Review

MicroRNAs as emerging diagnostic and prognostic marker in cancer biology and therapy

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ABSTRACT

MicroRNAs (miRNAs) contribute to cellular homeostasis and differentiation in many ways, and therefore play an important role in many pathophysiological events. The knowledge of small non-coding RNA molecules has developed our understanding towards basic processes of cancer biology and the molecular mechanisms underlying tumor initiation and progression. MiRNA research field has grown to be more and more attractive as evidence is emerging that miRNAs possibly play vital regulatory roles in all fundamental biological processes. Notably, as research continues to reveal the mechanisms underlying cancer therapy efficacy, it is apparent that miRNAs contribute to responses to drug therapy and are themselves modified by drug therapy. One important field for miRNA research is to identify functions of miRNAs and the associated signaling pathways in the initiation, progression, metastasis and drug-resistance of tumors in order to propose novel, efficient target based therapeutics that directly target pathologically essential miRNAs and their allied target genes. Currently, miRNA signatures have increasing importance and use in the diagnosis and prognosis of various types of cancers. In this review, we have highlighted the role of various miRNAs in various cancers and other disease so that future of miRNA research will provide more interesting outcomes in terms of therapy and cure. JMS 2016; 19(2):47-58

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INTRODUCTION

MicroRNAs (miRNAs) are small non-coding RNAs that vary in size from 19 to 25 nucleotides. They are endogenous, stable, conserved and play an important role by targeting mRNAs for translational suppression or degradation. MiRNAs were first discovered in 90s, since then at least two thousand human miRNAs have been identified and classified, which have been proven to play an essential part in various biological processes i.e. cell proliferation, cell cycle progression, apoptosis and differentiation¹. Additionally, microRNAs include one of the most abundant classes of gene regulatory molecules in multicellular organisms and probably influence the output of many genes encoding proteins. Furthermore, promising confirmation suggested a wide range of essential cellular processes such as cell proliferation, progression, growth,

mobility, metastasis and apoptosis, as well as carcinogenesis. The expression patterns of microRNAs exhibited a relationship with characteristic clinico-pathological parameters in cancer subtypes thereby highlighting microRNAs as promising diagnostic and prognostic biomarkers for different human cancers. Moreover, in various cancers, large number of miRNAs have been identified and they are known to be involved in modulating cancer cell characteristics and behavior². It has been observed that miRNAs dysregulation is responsible for the pathogenesis of majority of cancers starting from initiation to metastatic phase³. Moreover, circulating miRNAs are reproducible and stable in the body fluids of many cancer patients, and are deregulated in pancreatic, breast, colon, leukaemia and lung cancer⁴. Notably, the role of miRNAs in the development and overall regulation of tumors shows great promise to screen therapy targets. Despite the fact that molecular targeted therapies to various cancers have shown potential results, no promising targeted therapy has been useful for a large number of cancer patients. Although, there has been improvement in early diagnosis, most cancers are still diagnosed at the last stage. Hence the recognition of novel diagnostic biomarkers or treatment strategies is critical and indispensable for the

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control of cancer.

Role of MiRNA in Cancer

Colorectal cancer

Currently, miRNAs have been shown to be promising sensitive and specific early detecting molecular biomarkers. There are reports that plasma levels of miR-29a and miR-92 (Table 1) are significantly increased whereas levels of miR-601 and miR-760 are significantly decreased in the early stage of CRC as compared to controls ⁵. Recently, it was reported that in CRC, four cell-free miRNAs i.e. miR-31, miR-181b, miR-92, miR-203 (Table 1) are down-regulated and two miRNAs i.e. miR-21, let-7g (Table 1) are up-regulated, these being more sensitive and specific in the identification of CRC than any single protein biomarker like carcino-embryonic antigen (CEA) or cancer antigen 19.9 (CA19-9) ⁶. Moreover, it has been reported that a combination of seven exosomal miRNAs (let-7a, miR-23a, miR-21, miR-150, miR-223, and miR-1229) might be used for early detection of CRC, being significantly increased as compared to healthy groups. In addition, high levels of serum miR-200c (Table 1) in CRC patients have been reported to have a powerful interrelationship with lymph node metastasis ⁷.

