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microRNA as Biomarkers and Diagnostics

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Abstract

MicroRNAs (miRNAs) are a group of small non-coding RNAs that are involved in regulating a range of developmental and physiological processes; their dysregulation has been associated with development of diseases including cancer. Circulating miRNAs and exosomal miRNAs have also been proposed as being useful in diagnostics as biomarkers for diseases and different types of cancer. In this review, miRNAs are discussed as biomarkers for cancer and other diseases, including viral infections, nervous system disorders, cardiovascular disorders, and diabetes. We summarize some of the clinical evidence for the use of miRNAs as biomarkers in diagnostics and provide some general perspectives on their use in clinical situations. The analytical challenges in using miRNAs in cancer and disease diagnostics are evaluated and discussed. Validation of specific miRNA signatures as biomarkers is a critical milestone in diagnostics.

Keywords

microRNAs; biomarkers; disease; cancer; diagnostics

Introduction

MicroRNAs (miRNAs) are a class of small non-coding RNAs of 17–25 nucleotides in length that are conserved across species. They were first discovered in *Caenorhabditis elegans* at the beginning of the 1990s (Lee et al., 1993). Numerous studies have established that miRNAs are expressed in different tissues and cell types and deregulated expression of these small RNAs have significant impact on health and disease. miRNA encoding sequences account for 1%–3% of the mammalian genome (Bartel, 2004); over 1900 miRNAs have been reported that have critical regulatory functions and are involved in virtually all physiological processes, such as cellular development, proliferation, and differentiation; metabolism; and homeostasis (Bartel, 2004; Wang and Sen, 2011).

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miRNA transcripts are generated from the transcribed stem-loop precursors and form the primary precursor miRNA. The stem loop, which is asymmetrically cleaved by the miRNA processing complex comprising the RNase III Drosha and its cofactor DGCR8, produces the precursor miRNA (pre-miRNA) in the nucleus. The pre-miRNA is transported to the cytoplasm by the nuclear transport receptor exportin-5 and the nuclear protein Ran-GTP. It is then cleaved by Dicer to produce a short duplex molecule of mature miRNA of about 22 nt. These molecules are loaded by Dicer-TARBP2 complex into a member of the Argonaute protein subfamily and form the miRNA-induced silencing complex (RISC) (Wang et al., 2014b). miRNAs regulate the expression of at least half the human transcriptome by either repressing the translation of or causing the degradation of multiple-target mRNAs. The silencing mechanism may be determined by the extent of base pairing between the miRNA and the target mRNA when mRNA binds to the complimentary target sites located in the 3' untranslated region of the target mRNA (Ambros, 2004; Gregory et al., 2005).

Aberrant expression of miRNAs affects the regulation of many cellular functions and gene networks; it was found in tissues and in sera from patients with different forms of malignant tumors (Wang and Sen, 2011). The detection of a small number of miRNAs provides more information about the developmental lineage and differentiation stage of tumors than does the detection of a large number mRNAs (Lu et al., 2005). As prognostic biomarkers, miRNAs also enable the prediction of the course of a disease (Segura et al., 2010; Wang et al., 2014b; Yu et al., 2008). In addition to cancer, sufficient evidence exists to suggest that miRNAs are deregulated in viral infections (Lecellier et al., 2005), nervous system disorders (Mehler and Mattick, 2007), cardiovascular disorders (Ai et al., 2010; Hebert and De Strooper, 2009; van Rooij et al., 2006a; Wang et al., 2010), muscular disorders (Eisenberg et al., 2007), diabetes, and other diseases (Nielsen et al., 2012), which implies that utilizing these aberrantly expressed miRNAs as biomarkers for diseases is a valuable diagnostic strategy.

Circulating miRNAs and exosomal miRNAs as Disease Biomarkers

miRNAs have shown high stability in formalin-fixed, paraffin-embedded tissues from hepatocellular carcinoma (Hoshida et al., 2008), lung cancer (Barshack et al., 2010), melanoma (Barshack et al., 2010), pancreatic cancer (Szafranska et al., 2008), papillary thyroid carcinoma (Tetzlaff et al., 2007), and renal tumor (Fridman et al., 2010) patients and in human plasma, raising the possibility that miRNA expression analysis from archived tissue samples and body fluids including blood will be useful for characterizing disease states. The vast majority of miRNA expression profiles from solid tumor tissues and body fluids indicated that circulating miRNAs originate from tumor tissues and are protected from endogenous RNase activity (Mitchell et al., 2008; Wang et al., 2014b) reflecting the potential of developing circulating miRNAs as extracelluar biomarkers of cancer and other diseases (Chen et al., 2008b; Mitchell et al., 2008).

