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REVIEW

Circulating miRNAs as biomarkers for endocrine disorders

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Abstract Specific, sensitive and non-invasive biomarkers are always needed in endocrine disorders. miRNAs are short, non-coding RNA molecules with well-known role in gene expression regulation. They are frequently dysregulated in metabolic and endocrine diseases. Recently it has been shown that they are secreted into biofluids by nearly all kind of cell types. As they can be taken up by other cells they may have a role in a new kind of paracrine, cell-to-cell communication. Circulating miRNAs are protected by RNA-binding proteins or microvesicles hence they can be attractive candidates as diagnostic or prognostic biomarkers. In this review, we summarize the characteristics of extracellular miRNA's and our knowledge about their origin and potential roles in endocrine and metabolic diseases. Discussions about the technical challenges occurring during identification and measurement of extracellular miRNAs and future perspectives about their roles are also highlighted.

Keywords Circulating microRNA · Biomarker · Endocrine tumor

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Introduction

MicroRNAs (miRNAs) are small, protein non-coding RNAs that regulate gene expression post-transcriptionally, through RNA interference by targeting mRNAs at the 3′, 5′ untranslated regions or even the coding sequence [1–4]. The 60–70 nucleotide (nt) primary miRNAs are generated through transcription by RNA polymerase II, which then are cleaved to the shorter precursor miRNAs (pre-miRs) by Drosha. The pre-miRNA molecule is transported to the cytoplasm by Exportin-5 and processed by another RNase III enzyme (Dicer). The product is an approximately 21 nt miRNA:miRNA* duplex, one strand of which is incorporating into miRNA-induced silencing complex (miRISC) [5]. In the miRISC complex, through base pair alignment miRNAs cause translational repression, mRNA destabilization or mRNA cleavage. The other strand (passenger strand or miRNA*) is usually degraded [6]. It is thought that approximately 30–50 % of all protein-coding genes might be controlled by miRNAs [7, 8]. One miRNA potentially affects the expression of several proteins, and one protein is influenced by numerous miRNAs. Their role is considered to set the gene expression to the optimal level, or with other words to provide "fine tuning" and adaptive setting of gene expression [9].

Their roles have been demonstrated in the regulation of various physiological and pathophysiological cellular processes such as proliferation, differentiation, metabolism and apoptosis. Differential miRNA expression in endocrine disorders including malignancies has also been reported [10–13].

MiRNAs as biomarkers in extracellular fluids ("cell-free systems") recently have been investigated and linked to diagnosis, prognosis and recurrence detection [14, 15]. Many reports showed correlations between miRNAs dysregulation in the peripheral blood and pathophysiological

conditions. Related to endocrine diseases, dysregulated miRNAs have been described in diabetes mellitus [16], in disorders affecting reproductive tissues [17], vitamin D signaling and bone [18], thyroid [19, 20], adrenal [21] and pituitary gland [22]. miRNAs have also been implicated in developmental processes of pituitary through regulating Lef-1 transcription factor [23], in pancreas through HES-1 and neurogenin 3 [24, 25] and in the female reproductive system as well [26]. In addition, expression of mature miRNAs, genetic variations and polymorphisms of miRNAs encoding genes were associated with the prognosis and/or progression of diseases and drug responses [27–30].

A new chapter in miRNAs-related research has been starting by their identification outside from cells, in biofluids. These extracellular miRNAs have been considered as a novel type of signaling molecules and being secreted and taken up by various cells they may indeed function similarly to hormones or cytokines. In this review we present recent data about the origin and function of these extracellular miRNAs focusing on endocrine and metabolic diseases.

Extracellular (EC) miRNAs

Origin and function

Extracellular miRNAs have been detected in a wide variety of body fluids such as serum, plasma, urine, saliva, tears, peritoneal, pleural and cerebrospinal fluid, bronchoalveolar lavage, breast milk, amniotic and seminal fluid [31].

Unprotected “naked” miRNAs are sensitive to degradation mainly through RNAses present in large amount in these fluids. Protection of miRNAs against RNases is provided by association of miRNAs with Argonaute (AGO) proteins and by packing them in microvesicles [32, 33] (Fig. 1). AGO proteins have been demonstrated in microvesicles as well suggesting their essential role in miRNA’s protection [34]. Microvesicles are secreted by nearly all kinds of cell such as like neural, stem cells, epithelial cells, dendritic cells and lymphocytes [35–40].