Gastric cancer

For Gastric cancer (GC) diagnosis, fewer numbers of sensitive and specific markers are available. Several studies reported that many extracellular miRNAs are promising and sensitive specific biomarkers for early diagnosis of GC ³⁴. More recently, it was reported that plasma levels of miR-18a (Table 1) are significantly increased in GC patients ⁸. In addition, panel of five miRNAs (miR-16, miR-25, miR-92a, miR-451, and miR-486-5p) was identified in plasma as a potential biomarker for early diagnosis of GC³⁵. Moreover, another study showed that the plasma miR-122 was down-regulated and plasma miR-192 was up-regulated in GC patients and might be used for the early diagnosis of distant metastasis⁹ (Table 1).

Breast cancer

Breast cancer is a highly heterogeneous disease with different molecular alteration, which result in its classification into five intrinsic subtypes (luminal A and B, HER2-enriched, basal-like and normal-like) ¹⁰. Recently, several studies reported that deregulation of miRNAs expression is strongly associated with molecular breast cancer subtype. In plasma, combination of four (miR-29a,

miR-181a, miR-223, miR-652) (Table 1) down-regulated and three (miR-29a, miR-181a, miR-652) up-regulated miRNAs has been shown to be significantly and reliably associated with luminal A tumor ¹¹. Similarly, tissue miRNA-342 has been found to be highly expressed in luminal B tumor and regarded as a very sensitive and specific biomarker in this type of breast cancer (64). Moreover, other miRNAs have been identified to distinguish the remaining subtypes, such as basal type (miR-18a, miR-135b, miR-93, and miR-155), HER2 type (miR-142-3p, and miR-150), and normal type (miR-145, miR-99a, miR-100, miR-130) ¹⁰.

Pancreatic cancer

Cancer of the pancreas is now recognized as one of the most important medical problems facing the male population. Notably, after initial reports indicating serum miR-141 to be very sensitive biomarker for PCa, different and contradictory results were obtained ¹². Other studies have reported that extracellular miR-375 and miR-141 are most optimistic markers in the diagnosis of this neoplasm ¹³. Urine, another important source of circulating miRNA, has been widely exploited for the diagnosis of urological cancer. It has been reported that miRs 107 and 574-3p were significantly higher in the urine of PCa patients compared to healthy groups, and would perform even better than PCA3 normalized to PSA in identifying the presence of PCa ¹⁴. Recently, it has been reported that urine miR-205 and miR-214 were significantly down-regulated in PCa patients with specificity of 80% and sensitivity of 89% ¹⁵.

Lung cancer

The lack of specific and sensitive tools for early diagnosis as well as inadequate targeted therapies contribute to poor outcomes of lung cancer. In lung cancer, a signature of five miRNAs has been used in the prediction of treatment outcome for non-small-cell lung carcinoma (NSCLC), among which high expression of miR-221 and let-7a is associated with good prognosis, as opposed to elevated miR-137, miR-372, and miR-182 associated with poor prognosis ¹⁶. Likewise, high expression of the miR-183 family (miR-183, miR-182, and miR-96) has been reported to be associated with overall poor survival in patients with lung cancer ¹⁷. Plasma miR-21, miR-145, and miR-155 (Table 1) used in combination helped in distinguishing lung cancer from healthy smokers with 69.4% sensitivity and 78.3% specificity ¹⁸. In combination of miR-205, miR-210

and miR-708 (Table 1) in sputum distinguished lung squamous cell carcinoma patients from normal subjects with 73% sensitivity and 96% specificity thus helping in the early detection of lung squamous cell carcinomas¹⁹. Furthermore, it has been found that high expression of serum miR-21 in lung cancer is associated with poor prognosis and the dynamic change of serum miR-21 between postoperative and preoperative lung carcinoma patients can potentially serve as biomarkers for disease recurrence after surgery²⁰.