Circulating miRNAs were first used as biomarkers in serum to examine patients with diffuse large B-cell lymphoma (Lawrie et al., 2007). Since then, many studies have reported dysregulation of miRNAs in different human diseases. microarray profiling, real-time PCR array, and next-generation sequencing (NGS) technologies were used in initial screening

of circulating miRNAs and generated miRNA signatures from body fluids (Wang et al., 2014b). Using NGS, we have reported identification of 13 miRNAs that are enriched in the cyst fluids derived from invasive carcinomas (Wang et al., 2015). Differentially circulating miRNAs have also been found in pancreatic juice samples from patients with pancreatic ductal adenocarcinoma compared with chronic pancreatitis and control samples using miRNA microarray analyses (Wang et al., 2014a). The levels of miR-10b, miR-141, and miR-155 in the sera of lung cancer patients were validated to be significantly higher in patients with malignant disease than in those with benign disease (Roth et al., 2011). Urine miR-1 and miR-133b were identified as possible diagnostic and even prognostic biomarkers of kidney disease (Ben-Dov et al., 2014; Trionfini et al., 2015).

Exosomes are 30–120-nm endocytic membrane-derived vesicles that participate in cell-to-cell communication and protein and RNA delivery (Lin et al., 2015). miRNAs have been identified in exosomes, which can be taken up by neighboring or distant cells and subsequently modulate physiology of the recipient cells (Zhang et al., 2015). Circulating miRNAs can bind to specific proteins and associate with multivesicular bodies and exosomes. Multivesicular bodies can release exosomes into body fluids (Cortez et al., 2011; Thery et al., 2002). Exosomal miRNAs have been detected in the peripheral blood and culture media of several cell lines (Taylor and Gercel-Taylor, 2008; Valadi et al., 2007) and might be useful for development of biomarkers associated with adenocarcinoma (Rabinowits et al., 2009). Exosomal miRNAs have also been found to be potential diagnostic biomarkers for cardiovascular disease (Kuwabara et al., 2011). Although they are still in the early discovery stage as “ideal” biomarkers, their potential value in clinical diagnostics for disease needs to be fully explored.

miRNAs as biomarkers for cancers

Many human miRNAs appear to be located in genomic regions associated with cancer or at fragile sites (Calin et al., 2004b) and control important processes such as cell proliferation, cell adhesion, apoptosis, and angiogenesis, dysregulation of which play important roles in the onset, progression, and metastasis of cancer. Numerous studies have shown altered miRNA profiles in multiple cancer types, such as breast cancer (Iorio et al., 2005), leukemia (Calin et al., 2004a), liver cancer (Qi et al., 2013), ovarian cancer (Iorio et al., 2007), pancreatic cancer (Wang and Sen, 2011), and prostate cancer (Porkka et al., 2007). Identification of tumor specific genetic alterations in the miRNA processing machinery, such as in the genes encoding TARBP2, AGO2, Dicer and Exportin-5 (XPO5) provide strong evidence of these pathways being relevant in cellular transformation process (Esteller, 2011). Our analysis of data from The Cancer Genome Atlas consortium (TCGA) revealed significant alterations in the miRNA machinery genes in tumor, especially AGO2, which has a high incidence of gene alterations across multiple cancer types (Huang et al., 2014).

miRNAs can act as oncogenes or tumor suppressors, depending on the cellular context and the genes targeted (Esquela-Kerscher and Slack, 2006; Welch et al., 2007; Yu et al., 2010). Oncomirs are miRNA oncogenes that have a causal role in the onset or maintenance of cancer phenotypes. The Let-7 family was the first set of oncomirs that was shown to regulate the expression of the Ras gene (Esquela-Kerscher and Slack, 2006). The oncomir,

