild-type replication. Host-derived miRNAs have been employed to suppress viruses in various biological contexts due to their abundance of miRNA targets and broad range of effective tissue- and species-specific miRNAs. Future research will examine the methods that have been developed to enhance the safety and stability of miRNA-attenuated viruses, which may be used as vaccines.

Take into consideration the research conducted by Hu et al.,[12] regarding the potential use of microRNA as a SARS-CoV-2 infection treatment strategy. They demonstrated how host miRNAs target specific regions on SARS-CoV-2 RNA to prevent the synthesis of essential viral proteins.

Furthermore, miRNAs are more immunogenic, less toxic, and more varied than protein-based therapeutic agents or even plasmidic DNA-based therapies. In fact, miRNA mimics can be used as a therapeutic strategy in the treatment of COVID-19,[12] even though their potential side effects are still unknown. Recent studies have shown that miRNAs can target the RNA virus genomes to control viral protein synthesis, replication, and pathogenicity.[28] The host cell's miRNAs can be altered by an RNA virus infection, and these changes may later lead to changes that promote infection. On the other hand, miRNAs can also stop viruses from spreading. This study highlights the importance of miRNAs in viral infection and discusses a novel miRNA delivery strategy that targets specific organs, such as the lung.

Conclusion

The benefits of creating immunizations to treat anxiety and depression are enormous, but the science underlying them is intricate and constantly changing. We can lower the incidence of these crippling mental health disorders worldwide if we keep funding research into them and take a multidisciplinary approach. In conclusion, the growing body of research demonstrating the connection between immune system malfunction and mental health issues gives optimism for the future of intervention and preventative initiatives. We may be able to minimize the burden of anxiety and depression by developing specific drugs and vaccines and increasing our understanding of the immune system's function in the brain in relation to these conditions.

The creation of a novel vaccination for mental health practices will require cooperation between researchers, clinicians, and legislators. In the end, this might result in better mental health outcomes and lower societal expenses related to these illnesses. In light of all of this, future studies will provide the information needed to develop a vaccination against depression using microRNA-attenuated viruses.

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Conflicts of interest

Author declares that there is no conflict of interest.

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