Prostate cancer

Prostate-specific antigen (PSA) that is currently available as a biomarker for prostate cancer, displays an inferior sensitivity and specificity. In prostate cancer, miRNAs such as miR-141 and miR-375 (Table 1) have been connected to prognosis of PC, which in turn correlate with high Gleason score or lymph-node positive status²¹. Studies have shown relationship of two miRNAs (miR-182 and miR-187) most differentially expressed in prostate cancer with the clinicopathological characteristics and outcome of patients, and it was observed that miR-187 expression was decreased in advanced prostate cancer cases²². In another study, a distinct set of 11 miRNAs was present at significantly greater amounts in prostate cancer patients with metastasis compared to those without metastasis. Moreover, differential expression profiles of miRNAs either downregulated or upregulated have been observed in prostate cancer²³. It is also depicted that the tumor-associated miRNAs in serum (miR-26a, miR-32, miR-195, miR-let7i) allow noninvasive discrimination of prostate cancer (PCa) and benign prostatic hyperplasia (BPH)²⁴. Several reports indicate that circulating miR-26a-1 and miR-141 are associated with stage²⁵, grade²⁶ and cancer recurrence in patients with prostate cancer²⁷.

Hepatocellular carcinoma

Current diagnostic methods available for Hepatocellular carcinoma (HCC) are insufficient for detecting the disease at early stages. Accurate, noninvasive biomarkers for the early detection of HCC are urgently needed to reduce worldwide morbidity and mortality related to HCC. MicroRNAs (miRNAs) have shown great promise as tissue-based markers for HCC diagnosis and prognosis. Moreover, they are stably expressed in serum and urine, and these circulating microRNAs (cmRNAs) are emerging as novel noninvasive biomarkers for the early detection and

prognosis of HCC. It has been reported that four miRNAs (miR-92, miR-20, miR-18 and precursor miR-18), were associated with the HCC differentiation status²⁸. Furthermore, different subsets of miRNAs may be involved in the distinct biological characteristics of HCC. For example, epithelial cell adhesion molecule-positive human liver cancer stem cells are positively correlated with the expression of miR-181²⁹. A study that was based on the analysis of clinical sample data, identified a 20-miRNA metastasis signature that could predict primary HCC with venous metastases³⁰. In addition, a number of studies have indicated that certain miRNAs are associated with distinctive liver tumor risk factors. These include the observation that miR-26a-1 expression exhibits gender differences³¹, that miR-96 is overexpressed in HBV-related HCC, and that the downregulation of miR-126 is associated with alcohol use³². Previous studies have revealed that miR-221/222, miR-21, miR-224 and miR-34a that are known to promote tumor progression are consistently upregulated in HCC³².

Esophageal cancer

Esophageal cancer (EC) is one of the most common malignant tumors worldwide. The incidence and mortality of esophageal cancer (EC) are high, and rank eighth and sixth, respectively, out of all types of cancer, affecting more males than females³³. Notably, aberrant expression of 46 miRNAs in EC tissues, of which 7 miRNAs (upregulation of miR-25, miR-424 and miR-151; downregulation of miR-100, miR-99a, miR-29c and miR-140) can be used as biomarkers to distinguish malignant EC lesions from adjacent normal tissue. Moreover, miR-335, miR-181d, miR-25, miR-7 and miR-495 were associated with the general pathological type of EC; miR-25 and miR-130b were associated with the degree of differentiation of EC and the expression level of miR-103/107 was negatively correlated with the survival rate of EC patients and may be used for early diagnosis as well as gene therapy targets for EC³⁴. Downregulation of miR-203 and miR-205 compared with normal epithelium in EC, while as overexpression of miR-21 (Table 1) in the two types of EC has been reported. Similarly, miR-200c, miR-194 and miR-192 have been shown to be downregulated in ESCC, but significantly upregulated in EAC³⁵.

