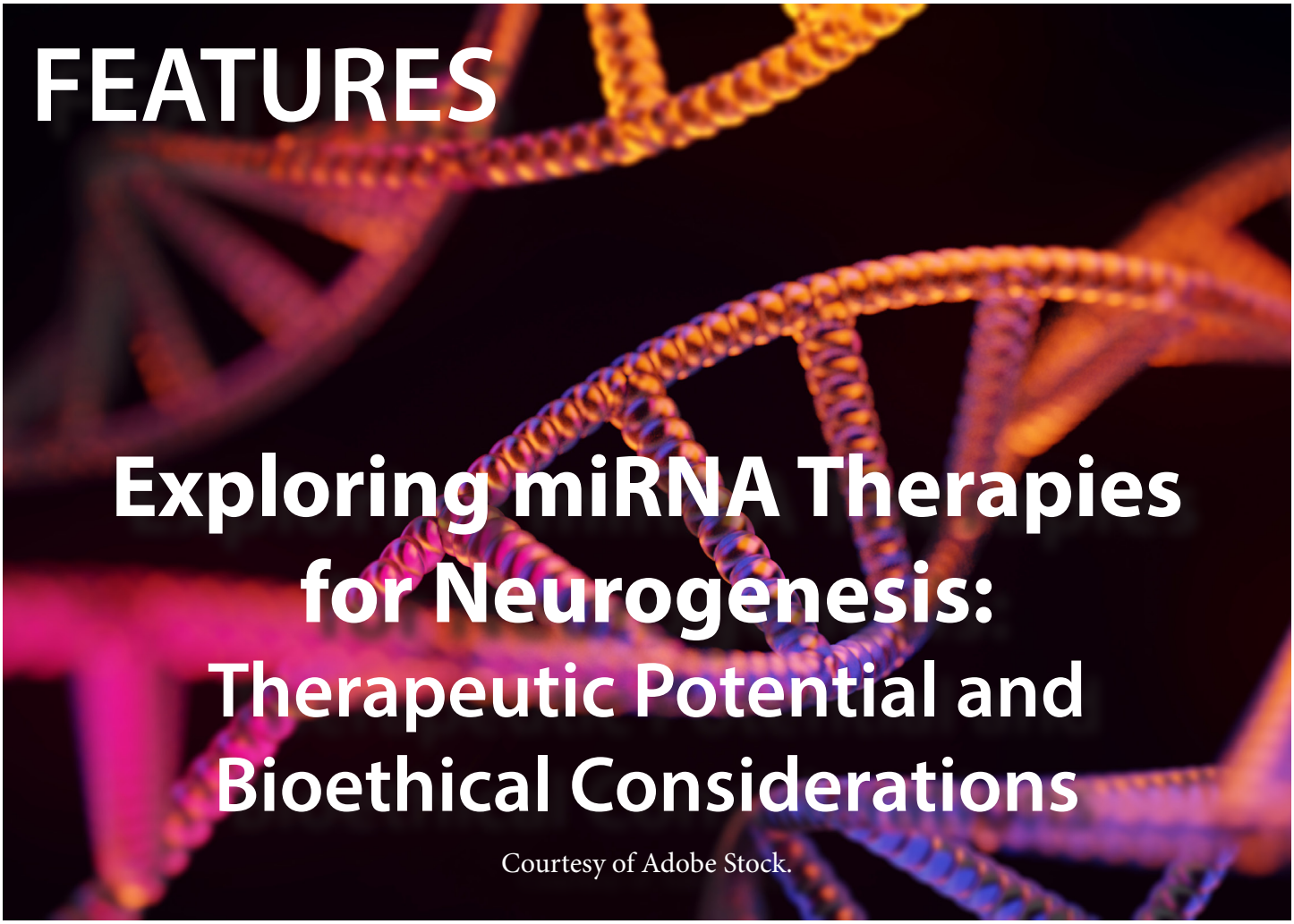

Exploring miRNA Therapies for Neurogenesis: Therapeutic Potential and Bioethical Considerations

