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Mini Review

Circulating MicroRNAs as Cancer Biomarkers: Can They Play a Role in Clinical Practice? Short Review

Abstract

microRNAs (miRNAs) are a large family of short noncoding RNA sequences which modulate gene expression and regulate a wide range of biological processes. There is evidence that miRNAs may have a role in molecular mechanisms linked to tumorigenesis and a lot of studies have proven that some miRNAs are closely correlated with cancer. miRNAs are not only contained in tissue cells but they are also detectable in extracellular sites, as plasma, urine, cerebrospinal and other body fluids where they are remarkably stable, so that may be identified and measured. Since tumors alter the normal concentrations of circulating miRNAs, these oligonucleotides can be used as cancer biomarkers. Circulating miRNAs detection may be used for early diagnosis, staging, follow up, assessment of therapeutic responses and therapy outcomes in several types of human cancer as colorectal cancer, pancreatic adenocarcinoma, lung cancer and malignant pleural mesothelioma, urinary and prostate cancer, breast cancer, hematologic malignancies, glioblastoma and others. Quantitative real-time Polimerase Chain Reaction (qRT-PCR) is one of the most sensitive techniques for quantifying circulating miRNAs. Deep sequencing technology has recently emerged as an attractive approach for miRNA analysis; in some cases this technique showed more specificity and sensitivity compared to qRT-PCR and Microarray, also allowing identification of novel MiRNA isoforms. Given that current serological cancer biomarkers, commonly employed in follow up, have low specificity and sensitivity, it is plausible that circulating miRNA detection can be included in future routine clinical examinations for management of cancer patients, although costs and wide availability of quantifying techniques could represent a critic limit. Further comparative studies will be required.

Introduction

microRNAs (miRNAs) are a large family of short noncoding RNA sequences [1] which modulate gene expression and regulate a wide range of biological cell processes [2].

There is evidence that miRNAs may have a role in molecular mechanisms linked to cellular pathways of certain diseases, as viral infections, diabetes and cardiovascular disease; moreover, miRNA have been shown to regulate several processes involved in tumorigenesis [2-5].

miRNAs are not only contained in tissue cells but they are also detectable in extracellular sites, as plasma, urine, cerebrospinal and other body fluids; miRNAs are carried in body fluids within small membrane vesicles (exosomes), in the form of high-density lipoprotein complexes, or complexed to carrier proteins (argonaute-2 proteins). Extracellular microRNAs in exosomes may be transferred to other cells, altering gene expression and changing the functional effects of receivers [6-8].

The presence of endogenous miRNAs in microparticles makes circulating miRNAs remarkably stable in the bloodstream even under conditions as harsh as boiling, low or high pH, long-time storage at room temperature, and multiple freeze-thaw cycles, so that they may be identified and measured in the circulation and can be used as potential disease biomarkers [5].

A lot of studies have proven that expression of some miRNAs is closely correlated with cancer development and altered levels of miRNA have been related to the maintenance of cancer stem cells, neoangiogenesis, metastasis and epithelial-mesenchymal transition, which contribute to the malignancy [9-11]. It has also been shown that microRNAs may be responsible for other biological processes, such as cancer-associated inflammation and tumor drug resistance [12].

Aim of the Research

The purpose of the present review was to examine the latest evidences on circulating miRNAs as cancer biomarkers and evaluate whether the detection of these nucleotides can play a role in daily clinical practice.

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Material and Methods

A review of recent literature has been carried out via Pub Med database, using these search term: microRNA, cancer biomarkers, clinical practice. Search was not limited by language or human subjects. All the found items, published in the last five years were analysed. Additional articles were selected from the bibliographies of the quoted references.

Results

91 items were obtained: 55 reviews (9 systematic reviews), 4 meta-analysis, 2 clinical studies, 1 randomized phase III clinical trial, 1 editorial, 1 comment; 35 items were research support and 14 were laboratory studies; the remaining items were prevalently other journal articles or other publication types. Comparative studies were not found, neither laboratory trials nor guidelines nor consensus. Article types was determined using filters available on Pub Med database. Other data were deduced from retrospective analysis and by careful assessment of the obtained items and their references.