TABLE 1 | Expression and source of miRNA in various human cancers

Cancer Type	MiRNA	Source	Expression
Lung cancer	miR-25, miR-223	Serum	Up
	miR-1254, miR-574-5p	Serum	Up
Breast cancer	miR-155, miR-197, miR-182,-21,-126	Plasma	Up
	miR-145		Down
	miR-17-3p,-21,-106a,-146,-155,-191, -192,-203,-205,-210,-212,-214	Exosome	Up
	miR-205,-210,-708	Sputum	Up
	MiR-21, miR-29b	Tissue	Up
	miR-373,-155	Serum	Up
	miR-34a,-17		Down
	miR-222,-103,-23a,-29a,-23b, -24,-25		Up
	miR-148b,-37b,-409-3p,-801, miR-181a, miR-652	Plasma	Up
	miR-342	Tissue	Up
Colorectal cancer	miR-29a, miR-92, miR-601, miR-760	Plasma	Differential
	miR-31, miR-181b, miR-92, miR-203	Serum	Differential
	and miR-21, let-7g		
Prostate	miR-200c	Serum	Up
	miR-375, miR-141	Plasma	Down
	MiR-107, miR-574-3P	Urine	Up
Gastric cancer	miR-205, miR-214	Urine	Down
	miR-18a	Plasma	Up
	miR-122, miR-192	Plasma	Differential
	miR-106b,-20a,-221,-223	Plasma	Up
	miR-221,-376,-744	Serum	Up
Hepatocellular carcinoma	miR-1,-20a,-7a,-34,-423-5p	Serum	Up
	miR-16, miR-199a	Serum	Down
	MiR-15b, miR-130b, and miR-16	Serum	Up
Cervical	miR-21,-1,-25,-206,let-7f	Serum	Up
	miR-625, miR-618, miR-532, miR-650, miR-516-5p	Urine	Differential
Cervical	miR-218	Serum	Down
Esophageal Bladder	miR-21	Serum	Up
	miR-125b and mir-126	Urine	Differential
	miR-129,-133b	Blood	Up
	miR-26-b-5p,-144-5p,-374-5p	Blood	Up

B-cell Lymphoma	miR-21, miR-155 and miR-221	different	Up
	miR-10393-3p	Tissue	Up
	miR-10397-5p, NOVELMOO288M	Tissue	Up
	miR-5586-5p	Tissue	Up
T-cell Lymphoma	miR-30b	Tissue	Down
	miR-515-3p, miR-155, miR-598, miR-625	Tissue	Differential
	miR-199a-5p	Tissue	Differential
	miR-652, miR-627, miR-519e, miR-487b,		
	miR-124, miR-325, miR-181a, miR-618		
	miR-512-3p, miR-886-5p, miR-886-3p,	Tissue	Up
	miR-708, miR-135b	Tissue	Down
	miR-146a, miR-155		
Leukemia	miR-210, miR-197, miR-191, miR-512-3p	Tissue	Up
	miR-451, miR-146a, miR-22, miR-455-3p,	Tissue	Down
	miR-455-5p, miR-143, miR-494		
	miR-150, miR-342	Plasma	Up
	miR-155	Plasma	Up
Pancreatic cancer	miR-141, miR-375	Serum	Differential
	miR-107, 574-3p	Urine	Differential
Renal cell carcinoma	miR-195, miR-15b, miR-99a, miR-191	Tissue	Up
	miR-200b	Tissue	Up
	miR-211	Tissue	Up
	miR-210	Tissue	Up
Thyroid	let-7f, miR-151-5p, miR-222	Serum	Up
Brain	miR-15b*, miR-23a, miR-133a, miR-150*, miR-197, miR-497, miR-548b-5p	Serum	Down
Head and neck	miR-125a, miR-200a	Saliva	Down
Ovarian cancer	miR-205, miR-let-7f	Plasma	Differential
	miR-21,-92,-93,-126,-29a	Serum	Up

Bladder cancer

Recently, numerous studies demonstrated that microRNAs are emerging as diagnostic biomarkers for bladder cancer. Specific miRNA profiles have been identified for several samples from patients with bladder cancer. In BC, 10 miRNAs has been found up-regulated³⁶, the most commonly up-regulated miRNA in BC being miR-129³⁷. The authors found that the levels of miR-200 family members miR-141, miR-155, and miR-429 were lower in urine sediment in BC patients. Levels of miR-200a, miR-200b, miR-200c, miR-141, miR-429, miR-205, miR-192, and miR-146a increased significantly after surgery. These findings suggest that miR-200-family miRNAs (miRs-141, -429, -192, -146a, -141, and others) are promising as non-invasive, diagnostic, and prognostic markers. Also, studies have reported that miR-100, miR-125b, miR-130a, miR-139-5p, miR-145, miR-199a-3p, miR-214 and miR-222 are down-regulated in invasive bladder tumors compared to superficial tumors, as well as in other tumor entities whereas expressions of miR-20a, miR-106b, miR-141, miR-130b, miR-200a, miR-200a and miR-205 were found to be up-regulated in bladder cancer³⁸.

