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Non-coding RNAs as clinical biomarkers for cancer diagnosis and prognosis

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Developing more precise diagnostics approaches to predict cancer progression and prognosis is the key to precision medicine. Overwhelming evidence now suggests that small non-coding RNAs such as miRNAs can be useful tools as biomarkers for molecular diagnostics. miRNAs can serve as biomarkers in a variety of diseases, such as neurological disorders, cardiovascular disease, Type II diabetes, cancer and so on. miRNAs can not only be utilized for monitoring treatment but also for patient stratification and hence are promising predictive biomarkers in cancer progression and prognosis, as well as in predicting drug response. This article focuses on some of the recent findings in the field of miRNA biomarkers and discusses its implications for cancer diagnostics and precision medicine.

Small non-coding RNAs such as miRNAs are emerging as a new class of biomarkers. The cancer research field has been at the forefront of understanding miRNA biology and establishing miRNA as biomarkers for over a decade now [1]. This has been made possible not only by the availability of tumor tissue samples in the clinic but also recent advancements in the field of miRNA detection and sequencing technologies. miRNAs are now well established as regulators of tumorigenesis. In cancer, miRNA expression varies across different stages of tumor progression and its levels are altered (overexpressed/underrepresented) during malignancy [1,2]. Overexpressed miRNAs in cancer may act like oncogenes by downregulating tumor suppressor genes. The opposite is also true; down-modulated tumor suppressor-like miRNAs result in upregulation of oncogenes, thereby functioning as tumor suppressors. Hence, in a malignant tumor, the oncogenic miRNAs are upregulated and tumor suppressor miRNAs are downregulated, which can be exploited as a biomarker. miRNAs are also tissue specific and may be unique identifiers of tumor type and origin [3]. An increasing number of miRNAs have now been identified and utilized as prognostic miRNAs to predict drug response.

Circulating miRNAs in bodily fluids, such as plasma, blood and urine, are promising candidates as noninvasive biomarkers for cancer. Circulating miRNAs are secreted by cancer cells in the surrounding tumor microenvironment in microvesicles or exosomes. Circulating miRNA signatures have been identified as being associated with a variety of cancer types, such as ovarian cancer [4], gastric cancer [5], breast cancer [6], multiple myeloma [7], lung squamous cell carcinoma [8], brain cancer [9], prostate cancer [10] and Hodgkin's lymphoma [11]. For example, it has been shown that exosomic miRNAs, such as miR-21 and miR-29a, can be engulfed by the immune cells from surrounding cancer cells and can bind to Toll-like receptor 8 in the immune cells to induce secretion of interleukin-6 and TNF-α, which is associated with tumor growth [12,13]. Recently, it has been reported that Let-7 family members are secreted into the extracellular space via exosomes [5]. Furthermore, high levels of circulating miR-200 family members have been reported in epithelial ovarian cancer [14] as well as gastric cancer [15]. Moreover, the circulating miRNAs present a promising opportunity for cancer diagnostics and precision medicine.

EXPERT REVIEWS

Keywords: biomarker • circulating microRNAs • diagnostics • miRNA • miRNA polymorphisms • microvesicles or exosomes • pharmacogenomics • precision medicine • prognosis • variants

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Tissue slide-based assays to guide treatment options are routine in clinical pathological laboratories. Recently, tissue slide-based approaches have been developed for miRNA detection and their efficacy has been tested in pancreatic cancer. Changes in the levels of miRNAs between normal and tumor tissues in pancreatic cancer have been documented [16]. The pancreatic tissue is very diverse and only some pancreatic cells are prone to developing cancer. Hence, it is important to know the miRNA changes in the cancer-prone cells and not the normal cells. A tissue slide-based staining assay in a chemiluminescence immunoassay-certified environment was developed utilizing *in situ* hybridization to identify specific miRNAs' alterations (examples are miR-21 and miR-34a) in the pancreas of mice that develop pancreatic cancer. The technique could be potentially useful in measuring miRNA levels and their location within cellular compartments in pancreatic tissue and have potential diagnostic applications [17].

miRNAs have been identified as predictive biomarkers for many cancer types [1]. For example, in colorectal cancer, miR-215 was identified as suppressing the expression of both thymidylate synthase and dihydrofolate reductase and its expression was associated with colorectal cancer patient survival [18]. Another miRNA, miR-140, was found to modulate chemosensitivity by suppressing histone deacetylase 4 expression, and the levels of both miR-140 and miR-215 were elevated in colon cancer stem cells [19]. To predict metastasis and prognosis in clear cell renal cell carcinoma a 4-miRNA signature was identified [20,21]. Of interest, the signature can be validated on a formalin-fixed paraffin-embedded tissue and reverse transcription-polymerase chain reaction-based assay and serve as a predictive biomarker for clear cell renal cell carcinoma. Taken together, these few examples demonstrate that miRNAs can be utilized in predicting patients' prognosis and survival in the clinic.

Variants or polymorphisms in miRNA can be also utilized as tools for prognosis and progression of diseases and drug responses. These genetic variations are emerging as powerful tools to study biology of many diseases including cancer [22,23]. miRNA variants or polymorphisms (miR-polymorphisms) can be defined as polymorphisms (chromosomal changes, single nucleotide polymorphisms, mutations, alterations, variations and epigenetic defects) that may functionally interfere with miRNA-mediated regulation of cellular functions. These variations can be present not only in the miRNA target gene but also in pri-, pre-, mature-miRNA sequences, in the genes involved in miRNA biogenesis and in miRNA *cis*-regulatory elements (such as a promoter) [24]. Presumably, a polymorphism in a mature miRNA sequence may affect the expression of a number of genes and have deleterious effects on cell function. On the other hand, a variant in the target site of a miRNA may be more gene and/or pathway specific [24]. The discovery of the role of miRNA in drug resistance and miRNA variations to predict drug response has led to the development of a new field in biomedical science called miRNA pharmacogenomics, a study of the miRNAs and miRNA variants affecting expressions of drug target genes, to predict drug behavior and to improve drug efficacy. Taken together, the data suggest that detection of miRNA-polymorphisms can potentially improve diagnosis, treatment and prognosis in patients and has profound implications in the fields of pharmacogenomics and precision medicine [25].

In conclusion, the role of miRNA in tumorigenesis is now well established [1]. miRNAs can be exploited as novel biomarkers for the cancer diagnosis and prognosis and to predict drug response. Detection of circulating miRNAs (e.g., from blood, urine and so on) may present a noninvasive tool for cancer diagnostics. Technologies utilizing tissue slide-based miRNA detection methods may be useful in finding tissue specific localization of miRNAs. Finally, miRNA variants can be utilized to predict diagnosis, treatment and prognosis in cancer patients. Taken together, these new findings indicate that levels of miRNA in cancer can be utilized in developing a personalized anticancer therapy.

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