miR-21, targets PTEN (Meng et al., 2007) and SPRY2 (Sayed et al., 2008), promoting invasion and migration, as well as tumorigenesis by inhibiting the negative regulators of the Ras/MEK/ERK pathway (Hatley et al., 2010). Elevated expression levels of miR-21 have been found in a diverse subset of cancer cell lines and tissues, including glioblastoma, breast, colorectal, lung, pancreas, skin, liver, gastric, cervical, and thyroid cancer (Volinia et al., 2006). miR-34a, as a key regulator of tumor suppression, controls the expression of a plethora of target proteins involved in the cell cycle, cell differentiation, and apoptosis (Misso et al., 2014). Expression of miR-96 decreased cancer cell invasion and migration and slowed tumor growth, associated with KRAS downregulation (Yu et al., 2010). Reduction in miR-96 levels suppressed the proliferation and colony formation of glioma cells (Yan et al., 2014). Tumor-suppressor miRNAs such as miR-96 and miR-34a are repressed in primary tumors (Welch et al., 2007; Yu et al., 2010), but serum miR-34a was found markedly up-regulated in gastric cancer patients compared to in controls (Liu et al., 2011). miR-29a may act as a tumor suppressor in lung cancer (Fabbri et al., 2007), hepatocellular carcinoma (Xiong et al., 2010)], and leukemia (Pekarsky and Croce, 2010) but is significantly elevated in the plasma of patients with advanced colorectal neoplasia (Huang et al., 2010) and ovarian cancer (Resnick et al., 2009). Although the underlying mechanisms of inverse relationship between tissue and circulating miRNAs levels in cancer patients are not known, it appears that levels of extracelluar miRNAs reflect deregulated pathways in cancer cells (Wang et al., 2014b). In view of these findings, differentially abundant miRNAs detected in blood (Heneghan et al., 2010), cystic fluid (Wang et al., 2015), plasma (Huang et al., 2010; Wang et al., 2009), pancreatic juice (Wang et al., 2014a), serum (Chen et al., 2008b), sputum (Xing et al., 2010), and urine (Ben-Dov et al., 2014) samples have been proposed as candidate biomarkers of different types of cancer.

Polymorphisms in miRNA genes have been associated with a high risk of developing cancer; we have found that single-nucleotide polymorphisms in miR-196a2 C > T and miR-499 C > T confer hepatocellular carcinoma risk (Qi et al., 2014). Polymorphisms of miRNA-196a2 rs11614913 may be risk associated biomarkers of lung cancer (Chen et al., 2013). Thus, functional miRNA-single-nucleotide polymorphisms in miRNAs may be biomarkers of disease risk and can predict the clinical outcome in cancer.

Dysregulation of cellular miRNAs in viral infections

miRNAs have been associated with several viral infections, including HBV (hepatitis B virus), HCV (hepatitis C virus), HIV (human immunodeficiency virus), and EBV (Epstein Barr virus); these miRNAs control viral replication when the virus infects cells and control viral infection (Chen et al., 2014a; Jopling et al., 2005; Kutok and Wang, 2006; Luna et al., 2015; Murakami et al., 2009; Scaria et al., 2006; Zhang et al., 2010a). For example, miR-199a and miR-210 reduced HBV replication by binding to the HBV S protein coding region and pre-S1 region (Zhang et al., 2010a). miR-122 facilitated replication of the HCV viral RNA by binding selectively to the 5’ non-coding end of the viral genome (Jopling et al., 2005; Scaria et al., 2006), and knockdown of miR-122 resulted in a significant loss of autonomously replicating HCV viral RNAs (Jopling et al., 2005). On the other hand, inhibition of miR-122 by HCV RNA may result in global de repression of host miR-122 targets (Luna et al., 2015). miR-199a* was found to be a negative regulator of

HCV replication, and the downregulation of miR-199a* in chronic liver injury tissue was correlated with hepatocarcinogenesis (Murakami et al., 2009). miR-32 effectively restricted the accumulation of the retrovirus primate foamy virus type 1 (a retrovirus akin to HIV-1) in human cells by targeting a primate foamy virus type 1-encoding protein (Lecellier et al., 2005). Infection of primary cultured B-cells with EBV resulted in significant repression of miRNAs in B-cells (Kutok and Wang, 2006). Exogenous miRNAs in miRNA-overexpressing cells can disrupt the HIV RNA-mediated assembly of Gag into viral particles by competing with HIV RNA for binding to Gag at the plasma membrane (Chen et al., 2014a). Host cellular miRNAs may target a specific viral RNA to restrict infection and protect the host cell. Moreover, circulating miR-122, miR-22, and miR-34a have been correlated with the etiology of liver injury in HIV patients (Anadol et al., 2015).