B-cell lymphomas

B-cell lymphomas make up a heterogeneous group of lymphoproliferative disorders that originate from B cells and whose pathogenesis is still largely unknown. Accurate lymphoma diagnosis, prognosis and therapy still require additional markers. Diffuse large B-cell lymphoma (DLBCL) represents the most common lymphoid malignancy. DLBCL was one of the first lymphomas to be linked with aberrant miRNA expression, in particular the observation that miR-155 (Table 1) is highly expressed in this malignancy³⁹. The levels of six miRNAs (miR-223, miR-217, miR-222, miR-221, let-7i and let-7b) have been found to be differentially expressed between cases of FL (follicular lymphoma) that underwent high grade histological transformation compared to those that did not.

T-cell lymphomas

T-cell lymphomas form a diverse group of T-cell derived lymphoid neoplasms comprising 10-15% of non-Hodgkin's lymphomas. Increased expression of miR-122 in CTCL (Cutaneous T cell lymphoma) prevents chemotherapy-induced apoptosis. Therefore, targeting miR-122 may improve the outcome of chemotherapy⁴⁰. Downregulation of miR-342 and upregulation of miR-17-5p were found to

decrease and increase cell apoptosis in SzS respectively, which is involved in pathogenesis of the disease⁴¹. Upregulation of miR-21, miR-486, and miR-214 is involved in promoting cell survival in SzS, and contributes to resistance to apoptosis in CTCL cell lines, and even may be a new diagnostic or prognostic biomarker for this type of incurable CTCL. MiR-155 (Table 1) is upregulated in MF⁴². Expression level of miR-21 and miR-155 is specifically higher in NK-cell lymphoma line than normal NK cells⁴³.

Renal cell carcinoma

Renal cell carcinoma (RCC) is the most common malignant solid tumor in adults. It has been reported reported that there is upregulation of miR-28, -185, -27, and let-7f-2 in RCC compared to normal kidney⁴⁴. Reports from other group showed that miR-34a, -224 and -21 were upregulated, whereas miR-141, -149 and -429 were downregulated in the clear cell RCC tissues⁴⁵. Also it has been found that the expression of miR-21 was significantly upregulated in RCC compared with healthy kidney. In another study, miR-34a, -21 and -224 were upregulated, miR-141 was downregulated in the sera of patients with ccRCC, and the serum miR-21 expression levels were significantly correlated with the clinical staging of the patients with ccRCC⁴⁶. It was found that RCC patients presented higher circulating expression levels of miR-221 and -222 than healthy individuals⁴⁷. MiRNA-based therapies (miR-381, miR-185, miR-141) may also be used together with other therapeutic strategies in pre-clinical studies⁴⁸.

Cervical Cancer

Cervical cancer is a primary cancer of the uterine cervix in females and has a high incidence and mortality. miR-126 and miR-21 found in the serum have been found to be associated with cervical cancer⁴⁹. Overexpression of miR-21, miR-27a, miR-34, miR-34a, miR-146a, miR-155, miR-196a, miR-203, and miR-221 has been detected in the serum, with miR-21, miR-27a, miR-34, miR-34a, and miR-196a being particularly highly expressed in squamous cell carcinoma of the cervix⁵⁰. These results indicate that miRNA levels in serum can be used for diagnosis of cervical cancer and that some miRNAs may be useful for prediction of tissue type and for early diagnosis of cervical cancer. Several miRNAs in serum have been identified as candidate markers for lymph node metastasis in cervical cancer. A study conducted by researchers showed miRNA in patients with small cell carcinoma of the cervix (SCCC). Expression

levels of 7 seven miRNAs, let-7c, miR-10b, miR-100, miR-125b, miR-143, miR-145, and miR-199a-5p, were markedly suppressed in patients with advanced SCCC in comparison with those in patients with early SCCC. In patients with lymph node metastasis, expression of let-7c, miR-100, miR-125b, miR-143, miR-145, and miR-199a-5p was particularly suppressed⁵¹. Hypermethylation of miR-149, miR-203, and miR-375 has also been found in HPV-positive high-grade dysplasia⁵², and miR-203 and miR-375 may be markers for precancerous conditions in the uterine cervix.