The term microvesicle is often used generally for any type of vesicle regardless of the size or its origin. Exosomes are small (approximately 30–100 nm) membrane-limited secreted vesicles [41]. They are formed in the endosomal compartments of cell (multivesicular endosomes or MVEs). In this compartment, extracellular molecules are stored, released or degraded by fusing with lysosomes after endocytosis. Exosomes can be released by fusion of the multivesicular endosomes with the plasma membrane [41]. Cells can release other types of vesicles as well by directly budding or shedding off the plasma membrane. These vesicles are also referred as microvesicles, shed vesicles, or ectosomes but their size is more variable (typically between 50 and 1000 nm) than the exosomes. Both exosomes and other microvesicles contain various molecules including mRNA, miRNA, proteins, cytokines and different surface receptors specific for their cell origin [42].

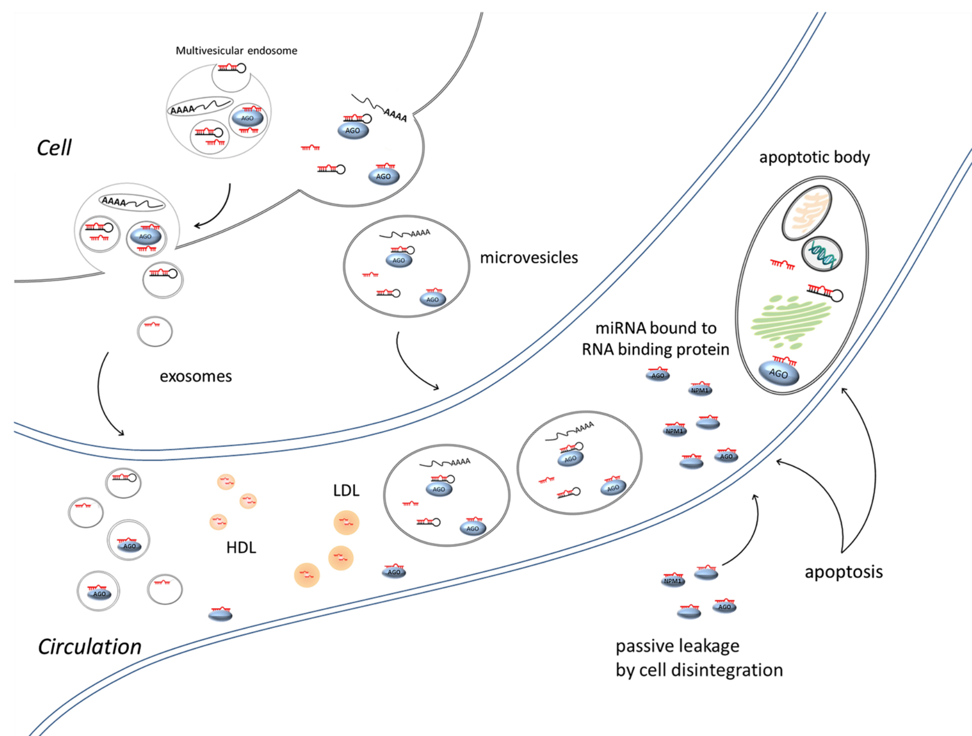

Fig. 1 Extracellular microRNAs in circulation. See detailed description in the text

Beside exosomes and microvesicles, several miRNAs were found in high-density lipoprotein (HDL) particles and, therefore, their extracellular uptake by the host cells is dependent on the presence of HDL receptors [34].

It is described that one part of the extracellular miRNAs is byproduct of cell death, and it is also shown that the amount of miRNAs correlates with cell death in vitro [34]. But, interestingly, not all mRNA molecules were found in exosomes, and literature data suggest that different RNA species can specifically be packaged by active sorting [35, 43, 44].