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Introduction

Traumatic brain injuries (TBIs) impact approximately 190 individuals each day and highlight a substantial need for effective neurological therapies to treat these injuries (Centers for Disease Control and Prevention, 2024). While the body is capable of cell regeneration following some injuries—for example, epidermal skin cells are fully replaced every month—neurons have historically been considered a notable exception. The reigning belief for much of the 20th century was that humans were born with a fixed number of neurons, limiting neurological treatment strategies to symptom management rather than neural regeneration. However, evidence from recent decades reveals that neurogenesis—the process of creating new neurons—can occur in specific regions of the adult brain such as the hippocampus, which is primarily associated with memory function (Costa et al., 2015). These findings have opened new avenues in neurodegenerative research and indicate the potential for full recovery after severe brain injury and degeneration.

In parallel, the discovery of microRNAs (miRNAs) has revolutionized the understanding of gene regulation. Filling critical roles in post-transcriptional gene regulation, these noncoding RNA molecules affect processes such as cellular proliferation and differentiation, which are important to human growth and development (O’Brien et al., 2018). Due to their ability to influence multiple genes simultaneously, miRNAs have shown promise in helping create biotechnological therapies for neurological disorders, especially those caused by dysregulation in gene expression (Broderick & Zamore, 2011). miRNAs significantly affect cellular processes like programmed cell death and inflammation in response to toxic substances, which are central to neurodegenerative and injury-induced neuropathies, suggesting that they may also play an essential molecular role in facilitating neural repair and regeneration.

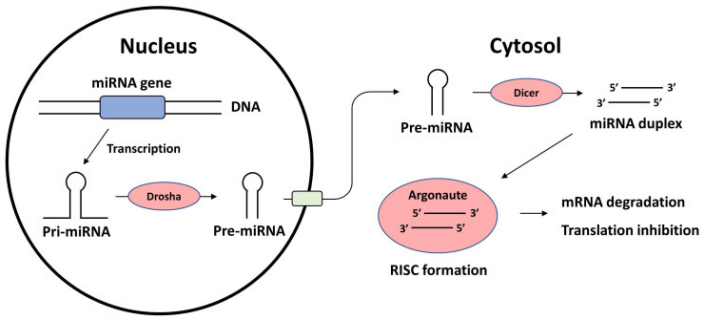


Figure 1. miRNA biosynthesis and mechanism in regulating gene expression (Jung et al., 2021)

