Newborns' MicroRNA Expression as Potential Biomarkers for Disease Diagnosis

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Abstract

The work emphasizes the need for additional research to create novel biomarkers based on the use of microRNAs as a less invasive and precise diagnostic technique for identifying diseases in newborns.

Mini-reviews Article

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Peer-Reviewed Article

DOI: 10.14302/issn.2998-4785.ijne-24-5138

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Keywords:

Newborn, microRNA, biomarker, Diagnosis.

Received: May 27, 2024

Accepted: June 21, 2024

Published: June 25, 2024

Academic Editor:

Oliver Chukwujekwu Ezechi, Nigerian Institute of Medical Research, Division of Clinical Science Lagos.

Citation:

Raúl Isea (2024) Newborns' MicroRNA Expression as Potential Biomarkers for Disease Diagnosis. International Journal of Neonatology - 1(1):22-27. https://doi.org/10.14302/issn.2998-4785.ijne-24-5138

Introduction

Traditional indicators, such as a newborn's weight and height, are still utilized since they can approximate a child's future risk of getting any disease. However, the implications of these indicators on the child's future adult development remain uncertain; for example, infants who are overweight or short in stature may suffer insulin insufficiency at birth, increasing their chances of developing diabetes as adults[1].

In fact, a mother's nutritional and hormonal state during pregnancy (including the postpartum period) can affect various aspects of his or her child's adult life, including the development of metabolic diseases like obesity, high blood pressure, hypercholesterolemia, hyperlipidemia, and so on[2].

One method for diagnosing potential abnormalities in neonates is the detection of acidosis, which is a pH shift in the umbilical cord that suggests hypoxic stress in the developing baby[3]. The cord's low pH was shown to be independent of the existence of hypoxic ischemic lesions[4].

The majority of the diagnostic procedures done on babies in the first few days after delivery are called neonatal screening (NS)[5]. On this test, a heel pinch is used to draw blood, which is then stored as a drop of dried blood (DBS) on neonatal detection cards (NSCs). This makes it possible to diagnose diseases including cystic fibers, phenylcetonuria, biotinidase deficiency, galactosemia, central congenital hypothyroidism, primary congenital hypothyroidism, and congenital adrenal hyperplasia[6].

On the other hand, despite improvements in neonatal care and scientific knowledge, neonates may also die from sepsis, suffer significant impairment, or undergo neurological deterioration—a condition that affects 4 out of 10 newborns on average in affluent nations[7,8].

It's important to remember that neonatal sepsis, along with other clinical symptoms and hemodynamic alterations that raise newborn morbidity and mortality, is a systemic inflammation brought on by bacteria, viruses, or fungi[7].

Neonatal sepsis still has few pharmacological therapy options, most of which center on supportive care and early antibiotic administration. Various clinical and blood markers have been examined in this context in order to identify sepsis and characterize its severity and cause[9].

On the other hand, neonates with neonatal pneumonia (NE) are among the most common causes of death in neonatal intensive care unit (NICU) because of the high chance that they will experience neurological difficulties and disabilities throughout their lifetimes[10].

In parallel, microRNA was discovered during research on the nematode *Caenorhabditis elegans*[11], and their use as a diagnostic tool has only recently begun because they are useful for determining the onset and progression of disease due to their high specificity for different tissue or cell types. MicroRNAs have been shown to be sensitive, with levels fluctuating in response to treatment or the rate at which the disease advances[12].

There is a growing focus on the application of microRNA-based biomarkers for real-time therapeutic decision-making in the context of neonatal sepsis and other disorders affecting neonates[10]. The primary benefit is that the patient can receive highly accurate disease diagnosis and surveillance with the least invasive techniques.

For example, Dakroub et al.[13] discovered ten microRNAs in the group of newborns with NE when compared to healthy controls, where microARNs in these neonates experience significant alterations within a few hours of birth. Additionally, research has been done on microRNAs as early indicators of newborn sepsis[10].

Another example of how microRNAs benefit newborns is the range of macronutrients available in breast milk, which includes lactose, oligosaccharides, lipids, proteins, and nonprotein nitrogen. Breast milk is one of the most microRNA-rich biological fluids, with over 1400 distinct microRNAs accounting for approximately 25% of the total nitrogen in milk[14].

Two more examples. Ibrahim et al.'s study[15], for instance, children with asthma exhibit reduced expression of miRNA-196a-2 and elevated serum levels of Annexin A1 (ANXA1, an essential anti-inflammatory mediator that may be crucial in bronchial asthma), indicating their potential as diagnostic biomarkers and therapeutic targets as well as their involvement in the etiology of asthma. Finally, MicroRNAs' function in controlling the expression of sirtuin 1 (a potential target for slowing down aging)[16-19].