The function of microvesicles is still not yet clear; however, more and more studies proved their significant role in cell–cell communication in immunology and tumor biology. Exosomes secreted by dendritic cells carry antigens and are able to induce immune response [39]. They can mediate paracrine signals of cancer cells as well influencing tumor microenvironment by exosome secretion in promoting growth by inhibiting antitumor immune response and by facilitating angiogenesis, cell migration and metastasis [45–49]. Exosomal miR-21 and miR-29a were described to be internalized by immune cells surrounding cancer cells where they bind as ligands to the Toll-like receptor (TLR) family (TLR7 in murine and TLR8 in human) triggering a TLR-mediated prometastatic inflammatory response that ultimately may lead to tumor growth and metastasis [50]. Interestingly, tumor cells were found to exhibit self-promoting effect by secreting microvesicles in glioblastoma and renal cancer cell lines [49, 51]. On the other hand, it was also described that metastatic gastric cancer cells can eliminate tumor suppressor miRNAs by exosome secretion [52]. Taking these data together it is reasonable to hypothesize that in a malignant tumor overexpressed, oncogenic and downregulated tumor suppressor miRNAs can be exploited as potential biomarkers. As miRNAs are also tissue specific they may be unique identifiers of certain tumor types [27], and if they secreted they could be specific biomarkers to a certain diseases.

Extracellular miRNAs as biomarkers

MiRNAs are found to be very stable in extracellular fluids and miRNA levels were demonstrated to be reproducible across individuals, robust against enzymatic cleavage, thawing–freezing cycles or pH changes [53–55].

The major source of extracellular miRNA in blood is obviously the blood and endothelial cells; however, tissue-specific miRNAs, i.e., miR-122 from the liver, miR-124 from the brain or miR-208b from the heart [56–58] are also detectable in the blood.

Tissue-specific miRNAs as biomarkers have been linked to tissue injuries, as miR-499 and miR-208b specific for myocardial infarction or mir-122 for the drug-induced liver injury [57, 58]. Thus in malignant diseases, tumor-associated miRNAs were found in serum of patients with hematological diseases and in patients with solid tumors as well. For instance, the serum levels of miR-141, a miRNA expressed in prostate cancer, could distinguish prostate cancer patients from healthy individuals [55]. However, it is still not clear if extracellular miRNAs are derived from the tumor directly or derived from non-malignant cells as a response to cancer for instance from white blood cells or tumor-reactive immune cells [34].

The level and composition of extracellular miRNAs have been shown to correlate well with disease progression, i.e., miR-221 in renal cell carcinoma, let-7f and miR-30e-3p in breast cancer [15, 59] or to predict biochemical recurrence in prostate cancer patients [60] or response to chemotherapy in esophageal cancer [61].

Serum biomarkers in endocrine diseases

Microvesicles containing miRNAs can mediate autocrine, paracrine signaling and also can be transported substantially longer distances via the circulatory system, hence they can be considered as a new kind of hormone-like entities. In this part, we summarized the data about circulating miRNAs and their associations found in endocrine and metabolic diseases.

In diabetes and metabolic disorders, Guay and Regazzi excellently reviewed the role of circulating miRNAs [62]. In brief, in diabetes mellitus type 2 (T2DM), Zampetaki and colleagues found that reduced miR-15a, miR-29b, miR-126, miR-223, and elevated miR-28-3p levels preceded the manifestation of disease [63]. Another study performed by Kong et al. showed that 7 serum miRNAs (miR-9, miR-29a, miR-30d, miR34a, miR-124a, miR146a and miR-375) were significantly upregulated in patients with T2DM compared with patients having normal glucose tolerance (NGT) and five (miR-9, miR-29a, miR-34a, miR-146a, miR-375) were significantly upregulated in patients with T2DM compared with patients having pre-diabetes [64]. However, the authors could not show difference between NGT and pre-diabetes groups regarding these miRNAs [64]. Karolina et al. reported increased expression of miR-150, miR-192, miR-27a, miR-320a, and miR-375 in T2DM and metabolic syndrome compared to healthy individuals [65]. Expression of miR-27a and miR-320a displayed a strong positive correlation with fasting glucose level, thus highlighting their potential as key players in early-phase hyperglycemia, which could eventually result in the development of diabetes over time. Beside these miRNAs, miR-17 was found to be downregulated in T2DM, and the authors suggest a stronger implication of miR-17 in fully manifested diabetes, instead of early-phase dysglycemia as seen in patients having metabolic syndrome [65]. They found miR-144 to

be upregulated in T2D, but metabolic syndrome [65]. Zhang et al. found that the expression of miR-126 was significantly reduced in patients with T2DM and pre-diabetic individuals with fasting glucose between 6.1 and 6.9 mmol/L compared to healthy controls [66]. They proposed that miR-126 in circulation could serve as a potential biomarker for early identification of susceptible individuals to T2DM.