Advancements and Delivery Mechanisms of miRNA Therapies

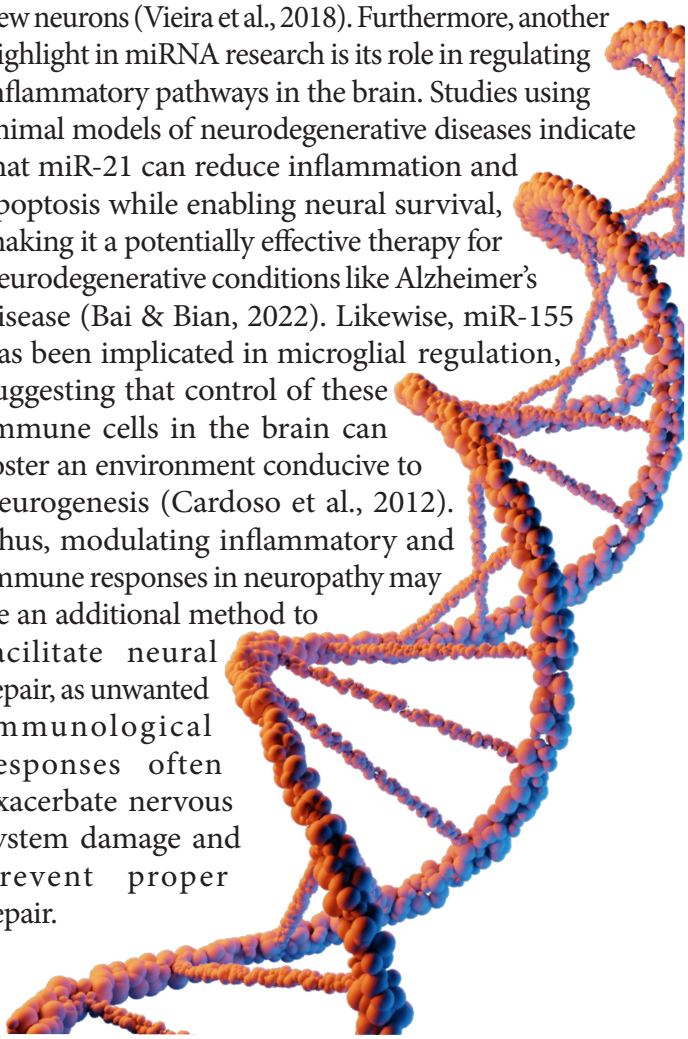
Although miRNAs offer significant potential for neuronal repair, their primary therapeutic limitation is the lack of appropriate delivery mechanisms (Segal and Slack, 2021). Delivering miRNA molecules directly to target tissues, especially the brain, presents several challenges such as ensuring the stability and specificity of the miRNA molecules and minimizing the immune response to these foreign particles (Lee et al., 2019). To this end, researchers have been particularly excited by two delivery systems: adeno-associated viral vectors (AAVs) and nanoparticle-based approaches (Han et al., 2011).

Discovered in the late 20th century, AAVs are small, non-enveloped DNA viruses used as a delivery mechanism for gene therapy—a medical treatment that utilizes genes to treat or prevent diseases—due to their ability to precisely transmit genetic information without causing disease (Issa et al., 2023). AAVs are especially advantageous for neurological therapeutics because they are able to cross the blood–brain barrier, which is a natural membrane that protects the brain from toxins in the blood but consequently limits effective drug delivery to the brain. Furthermore, AAVs reach their delivery sites with precision and are able to selectively target neural cells with minimal immune activation (Wang et al., 2019). Similarly, nanoparticles, which are ultrafine particles spanning the nanometer range, can encapsulate miRNAs as a means of transduction, allowing for spatial and temporal control over release (Lee et al, 2019). This enhances cellular uptake rates of the intended information and reduces unintended degradation.

By combining these miRNA delivery methods with stem cell therapies, neural stem cells may more effectively differentiate into neurons. For instance, miRNAs such as miR-21 and miR-124 have demonstrated potential in promoting neuronal survival and integration within damaged neural circuits, thus creating synergistic effects that facilitate neurogenesis and functional recovery (Liu et al., 2021). This combined approach could be particularly useful for treating TBIs and neurodegenerative diseases that are typically characterized by progressive neural loss and dysfunction, such as subarachnoid hemorrhages and Alzheimer's disease.

Current Research on miRNA in Neurogenesis and Neuropathy

The application of miRNAs to neurogenesis research proves their therapeutic versatility. For instance, miR-124 and miR-9 have been found to facilitate neural stem cell differentiation into mature neurons, promoting both neurogenesis and the assembly of functional neural circuits (Xue et al., 2016). These characteristics are particularly valuable in regenerative medicine, as they present potential strategies for restoring neural functions lost in injury or disease as well as the possibility of inducing the formation of new neurons (Vieira et al., 2018). Furthermore, another highlight in miRNA research is its role in regulating inflammatory pathways in the brain. Studies using animal models of neurodegenerative diseases indicate that miR-21 can reduce inflammation and apoptosis while enabling neural survival, making it a potentially effective therapy for neurodegenerative conditions like Alzheimer's disease (Bai & Bian, 2022). Likewise, miR-155 has been implicated in microglial regulation, suggesting that control of these immune cells in the brain can foster an environment conducive to neurogenesis (Cardoso et al., 2012). Thus, modulating inflammatory and immune responses in neuropathy may be an additional method to facilitate neural repair, as unwanted immunological responses often exacerbate nervous system damage and prevent proper repair.