miRNAs in nervous system disorders

Around 70% of the miRNAs are expressed in brain and many are specific to neurons (Cao et al., 2006) and mutations in the miRNA processing machinery are consistently found in various neurological disorders. For examples, mutations in the components of the Drosha microprocessor complexes, such as, Fus and TDP-43 caused familiar amyotrophic lateral sclerosis (Ling et al., 2010); fragile X syndrome was associated with mutations in the RISC component fragile X mental retardation 1 protein (Edbauer et al., 2010). Moreover, an increasing number of miRNAs and their targets have been found to be involved in regulating brain and neuron development (Bavamian et al., 2015; Hollins et al., 2014; Schratt et al., 2006); the importance of miRNAs in the nervous system is illustrated by the finding that 70% of known miRNAs are expressed in the brain (Sayed et al., 2007). Several brain-specific or brain-enriched miRNAs have been identified and characterized. The brain-specific miR-9 and miR-134 have been extensively studied in neurogenesis (Schratt et al., 2006; Zhao et al., 2009), have been reported in the nervous system more than in any other tissue, and are involved in different aspects of neural development (Sun and Shi, 2014). Aberrant expression of these miRNAs impaired neuronal differentiation and morphological features (Bavamian et al., 2015) and was associated with abnormal brain development and the pathogenesis of several neurodevelopmental diseases (Mehler and Mattick, 2007), including Tourette’s syndrome (Abelson et al., 2005), Alzheimer’s disease, Parkinson’s disease (Femminella et al., 2015; Margis et al., 2011; Qiu et al., 2014; Wang et al., 2008), schizophrenia, and schizoaffective disorder (Perkins et al., 2007). For example, low miR-107 expression is found in the cortex of Alzheimer’s disease patients, even at extremely early-stage pathological alterations (Wang et al., 2008), and the expression levels of miR-1, miR-22*, and miR-29 may be useful for distinguishing between those with non-treated Parkinson’s disease and healthy subjects (Margis et al., 2011). The evaluation of miRNA expression in nervous system disorders provides novel molecular information and introduces the possibility that expressing or inhibiting specific miRNAs may help clinical management of the disease processes.

miRNAs as promising biomarkers in diabetes and other metabolic diseases

In the past several years, metabolic diseases, including diabetes, have gained the attention of scientists and have become a major challenge in global health. miRNAs are important

regulators of the development and physiological state of metabolically active tissues. Alteration of their expression can result in impaired glucose and lipid homeostasis, which may have an important function in metabolic diseases (Lynn, 2009). Altered expression of miRNAs in diabetes causes malfunctions in insulin release and insulin resistance by regulating cellular membrane electrical excitability, insulin granule exocytosis, insulin synthesis in β-cells, and β-cell fate and islet mass formation (Chen et al., 2014b). miRNAs in body fluid appears be useful as biomarkers for monitoring the development and progression of diabetes mellitus and upregulation of 12 serum miRNAs (miR-152, miR-30a-5p, miR-181a, miR-24, miR-148a, miR-210, miR-27a, miR-29a, miR-26a, miR-27b, miR-25, and miR-200a) have been reported in type 1 diabetes patients (Nielsen et al., 2012). Serum miR-23a and miR-126 were suggested to be reliable biomarkers for early detection of type 2 diabetes (Liu et al., 2014; Yang et al., 2014). Similarly three serum miRNAs (miR-132, miR-29a, and miR-222) are were found to be predictive of gestational diabetes mellitus, with 66.7% sensitivity and 63.3% specificity (Zhao et al., 2011). miR-278 and miR-375 are regulators of insulin secretion and may be novel pharmacological targets for the treatment of diabetes (Poy et al., 2004). A recent study demonstrated that miR-122 regulated lipid metabolism in the liver, and miR-122 inhibition led to a decrease in plasma cholesterol and significant improvement in hepatic steatosis of mice (Esau et al., 2006). In addition, an unexpected role in glucose metabolism recently emerged for the tumor suppressor family of Let-7; the Lin28/Let-7 axis regulated glucose metabolism (Zampetaki and Mayr, 2012). Although more studies are necessary to validate the results, miRNAs are emerging as promising biomarkers in diabetes and possibly other metabolic diseases.