In type 1 diabetes mellitus (T1DM), Nielsen and colleagues identified twelve upregulated miRNAs (miR-152, miR-30a-5p, miR-181a, miR-24, miR-148a, miR-210, miR-27a, miR-29a, miR-26a, miR-27b, miR-25, miR-200a) in sera of children with newly diagnosed disease [67]. They also found miR-25 as being negatively associated with residual beta cell function, and positively associated with glycaemic control (HbA1c) 3 months after onset. The authors suggest that miR-25 might be a "tissue-specific" miRNA for glycaemic control.

However, not in serum but in blood lymphocytes, miR-326 was described to be overexpressed in T1DM subjects with ongoing islet autoimmunity compared to controls by Sebastiani et al. [68]. Similarly, not in cell-free serum, but in peripheral blood mononuclear cells miR-21a and miR-93 were shown to be downregulated in T1DM patients [69]. Based on in vitro and in vivo experiments, circulating miR-375 was identified as a biomarker of β cell death and diabetes in mice by Erener et al. [70]. Increased miR-375 level was detected after high-dose streptozotocin (STZ) administration, prior to the onset of hyperglycemia both in vitro and in vivo mice experiments.

Related to patients having metabolic syndrome, several circulating miRNAs were also identified in serum. miR-197, miR-23a, and miR-509-5p appeared as potential contributors of dyslipidemia in metabolic syndrome and miR-130a and miR-195 as contributors of hypertension (expression of these miRNAs correlated with blood pressure; $p = 0.019$ and 0.045, respectively) [65]. Decreased miR-221 and miR-28-3p and increased concentrations in plasma of miR-486-5p, miR-486-3p, miR-142-3p, miR-130b, and miR-423-5p were reported in childhood obesity [71]. Another study also found elevated miR-130b in a mouse model of obesity as well as in obese individuals. The authors showed that miR-130b was secreted during adipogenesis and was able to target muscle cells and reduce the expression of its direct target gene, PGC-1α (also known as PPARGC1A), which plays a key role in lipid oxidation in muscle. It is claimed that circulating miR-130b reflects the degree of obesity and could function as a metabolic mediator for adipose–muscle crosstalk [72].

Altered circulating miRNA expression was linked to non-alcoholic fatty liver disease (NAFLD). It was shown that serum levels of miR-122, miR-34a and miR-16 were significantly higher in patients with NAFLD compared to controls and positively correlated with disease severity [73]. The expression of these two miRNAs also correlated with liver enzymes levels, serum lipids, fibrosis stage and inflammation activity in NAFLD patients [73]. Vickers et al. reported that human HDL-miRNA profile of normal subjects is significantly different from that of individuals with familial hypercholesterolemia [74]. HDL containing miRNAs (miR-223 and miR-375) from atherosclerotic subjects induced differential gene expression with decrease of RhoB and Ephrin A1 in cultured hepatocytes [74]. Based on these results miRNAs embedded in HDL molecules can be delivered to the liver and mediate gene expression regulation.

Endocrine tumors

Compared to other tumor types in endocrine tumors, there is still a lot of opportunity to investigate extracellular miRNAs. There are several publications showing miRNA expression data in neuroendocrine tumors (NET) [75, 76], but there is a lack of information regarding, e.g., pituitary adenomas and pheochromocytomas. Serum miR-1290 was found to be overexpressed but statistically not significantly in pancreatic NET compared to normal controls (Table 1); however, it was able to discriminate pNETs from pancreatic cancer with 0.80 (95 % CI 0.67–0.93) AUC characteristic [77].

Regarding thyroid neoplasms, Yu et al. published that the expression of serum let-7e, miR-151-5p and miR-222 was increased in papillary thyroid cancer (PTC) compared to benign lesions and healthy controls [78]. The ROC analysis of the combination of these three miRNAs in discriminating PTC from benign nodules and healthy controls showed 0.917 and 0.897 AUC values, respectively. Moreover, the serum let-7e, miR-151-5p and miR-222 expression correlated well with nodal status, tumor size, multifocal status and TNM stage. Increased expression of miR-151-5p and miR-222 was detected in the tumor tissues as well, and in serum the level of the two miRs decreased after tumor excision [78].

