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Opinion Article

The Role of the Human miRNA Repertoire in Health and Disease: Implications for Diagnostics and Therapeutics

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DESCRIPTION

MicroRNAs (miRNAs) are small, non-coding RNA molecules, usually 20 to 24 nucleotides in length, that play a vital role in controlling gene expression. First identified in the early 1990s, miRNAs have since emerged as key players in virtually all biological processes, from development to disease progression. The human miRNA repertoire, a collection of all miRNAs expressed in human cells, is vital for understanding both the fundamental mechanisms of cellular function and the pathogenesis of numerous diseases, particularly cancer, cardiovascular disorders and neurological conditions. This article explores the importance of the human miRNA repertoire in advancing our understanding of human health and diseases, shedding light on its potential as a diagnostic and therapeutic tool.

miRNAs and their role in gene regulation

MiRNAs primarily function by binding to complementary sequences in messenger RNAs (mRNAs), leading to the repression of translation or degradation of the target mRNA. Unlike proteins, which can carry out complex biochemical functions, miRNAs regulate gene expression at the post-transcriptional level, acting as fine-tuners of cellular processes. A single miRNA can target hundreds of mRNAs, influencing entire gene networks. This makes miRNAs powerful regulators in processes such as cell proliferation, differentiation, apoptosis and stress responses.

Given the diverse biological roles of miRNAs, the comprehensive catalog of human miRNAs referred to as the human miRNA repertoire is a critical resource for understanding the molecular basis of health and disease. It consists of approximately 2,500 miRNAs in humans, though this number continues to grow as new miRNAs are discovered and the functional implications of many are elucidated.

miRNAs in health: Gene regulation and homeostasis

In healthy individuals, miRNAs help maintain cellular homeostasis and tissue integrity. By modulating gene expression, they ensure that cells respond appropriately to environmental cues, proliferate when necessary and undergo programmed cell death (apoptosis) when damaged or no longer needed. The fine balance between miRNA activity and gene expression is crucial for proper development and functioning.

One key example is the role of miRNAs in regulating the immune system. MiRNAs such as miR-155 and miR-146a are known to regulate immune responses, including inflammation and the activation of immune cells. This regulation ensures that the immune system responds adequately to infections while preventing excessive inflammation that can lead to autoimmune diseases.

Additionally, miRNAs play a role in the regulation of metabolism and the maintenance of normal cellular functions. For instance, miR-33 regulates cholesterol and fatty acid metabolism, influencing lipid homeostasis, while miR-122 controls the expression of genes involved in liver function. These examples illustrate how miRNAs are intricately involved in maintaining health at the cellular and systemic levels.

miRNAs in diseases: Implications for pathogenesis

The dysregulation of miRNAs is implicated in a wide range of diseases, including cancers, cardiovascular disorders, neurodegenerative diseases and metabolic syndromes. Altered expression of specific miRNAs can lead to abnormal cellular behaviour, such as uncontrolled cell proliferation, evasion of apoptosis or metastasis in cancer.

Cancer: The relationship between miRNAs and cancer is one of the most well-studied areas in miRNA study. Oncogenic miRNAs (oncomiRNAs) are miRNAs that promote cancer by suppressing tumor suppressor genes, while tumor-suppressive

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miRNAs inhibit cancer progression by regulating oncogenes. For example, miR-21 is overexpressed in many cancers, including breast, lung and colorectal cancer and promotes tumorigenesis by targeting tumor suppressor genes like Phosphatase and Tensin Homolog (PTEN) and Tropomyosin 1 (TPM1). Conversely, miR-34a, which is regulated by the p53 tumor suppressor gene, acts as a tumor suppressor by inducing cell cycle arrest and apoptosis in response to DNA damage.

Cardiovascular disease: miRNAs also have a crucial role in cardiovascular health. They regulate key processes in heart development, function and disease. For instance, miR-1 and miR-133 are involved in cardiac muscle contraction, while miR-21 is implicated in fibrosis and heart failure. Dysregulation of these miRNAs can lead to various cardiovascular diseases, such as arrhythmias, myocardial infarction and heart failure.

Neurodegenerative diseases: In the brain, miRNAs influence neuronal development, synaptic plasticity and neuroinflammation. Dysregulation of miRNAs has been linked to several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and Huntington's disease. For example, miR-9 and miR-124 are important for neurogenesis and maintaining neuronal health and their downregulation has been observed in Alzheimer's disease, contributing to the pathological processes associated with the disease.

Metabolic disorders: miRNAs also regulate the genes responsible for maintaining metabolic homeostasis. Altered miRNA expression can lead to metabolic diseases like diabetes and obesity. For example, miR-33 and miR-103/107 influence insulin resistance and glucose metabolism and their dysregulation has been linked to the development of type 2 diabetes.

miRNAs as diagnostic and therapeutic tools

Given their central role in disease pathogenesis, miRNAs hold great promise as both diagnostic biomarkers and therapeutic targets. In diagnostics, miRNAs can be detected in various body fluids, including blood, urine and saliva, making them non-invasive biomarkers for disease detection and monitoring. For example, circulating levels of miR-21 are used as a biomarker for detecting and monitoring cancer, while miR-126 is a potential biomarker for cardiovascular diseases.

In therapy, miRNAs can be targeted to either restore normal gene expression or inhibit the activity of disease-promoting miRNAs. Approaches such as miRNA mimics, inhibitors (antagomirs) and small molecules are being developed to modulate miRNA activity. Clinical trials are underway to test the efficacy of these therapies in treating cancers, cardiovascular diseases and other conditions.

CONCLUSION

The human miRNA repertoire represents a vast and intricate network of regulators that control key biological processes essential for health. The dysregulation of miRNA expression is central to the development and progression of a wide range of diseases, including cancer, cardiovascular disorders and neurodegenerative diseases. Understanding the complex interactions between miRNAs and their target genes is important for unravelling the molecular underpinnings of these conditions. As study progresses, miRNAs hold significant potential not only as diagnostic biomarkers but also as therapeutic targets, offering new hope for the treatment of diseases that currently lack effective therapies.