Thyroid Cancer

Thyroid cancer (TC) is a group of neoplastic disease arising from thyroid gland. Follicular cells of the gland give a rise for most of the TC (95%) while small portion of cancers (5%) is developing from para-follicular C cells and referenced as medullary TC. TC accounts for 95 % of all endocrine malignancies and its incidence is constantly increasing⁵³. The most consistently overexpressed miRNAs in well-differentiated TC types appear to be miR-221, miR-222, and miR-146b⁵⁴. Other commonly reported overexpressed miRNAs are miR-155⁵⁵ and miR-181⁵⁶. It has been reported that a set of four miRNAs (miR-146b, -221, -187, -30d) could differentiate a malignant thyroid lesion from a benign tumour⁵⁷. There are reports that the serum levels of let-7e, miR-151 and miR-222 (Table 1) are significantly overexpressed in TC patients⁵⁸. Another study has reported that miR-146b and -155 can be used to discriminate between benign and malignant tumours⁵⁹.

Ovarian cancer

Carbohydrate antigen-125 (CA-125) is the most frequently used biomarker for ovarian cancer detection⁶⁰, but it is only elevated in approximately 50% of stage I EOCs and 70%90% of advanced cases⁶¹. Hence, there is a clamant need for novel biomarkers that are more sensitive and specific for detecting OC when used alone or in combination with CA-125. Several microRNA signatures that are unique to ovarian cancer have been proposed, and serum-circulating microRNAs (miR-200a, miR-200b, miR-200c, miR-26a, miR-132, miR-145, and let-7b) have the potential to be useful diagnostic and prognostic biomarkers⁶². It has been reported that 4 miRNAs (miR-141, miR-200a, miR-200b, and miR-200c) were upregulated and 25 out of 29 were downregulated, including miR-199a, miR-140, miR-145, and miR-125b-1 in the

cancer samples when compared with normal tissues⁶³. This study also found that miR signatures were different between ovarian carcinoma histotypes (serous, endometrioid, clear cell, and mucinous). It has also been stated that clear cell histotype is characterized by higher expression of miR-30a-5p and miR-30a-3p, whereas mucinous histotype displays higher levels of miR-192 and miR-194⁶⁴. There are reports suggesting that targeting miR-92a may prove to be a novel and effective gene therapy for patients with ovarian cancer⁶⁵.

Brain tumor

Brain tumors are one of the top 10 causes of cancer deaths and a timely and accurate diagnosis is essential for disease management. Brain tumors could be classified into glial tumors (e.g. glioblastoma, astrocytomas, oligodendroglial tumors, ependymal tumors), embryonal tumors (e.g. medulloblastomas), tumors of the meninges (e.g. meningiomas), tumors of the hematopoietic system and tumor of the sellar region. Glioblastoma multiforme (GBM) is the most malignant and frequent brain tumor in adults, accounting for about 50% of diffuse gliomas⁶⁶. Studies have reported strong upregulation of miR-221 in glioblastoma while downregulation of miR-128, miR-181a, miR-181b, and miR-181c⁶⁷. Another study showed a downregulation of microRNA-124 and microRNA-137 in anaplastic astrocytoma and glioblastoma multiforme compared to normal brain and an upregulation of miR-21⁶⁸. High expression of miR-21 has been found to be significantly associated with poor patient survival, and in combination with other aberrant expressed microRNAs (low expression of miR-181b or miR-106a). MiR-21 profiling has potential application as novel diagnostic and prognostic indicator that may contribute to improve the selection of patients for adjuvant therapy and to predict the post-surgical outcome⁶⁹. The miRNAs analysis in the serum of malignant astrocytoma patients, compared to normal controls, revealed several miRNAs (miR-15b, miR-23a, miR-133a, miR-150, miR-197, miR-497 and miR-548b-5p) (Table 1) whose concentrations were significantly lower in serum of the patients. Moreover, the concentrations of miR-23a, miR-150, miR-197 and miR-548b-5p were markedly decreased in malignant cases if compared to the astrogliosis group⁷⁰. Several miRNAs are up- (let-7a, let-7f, miR-17, miR-21, miR-155, miR-17, miR-16, miR-26b, miR-374a, let-7d, miR-20a, miR-15b, miR-7b, miR-9) or down-