In another study, Lee et al. also published that miR-222, beside miR-146b, was overexpressed in PTC compared to healthy individuals [79]. Also, these two miRs' expressions in the plasma were higher in recurrent PTCs compared to non-recurrent disease. It was also described that miR-222 and miR-146b levels dropped in plasma following total thyroidectomy [79]. Another publication of this group showed that miR-146b and miR-155 were expressed at a higher level in plasma of patients having PTC compared to benign thyroid nodules [80]. They also found that miR-146b, miR-155 and miR-222 were slightly higher in patients with lymph node metastasis than in patients without lymph node involvement [80]. The third study identified miR-579, miR-95,

Table 1 Circulating miRNAs in endocrine tumors

Endocrine tumor	miRNA	miRNA level in disease	Comparison	Serum/plasma	References
Pancreatic neuroendocrine tumor (pNET)	miR-1290	iIncreased, but not significant	pNET vs. healthy control	Serum	[77]
Papillary thyroid carcinoma (PTC)	let-7e, miR-151-5p, miR-222	Increased	PTC vs. benign lesion/healthy control	Serum	[78]
Papillary thyroid carcinoma (PTC)	miR-222, miR-146b	Increased	PTC vs. healthy control; recurrent vs. non-recurrent PTC; pre- vs. postoperative patients	Plasma	[79]
Papillary thyroid carcinoma (PTC)	miR-146b, miR-155	Increased	PTC vs. benign lesion		[80]
Papillary thyroid carcinoma (PTC)	miR-579, miR-95, miR-29b	Decreased	PTC vs. benign lesion/healthy control	Serum	[81]
	miR-190	Increased			
Adrenocortical carcinoma (ACC)	miR-34a, miR-483-5p	Increased	ACC vs. ACA (adrenocortical adenoma)	Serum	[82]
Adrenocortical carcinoma (ACC)	miR-100, miR-181b, miR-184, hsa-miR-210, hsa-miR-483-5p	Increased	ACC vs. ACA (adrenocortical adenoma)		[83]
Adrenocortical carcinoma (ACC)	miR-195, miR-335	Decreased	ACC vs. ACA and healthy control	Serum	[84]
	miR-483-5p	Increased	detected only in aggressive ACC	Serum	

miR-29b as being downregulated and miR-190 upregulated in serum of PTC patients compared to patients with nodular goiter (NG) and healthy controls [81]. By combining expression data of miR-95 and miR-190, the authors developed a multivariate risk model which was able to differentiate PTC samples from NGs with 0.99 AUC [81]. In addition, miR-579 and miR-95 were significantly downregulated in PTC compared with NG, while miR-190 was upregulated in PTC both at tissue level and in serum samples.

Regarding adrenal neoplasms, several studies showed that adrenocortical cancer-specific miRNAs miR-34a and miR-483-5p were able to differentiate adrenocortical carcinoma (ACC) from adrenocortical adenomas (ACA) [82]. Moreover, they observed miR-34a and miR-483-5p secretion by ACC cells to cell culture media. Szabó and colleagues reported that the difference between expression of miR-210 and miR-181 [(dCT(miR-210)-dCT(miR-181b)] and the ratio of dCT(miR-100)/dCt(miR181b) could be used with high diagnostic accuracy in differentiating ACC from ACA [83]. In a third publication, Chabre et al. showed that miR-195 and miR-335 levels were decreased in both tumor tissues and serum samples compared to ACA patients or healthy controls [84]. They also found that miR-483-5p, which was markedly upregulated in ACC patients compared to ACA, was detectable only in the serum obtained from patients with aggressive ACC [84]. They also showed that high miR-483-5p and low miR-195 circulating levels were associated with shorter recurrence-free and overall survival, hence the authors claimed that these miRNAs could be used as a prognostic biomarker for clinical outcome of ACC patients. In all three studies, miR-483-5p was found to be upregulated in ACC patients; therefore, it is probably a very useful, non-invasive biomarker candidate for this very aggressive cancer.

In pituitary tumors, several targets have been validated at tissue level. For instance PTEN, BMI1, E2F1 in growth hormone-producing adenomas, SMAD3 in non-functioning adenomas and PRKCD in ACTH-secreting tumors have been proved to be targeted by several miRNAs [85–88]. Also, there are genes like HMGA1-2, WEE1, AIP, CCNA2 that are controlled by miRNAs in more than one pituitary adenoma type as well [89–92]. However, several miRNAs were identified correlating with clinical features such as tumor size [87, 93], disease recurrence [94] or treatment [95–97], there is no study yet profiling circulating miRNAs (or exosomes) as biomarkers in pituitary adenoma patients based on literature search [98]. However, Wang et al. investigated the plasma levels of three miRNAs (miR-21, miR-128 and miR-342-3p) in 10 pituitary adenoma specimens as control for identifying biomarkers for glioma, but those were proved to be specific only in glioma patients [99].