However, optimizing miRNA specificity and reducing its off-target effects remain critical areas of study to this day. Because miRNAs regulate multiple genes, the potential for unintended and harmful gene interactions is significant (Hua et al., 2006). Sequencing efforts to develop miRNA analogs specific to target pathways could potentially mitigate these effects, but more research is needed—particularly in brain applications where even small changes in gene expression can significantly impact cognition and behavior. Furthermore, manufacturing miRNA delivery mechanisms requires immense funding and is currently not very productive in delivering nucleotides or adjusting for proper dosages, prolonging the length of neurogenesis research (Zhang et al., 2021).

Bioethical Considerations of miRNA-Based Therapies

While a standardized, usable model of miRNA therapies in the context of neurogenesis may be physiologically beneficial, its ethical implications warrant scrutiny. The traditional view in cognitive science is that the brain is an indispensable part of identity. Therefore, any regeneration therapies, including miRNA-mediated stem cell therapy, could introduce unfamiliar entities that affect the behaviors and actions of the individual, thus potentially changing a part of the patient's identity. However, these therapies have the potential to heal chronic pain and injury in life-altering or life-threatening situations. As a result, these therapies raise critical philosophical questions about the extent to which it is acceptable to prioritize physical well-being over self-identity.

For example, one central philosophical debate is the continuity of the self, referenced in the famous Greek analogy of the Ship of Theseus (The Editors of Encyclopædia Britannica, 2024). If all parts of the ship are gradually replaced, then would it still be the same ship? If not, when would it become a different ship? Similarly, if individual neurons within the brain are continually regenerated or altered through miRNA-induced neurogenesis, could this influence aspects of an individual's identity? While the body naturally replaces cells like skin cells, which are not directly involved in cognitive processes, research has identified neurons as unique in encoding memories and self-perception. As such, artificial neurogenesis raises unique considerations regarding potential shifts in memory, personality, and behavior—more so than other non-neuronal cells of the body—and how changing the physical neurons might affect our fundamental identities.

Manipulating neural circuits using miRNA therapies also inherently brings the risk of misuse, particularly in the realms of autonomy and patient consent. For instance, a potential concern is that these therapies may impact thoughts and behaviors in ways that compromise individual free will. In model organisms like Drosophila melanogaster (fruit flies), scientists have observed that specific neurons control distinct behaviors: for instance, Moonwalker Descending Neurons can be optogenetically activated to induce the involuntary action of walking backward, suggesting that future research could uncover similar structures in humans (Sen et al., 2017). Thus, specific human behaviors may be attributed to specific circuits or characterizable networks as the scientific literature grows, and their changes in conjunction with neurogenesis may affect free will, either explicitly through misuse by bad actors or implicitly through bias. In the past year, studies have found that neural activity could be used to accurately predict specific behaviors or speech patterns, a discovery that holds great potential in the advancement of brain-computer interfaces (Doctrow, 2024).

Conclusion

Based on current research and its implications, miRNA therapies may serve as a promising strategy for promoting neurogenesis and neuroregeneration, offering hope for patients with TBIs and neurodegenerative conditions. By modulating apoptosis, inflammation, and neural differentiation, miRNAs could provide a means of treating neural damage at a cellular level, moving beyond symptomatic management toward true regeneration. However, as these treatments advance, it is crucial to address the accompanying ethical and philosophical issues, particularly those pertaining to personal identity, autonomy, and the potential for unintended behavioral effects. Only by addressing these complexities can miRNA therapies be developed responsibly with an emphasis on patient welfare and a nuanced understanding of the profound implications they hold for the human experience.

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