The analysis of obtained data showed that a lot of miRNA is associated with cancer and many types of miRNA have been identified in several types of human cancer, as summarized in Table 1.

There is wide evidence that tumors alter the normal concentrations of miRNAs in biological fluid, thus these oligonucleotides may serve as cancer biomarkers. These findings will be discussed in this brief review with related references.

In cancer management, circulating miRNAs detection may be used for early diagnosis, cancer staging, prognosis and patient follow up to individuate early relapses; moreover, there are promising data to extend this assay for predicting specific therapeutic responses and also to assess therapy outcomes (Table 1).

Discussion

microRNAs (miRNAs) are a large family of short noncoding RNA sequences, approximately 20-22 nucleotides, synthesized in the nucleus, through a complex multi-step biosynthetic process, starting from RNA polymerase II; it is estimated that the human genome contains more than 2500 mature miRNAs [1,2].

These nucleotides modulate gene expression, by binding the 3′-untranslated region of target messenger RNA (mRNA), both degrading mRNA and inhibiting translation into protein. miRNAs regulate a wide range of biological processes as cell differentiation, proliferation and development, cell-to-cell communication, cell metabolism and apoptosis [2,3].

In 2002, for the first time, the link between miRNA and cancer was reported in patients with B-cell chronic lymphocytic leukemia; in these patients was found a down-regulation of miR-15a and miR-16-1 [13]. Subsequently, a lot of studies have proven that expression of some miRNAs is closely correlated with cancer development and some miRNAs can function as oncogenes or tumor suppressors. Indeed, there is evidence that some of these oligonucleotides act as oncogenes (oncomiRs) and their overexpression leads to cancer growth; conversely, other miRNAs are tumor suppressors (anti-oncomiRs) in normal cells, so that their underexpression correlates with tumor progression [9-11].

Since miRNAs are also detectable in extracellular sites, as plasma and other body fluids where they may be measured and since tumors alter the normal concentrations of circulating miRNAs, these oligonucleotides can be used as biomarkers for cancer detection [14].

The study of miRNA has thus become a rapidly emerging field in oncology and the detection of miRNA expression is a very important first step in miRNA exploration.

Several techniques are available for quantifying circulating miRNAs, such as quantitative real-time Polimerase Chain Reaction (qRT-PCR) [15], Northern blotting [16], bead-based flow Cytometry [17], Microarray [18] or Deep sequencing [19]. However, of these assay, qRT-PCR seems superior because of its high sensitivity, specificity and reproducibility; moreover qRT-PCR requires less amount of RNA sample, usually more than 1 μg, but the number of miRNAs possible to analyze and RNA quantity may represent limitations for this assay [15]. Conversely, Deep sequencing technology has recently emerged as an attractive approach for miRNA analysis; in some cases this technique showed most specificity and sensitivity compared to qRT-PCR and Microarray, also allowing identification of novel miRNA isoforms [20]. Actually, it is well known that a single gene may, in turn, be regulated by multiple miRNAs, therefore, given the large number of miRNAs annotated in the human genome, 30%–80% of human genes are predicted to be influenced by miRNAs. Moreover, a single miRNA influences the expression of hundreds of unique miRNAs and aberrant miRNA expression may affect a multitude of transcripts and profoundly influence cancer-related signaling pathways. This situation generates a complex network, and the analysis of miRNA panels is consequently more efficient in cancer studies than the analysis of a single miRNA [21].

Thanks to these analysis methods and techniques that allow measurement of multiple miRNA types, these circulating nucleotides may be used for early diagnosis, staging, follow up, assessment of therapeutic responses and therapy outcomes in several types of human cancer as colorectal cancer, pancreatic adenocarcinoma, bladder cancer, lung cancer and malignant pleural mesothelioma, urinary and prostate cancer, breast cancer, hematologic malignancies, glioblastoma and others [22].

Currently, conventional cancer biomarkers commonly utilized in clinical practice as, carbohydrate antigens, oncofetal antigens, hormones, enzymes, tissue polypeptide antigen and others, are usually employed in follow up of cancer patients; however they have low specificity and sensitivity so that monitoring disease is, perhaps, the most common clinical use of these tumor markers [23-26]. Thus miRNA detection could be a new effective tool in the clinical management of cancer.