regulated (miR-132, miR-134, miR-7, miR-330-3p, miR-127-3p) in oligodendrogliomas compared to non-neoplastic samples⁷¹. Some studies have identified 28 miRNAs (miR-10a, miR-17-5p, miR-19a, miR-19b, miR-20a, miR-21, miR-32, miR-34a, miR-106b, miR-130a, miR-135a, miR-142-3p, miR-193a, miR-210, miR-301, miR-449b, miR-502, miR-518b, miR-551b, miR-565, miR-591, miR-594, miR-60, miR-139, miR-323, miR-383, miR-433 and miR-485-5p) that were differentially expressed in ependymoma samples⁷². MiR-203 has been proposed as a biomarker for management of disease progression in ependymomas and as a predictor for the likelihood of relapse. Metastatic behavior of medulloblastoma has been reported to involve let-7 microRNAs⁷³.

Leukemia

Studies have revealed that miRNAs may serve as biomarkers in clinical diagnosis of leukemia. It has been demonstrated that miR-128a, miR-128b, let-7b and miR-223 are the most significant and discriminatory between AML and acute lymphoblastic leukemia (ALL)⁷⁴. Further it has been confirmed that miR-128, let-7b, miR-223 and miR-181a have a diagnostic value in acute leukemia patients⁷⁵. Another study demonstrated that the expression level of miR-142-3p and miR-29a in peripheral blood mononuclear cells (PBMC) could be used as novel diagnostic marker in AML⁷⁶. In CLL, several miRNAs including miR-181, miR-30d and let-7a that are differentially expressed between CLL lymphocytes and CD19+ control cells have been identified⁷⁷. Downregulation of miR-326 has been reported in chronic myelogenous leukemia (CML)⁷⁸. In ALL, miR-148, miR-151 and miR-424 were identified as discriminative of T-lineage versus B-lineage ALL⁷⁹. Accumulating evidence has shown that miRNAs can be used as biomarkers to predict the prognosis of patients. Specific extracellular miRNAs in body fluids and circulating miRNAs that have been found to be involved in leukemia include miR-92a, miR-638, miR-150, miR-342 and miR-181b-5p (191,192,193) (Table 1).

Head and Neck cancer

Head and neck cancer (HNC) is the sixth most common cancer in the world⁸⁰, referring to cancers of the aerodigestive tract, including lip, oral cavity, nasal cavity, paranasal sinuses, pharynx, larynx, oropharynx, hypopharynx, salivary glands, and local lymph nodes⁸¹. It

has been suggested that specific miRNAs can be used as diagnostic markers for HNSCC (head and neck squamous cell carcinoma), such as overexpression of miR-21 and -205⁸². It has been suggested that high expression of miR-21 can be used as an independent predictor of poor survival for patients with tonsillar SCC (squamous cell carcinoma) and a significantly lowered 5-year survival in patients with HNSCC⁸³, while lowered miR-205 expression⁸⁴ and increased miR-451 expression⁸⁵ have been significantly correlated with locoregional relapse of HNSCC irrespective of disease severity at diagnosis and treatment. MiR-125a and -200a (Table 1) are two salivary miRs that have been shown to be markedly reduced in oral carcinoma patients versus healthy controls⁸⁶. Moreover, plasma miRs have been shown to be reduced after tumor resection, implying that these miRs may be released from cancerous tissues into circulation and their potential use as a marker for disease progression. This was seen in plasma and salivary miR-31⁸⁷ and plasma miR-184⁸⁸.

CONCLUSION

In conclusion, miRNAs modulate the expression of target mRNAs in different pathways and themselves are also regulated by multiple factors. Based on increasing numbers of specific miRNA functional study, it is indispensable for us to construct a global view about miRNA regulation mechanisms and understand miRNA as diagnostic and prognostic marker.

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