But, what are microRNAs?

MicroARN are short ARN molecules ranging in size from 18 to 22 nucleotides that bind to ARNm, resulting in translational and genetic suppression, and are found in all eukaryotic cells[20]. MicroRNAs (sometimes abbreviated as miRNAs) have crucial regulatory roles in several biological and cellular processes[21]. Its presence in biological fluids such as blood, saliva, tears, and even mother's milk has sparked concern about its potential influence on human health and early disease detection[22]. Although several studies have been published on the presence of microARN in breast milk, further research is needed to fully understand their role[23].

Rapid advances in sequencing techniques have improved the sensitivity of detection, resulting in the discovery of several microRNAs in serum and blood[24]. MicroRNAs are highly stable in peripheral blood, which contains ribozimas and other microRNAs, and their levels vary significantly across patients with various diseases[25]. MicroRNAs expression levels in peripheral blood correlate with clinical-pathological factors, potentially serving as a diagnostic biomarker for disease detection and

monitoring[26].

The microRNA nomenclature involves the suffix "mir" and a unique identification number. The identification numbers are assigned progressively, independent of the organism. Identical or comparable miRNA sequences within a species might be assigned the same number. For example, the transcripts of *Drosophila* mir-13a and mir-13b differ slightly in sequence, although mir-6-1 and mir-6-2 are identical[27].

MicroRNA Biogenesis

The biosynthesis of microRNA involves several phases, beginning in the nucleus and ending in the cytoplasm[27]. The transcription phase is first carried out by RNA polymerase II (pol II), followed by the production of capped, spliced, and polyadenylated miRNAs. Drosha and DGCR8 then digest these to produce 70–100 nucleotide pre-miRNAs. Exportin-5 transports these to the cytoplasm. Another RNAse called Dicer cuts the pre-miRNA into double-stranded RNA, which is then added to the RISC complex, which includes the Argonaute protein (Ago-2)[28]. This inclusion causes translation inhibition, or mRNA cleavage. MicroRNAs can also be processed using the miRtron, an intron of a protein-coding gene involved with host gene expression[29].

MicroRNAs are small non-coding RNAs that regulate gene expression by silencing messenger RNAs (mRNA)[28]. They are almost 22 nucleotides long and occur predominantly via the canonical pathway, which involves Drosha processing pri-miRNA to pre-microRNA and Dicer splicing the pre-miRNA into mature miRNA[30]. The classic microRNA genesis route terminates with the 5p or 3p strand binding to argonaute (Ago) proteins in an ATP-dependent manner[28]. The choice of strand for Ago integration is based on thermodynamic stability at the 5' end of the miRNA duplex or a 5' uracil at the first nucleotide position[20].

Finally, demonstrating the advantages of using microRNA-based biomarkers

An example of the application of microRNA-based biomarkers in the diagnosis of diseases is, for example, neonatal hypoxic-ischemic encephalopathy (HIE)[31], the clinical phenotype resulting from hypoxic-ischemic brain injury (HIBI), a severe neurological lesion that happens during the perinatal period[32].

Neonatal hypoxic brain damage (HIBI) is characterized by rapid free radical generation and enhanced biomolecule oxidation, particularly during the secondary phase[33]. The majority of previous research on microRNAs in newborn HIBI has focused on a subset of microRNAs known as hypoxamiRs, which are regulated by hypoxia and modulate the cell's response to low oxygen[32]. These include not only the well -known miR-21 and -210 but also miR-335, mir-137, and mir-376c. It has been proven that these hypoxamiRs play a significant role in a variety of clinical disorders, including cancer and heart injury, and altering brain microRNA levels may provide neuroprotection following HIBI[32].

Conclusions

The purpose of the study is to emphasize the benefits of implementing microRNA-based biomarkers for diagnosing and monitoring diseases in newborns. However, there is a lack of study into detecting a wider range of illnesses.

The main benefit of using microRNA-based biomarkers is that they are selective and minimally invasive, making them ideal for newborn diagnoses. It is possible to apply procedures developed in

hospitals and clinics, such as newborn screening cards, but further research is required.

As a consequence of all this, the generation of new biomarkers employing microRNA could help in the early identification and development of individualized therapy for a variety of pediatric disorders. This approach isn't limited to the newborn period and could offer a substantial improvement over other diseases.

Acknowledge

I would like to thank the reviewers for their time spent evaluating the article and their comments, which helped me enhance the work.

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