In patients with pheochromocytoma miR-483-5p, miR-183, and miR-101 were proved to be diagnostic markers for

distinguishing malignant from benign pheochromocytomas at tissue level [100]. Though these miRNAs were detectable in patients' serum as well, their expression level was too low to obtain significant difference [100]. This study draws our attention to summarize those technical considerations which have to be considered during studying extracellular miRNAs.

Technical considerations

In general, an ideal marker should be easily measured by non-invasive sample collection. Therefore, blood and urine are the most commonly used matrixes used in laboratory testing. The marker should be specific to the pathologic condition bearing clinically acceptable (high) specificity and sensitivity and relatively inexpensive to quantify. Biomarkers that can be used to stratify disease and assess therapy response or disease progression are also valuable.

Compared to messenger RNAs, miRNAs are more stable and, therefore, they are attractive potential biomarker candidates. However, there are some inconsistencies among the results of different studies which may be related to different sampling, different detection techniques and/or selection of internal controls.

There is no clear recommendation whether serum or plasma is more suitable for investigating extracellular miRNAs. However, a higher miRNA concentration was observed in serum compared to the corresponding plasma samples. The difference between serum and plasma miRNA concentrations showed some associations with miRNA originated from platelets suggesting that the coagulation process may affect the spectrum of extracellular miRNA in blood [101]. Because a large amount of miRNAs are present in blood cells, it is important to avoid cell contamination and disruption, such as hemolysis. In this latter case, miRNAs characteristic to red blood cells can appear in the sample and may bias the miRNA expression profile [102].

To date, there are no standardized protocols for miRNA extraction from biofluids or quality/quantity assessment of the purified RNA either. Different, even commercially available extraction kits are available for cell-free total RNA extraction from biofluids. According to microvesicles, the most common used methods are differential centrifugation, combining ultracentrifugation and nanomembrane ultrafiltration. Extraction from cell-free body fluids usually yields very low RNA concentrations especially in case of urine or cerebrospinal fluid. Nanospectrophotometry is greatly affected by RNA concentration, and these low-concentration samples often do not pass through the conventional RNA quality criteria (A260/A230 and A260/A280). Even so, they typically perform well in real-time quantitative PCR (RT-qPCR) experiments.

Recent years resulted in several high-throughput techniques such as miRNA microarrays, PCR arrays or next generation sequencing which may be useful for an initial screening for identification of the miRNome expression profile and for selection of the specific biomarker candidates. However, regarding cell-free biofluids, they require a large volume of starting material. The analysis of miRNA expression by sequencing is challenging because the sequences are short, and there is a high homology among members of miRNA families (sometimes only one base difference), hence it is hard to achieve high sensitivity and specificity. The most widely accepted "gold standard" method is a two-step approach using looped miRNA-specific reverse transcription primers and TaqMan probes.

Another key factor in miRNA expression measurements is the reference standard. A proper endogenous control should be the same biotype molecule, stable, abundant and expressed irrespective of biological variance and medical conditions. A valid normalization could help to minimize the technical differences and remove systemic bias among different studies. Different small nuclear RNA (RNU) molecules or miR-16 are often used as endogenous control; however, lacking a valid housekeeping normalization by input volume is also applied using different spike-in controls [77, 103–105]. It is worth noticing that the same starting volume does not guarantee equal amount of RNA/miRNA content. For instance, the purified RNA yield can differ among samples from different individuals which make the normalization even more complicated.

Conclusion and future perspectives

Specific, sensitive, non-invasive and cheaply detectable biomarkers are always needed in diagnosis of diseases. Circulating miRNAs can be actively secreted and delivered to distant cell types. In this context, they can be considered as a new type of paracrine regulators, and a miRNA-mediated cell–cell communication can be hypothesized. Extracellular miRNAs are detectable in malignant diseases hence they can be diagnostic or prognostic biomarkers. To date, only limited data are available about the true diagnostic power of extracellular miRNAs. Harmonization of extraction and quantification methods is essential in identification of clinically significant miRNAs. In the future, there is still a need to improve simple standard assays for quantification, establish the specificity and sensitivity by comparing miRNA expressions among different types of cancer and healthy or pathological conditions.

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Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval All procedures performing in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent of the present retrospective study was waived.

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