miRNA-based diagnostics in cardiovascular diseases

Organogenesis of the vertebrate heart is a highly specialized process involving progressive specification and differentiation of distinct embryonic cardiac progenitor cell populations driven by specialized gene programming events. miRNAs have been found to be critical modulators of normal heart development and cardiac function (Bernstein et al., 2003; Philippen et al., 2015; Zampetaki and Mayr, 2012). They are quantitatively altered in certain disease entities, such as myocardial infarction, atherosclerosis, coronary artery disease, heart failure, atrial fibrillation, hypertrophy, and fibrosis (Corsten et al., 2010; da Silva and Silbiger, 2014; Fichtlscherer et al., 2010). Tissue specific deletion of miRNA machinery gene Dicer in mice can cause lethal phenotypes in myocardial and vascular lineages (Albinsson et al., 2010; Chen et al., 2008a). A comprehensive analysis of miRNA and mRNA expression levels in myocardial samples from patients with end-stage heart failure showed that miRNAs are more sensitive than are mRNAs for determining the functional status of end-stage heart failure, which is thought to be consistent with the important functions of miRNAs in the myocardial response to stress (Matkovich et al., 2009). Differential miRNA profiles have been reported for diseases such as heart failure (Thum, 2007; van Rooij et al., 2006b), ischemic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis (van Rooij et al., 2006b). Circulating miRNAs have been reported to have great potential as biomarkers for myocardial infarction, and miR-1 and miR-208a have been proposed as biomarkers for cardiovascular diseases (Ai et al., 2010; Wang et al., 2010).

miRNA in other diseases

Many autoimmune diseases are classified as rheumatic diseases. Altered expression of miRNAs in the synovial tissue and synovial fibroblasts of patients with rheumatoid arthritis has been reported, and increased expression levels of miRNA miR-155 and miR-146a were found in rheumatoid arthritis (Stanczyk et al., 2008). Exosomal miRNA signatures from the salivary glands were proposed as biomarkers of Sjögren's syndrome as systemic autoimmune disease (Michael et al., 2010). Blood biomarkers can indicate liver damage (Haybaeck et al., 2011), such as increased levels of miR-122 in the plasma of patients with virus-, alcohol-, and chemical-induced liver disease, and miR-122 showed good sensitivity, specificity, and reliability for the diagnosis of these diseases in blood samples (Zhang et al., 2010b). Some dysregulated miRNAs in autosomal dominant polycystic kidney disease are complicated to play roles in pathogenesis and are candidate biomarkers of kidney disease (Ben-Dov et al., 2014).

miRNAs for in vitro diagnostics

In the past few years, various approaches have been used to detect miRNAs, including Northern blot analysis (Sempere et al., 2004; Valoczi et al., 2004), in situ hybridization analysis (Kloosterman et al., 2006), real-time PCR analysis (Chen et al., 2005; Wang et al., 2009), miRNA microarray (Thomson et al., 2004; Wang et al., 2014a), and NGS (Wang et al., 2015). Some miRNAs have already been validated as diagnostic or prognostic biomarkers in various malignant diseases, demonstrating their clinical utility and their potential in the field of personalized medicine and diagnostics.

However, most studies and approaches have not considered factors such as age, sex, or prior treatments, and circulating miRNA research has not resulted in highly specific, validated disease markers. Data reproducibility is also a problem, and the results obtained by the same profiling method are not always consistent (Sato et al., 2009). Accurately determining the level of expression of miRNAs in a specific cell type, tissue, or body fluid is an essential step toward the establishment of miRNA signatures as biomarkers for in vitro diagnostics. Moreover, data processing, careful optimization, and standardization of analytical methods, including pre-processing of miRNA detection experiments and normalization, are necessary to minimize experimental or technical variations and ensure that results, both positive or negative, are reliable (Meyer et al., 2010; Witwer, 2015). Thus, we need to minimize batch effects in different laboratories to improve the prospects for clinical research utility. Despite the promise of miRNA biomarkers in diagnosis, the markers that have been identified have, in many instances, had poor diagnostic specificity and reproducibility. The methods of miRNAs detection in well annotated samples and adequately quality controlled data processing will need to be standardized prior to the use of miRNAs for diagnostic purposes, which will be helpful for generating research hypotheses and also discovering informative biomarkers for in vitro diagnostics.

Conclusions

Several studies have shown that miRNAs are differentially expressed in diseased tissues and differentially enriched in plasma, serum and other body fluids, potentially making them useful for routine clinical diagnosis. Researchers have mainly focused on finding miRNA signatures that are representative of diseases, including cancer, viral infections, nervous system disorders, cardiovascular disorders, muscular disorders, diabetes, and other diseases, and several studies have been specifically designed to validate miRNAs as biomarkers and clarify their role in regulating physiological and pathological processes. However, a greater understanding of the biological characteristics of these miRNAs in these diseases is needed to improve their use as biomarkers. The main challenges in the use of miRNA signatures in in vitro diagnostics are discovering specific miRNAs that can be consistently used as specific and reliable “ideal” biomarkers for diseases in a broad range of patients and the development of simple and inexpensive detection methods.

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