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Table 1: miRNAs in different types of cancer and their clinical significance.

miRNA	Cancer	Aim
miR-: 17-3p; 106a; 21, 29a, 125b	Colorectal	Diagnosis; Prognosis; Therapy Outcome
miR-: 126; 141; 21	Colorectal	Dignosis; Liver Metastasis
miR-: 18a; 20a; 21; 29a; 92a; 106b; 133a; 143; 145; 181b; 342-3p; 532-3p; 193a-3p; 23a; 338-5p; 19a-3p; 223-3p; 92a-3p; 422a	Colorectal	Early Diagnosis
miR-19a	Colorectal	Therapeutic Outcome
miR-: 29c; 429; 1; 20d; 486; 499; 652; 660	Lung	Diagnosis
miR-: 193b;301; 141; 200b; 92a; 486-5p; 566; 98; 30b; 30c; 32; 328; 331-3p; 342-3p; 374a; 376a; 432; 484; 148a; 148b; 17; 191; 223; 26a; 26b; 28-5p; 29a; 103; 126; 133b; 139-5p; 140-5p; 142-3p; 142-5p; 22; let-: 7a; 7b; 7d;	Lung	Early Diagnosis
miR-: 101; 25; 26b; 335; 433; 191; 223; 29a; 516	Pleural mesothelioma	Diagnosis; Staging; Prognosis
miR-103a-3p	Pleural mesothelioma	Diagnosis; Differential Diagnosis
miR-: 21; 126	Pleural mesothelioma	Diagnosis
miR-: 125; 99a	Bladder	Diagnosis, Prognosis
miR-: 210; 10b; 29c	Bladder	Diagnosis
miR-: 152; 148b-3p; 3187-3p; 15b-5; 27a-3p; 30a-5p	Bladder	Early Diagnosis
miR-: 200c; 125b; 30c; 141; 375; Let-7c	Prostate	Diagnosis
miR-: 103; 107; 130b; 106a; 26b; 451; 223; 93; 24; 30c; 874; 100; 146a; Let-7a	Prostate	Prognosis; Differential Diagnosis
miR-: 1; 92a; 133a; 133b; 145; 155; 382; 145; 451; 148b; 409-3p; 801	Breast	Diagnosis
miR-: 18b; 103; 107; 652	Breast	Prognosis
miR-21	Glioblastoma	Diagnosis
miR-: 128; 342-3p	Glioblastoma	Diagnosis; Prognosis
miR-: 10b; 21; 141; 200a; 200b; 200c	Glioblastoma	Differential Diagnosis
miR-: 15a; 16-1; 29c; 34a MiR-155	Large B-Cell Lymphoma	Diagnosis
miR-: 21; miR-210 MiR-155	Large B-Cell Lymphoma	Prognosis
miR-: 199b-5p; 301b; 326; 361-5p; 625; 655	Adult Acute Myelod Leukemia	Diagnosis; Therapy Outcome
miR-: 10a-5p; 93-5p; 129-5p; 155-5p; 181b-5p; 320d	Adult Acute Myelod Leukemia	Prognosis; Follow Up

The current methods used for miRNAs detection usually requires high costs and this aspect could limit their use in daily clinical practice. However, in this way, research should try to overcome this limiting aspect, although spending review in health care and cost-containment measures could represent a critical ethical problem in a delicate field as oncolgy [27].

In our research we have not found comparative studies, in terms of specificity, sensibility and costs, between miRNAs and other conventional cancer biomarkers commonly used in clinical practice. It is desirable that, in future, comparative studies will be undertaken.

Conclusion: circulating miRNAs detection may be used for early diagnosis, staging, follow up, assessment of therapeutic responses and therapy outcomes in several types of human cancer. Given that current serological cancer biomarkers, commonly employed in follow up, have low specificity and sensitivity, it is plausible that circulating miRNA detection can be included in future routine clinical examinations for management of cancer patients, although costs and wide availability of quantifying techniques could represent a critic limit. Research should try to overcome this limiting aspect by developing less expensive detection techniques and by initiating comparative studies. Particularly, new low-cost and non-invasive cancer biomarkers need to be developed to improve screening protocols and therapy and to provide information on chemoresistance and the risk of relapses.

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