



Circulating Micrnas as Novel Potential Biomarkers in Upper Gastrointestinal Cancers

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Abstract

Gastrointestinal (GI) cancers are among the most lethal malignancies with extremely poor prognosis. Despite advances in the identification of novel biomarkers, only a very small number of molecular markers have been launched for the detection of patients at earlier stages or management of GI patients. Recently, microRNAs (miRNAs) are emerged as a molecular regulator of genes involved in key signalling pathways in GI cancers. There is accumulating evidence showing aberrant expression of some known microRNAs in GI cancers, suggesting their potential as diagnostic or prognostic markers. On the other hand, miRNAs have turned out to play an essential role in drug resistance; indicating their values as a novel therapeutic approach to overcome chemoresistance. This mini review provides an overview on the clinical application of miRNAs, in particular circulating microRNAs, as prognostic/predictive biomarkers in gastrointestinal cancers.

Keywords: Gastrointestinal cancers; MiRNAs; Circulating miR

Introduction

Upper Gastrointestinal Cancers (UGI) includes those tumor cells originating in the oesophagus, gastro-oesophageal junction and stomach. UGI remains as the most common malignancies and major cause of cancer deaths worldwide. In particular colorectal and pancreatic cancer is the third and fourth leading cause of cancer related death, respectively, and most of patients are diagnosed at late stages. This poor prognosis at can be explained by several factors, including invasive behaviour and intrinsic resistance of these tumour types to most chemo/radiotherapy. Moreover, despite rapid advances in the identification of prognostic and predictive biomarkers useful for management of GI patients, only a small number of markers have been identified.

Recently microRNAs (miRNAs) are emerged as novel prognostic and predictive biomarkers in the management of upper gastrointestinal cancers. MiRNAs are short (20–24 nucleotides), highly conserved, stable RNA molecules that act as post-transcriptional regulators of gene expression, causing mRNA degradation or inhibition. MiRNAs play an essential role in the control of many biological processes. On the other hand, several studies have been shown the aberrant activation of some miRNAs in cancers which are involved in development, progression and invasive features of cancer.

There is growing body of evidence showing that miRNAs can be circulated in body via exosomes or microvesicles, which suggest their values as non-invasive biomarkers. Moreover, it has been reported that miRNAs are stable and can be found in different body fluid. In particular a recent systemic review and meta-analysis comparing circulating miRNAs levels in gastric cancer patients before and after operation showed the value of miR-21 as diagnostic and prognostic biomarkers for gastric cancer [1]. In this study we provided an overview on preclinical and clinical studies on the role of microRNAs as prognostic and predictive biomarkers in gastrointestinal cancers.

MiRNAs and Gastric Cancer

The potential role of circulating miRNAs for predicting gastric cancer (GC) prognosis has

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been investigated in several studies[2-4]. In particular, Wang et al. [5] observed that plasma levels of miR-17-5p/20a was correlated with poor overall gastric cancer survival. While Komatsu et al. [6] showed that the levels of miR-21 were significantly associated with survival of patients with gastric cancer. Song et al. [7] revealed the high serum levels of miR-21 and its correlation with an increased gastric tumor size. Moreover, other studies showed that the members of miR-200 family play a key role in cancer cell invasion and tumor metastasis [8-9]. Another study showed the diagnostic value of miRs-221/744/376c with 82.4% sensitivity and 58.8% specificity in gastric cancer patients, while the prognostic value of miR-221 and miR-376c was found in GC [10]. Also the association of 7 microRNAs, including miR-10b, miR-21, miR-223, miR-338, let-7a, miR-30a-5p and miR-126 was shown with relapse-free and overall survival in GC patients [11-12]. Conversely several other studies have been shown the predictive value of some microRNAs in response to cisplatin or 5-azacytidine resistance: such as miR-21, miR-106a, miR-195, miR-378 miR-508-5p and miR-449 [12-16].

MiRNAs and Colorectal Cancer

Colorectal cancer (CRC) is the third leading cause of cancer related death in the world. Increasing data show the biological impact of some dysregulated microRNAs involved in development and progression of CRC. Several studies have been shown the prognostic and predictive value of miR-21 in CRC [17-19]. In addition, several other data have demonstrated the value of miR-106b [20], miR-320 [21], miR-498, miR-125b [22], miR-145 [23], miR-185 [24], miR-215 [25] and miR-17 [26]. Furthermore, several other miRNAs have been found in stool as non-invasive marker to detect CRC. In particular, a recent study evaluated the expression pattern of some miRNAs in colonocytes isolated from feces of 197 CRC patients and 134 healthy subjects. Their findings showed that the expression patterns of miRNA could distinguish patients from healthy subjects with 74% sensitivity and 79% specificity [27]. In addition to diagnostic and prognostic miRNAs, several studies revealed the association of miR-21 with therapeutic outcome with 5FU-based therapies [28-29]. Moreover, the correlation of some other miRNAs (e.g., miR-140 [30], miR-215 [31], miR-224 [32], and miR-20a [33] in developing chemoresistance has been illustrated.

MiRNAs and Esophageal Cancer

Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two major oesophageal cancer subtypes. The overall 5-year survival rate is poor despite extensive efforts, due to invasive and metastatic features of esophageal carcinoma cells. Increasing evidence is showing the involvement of miRNA in EESCC C development and progression. For instance, Guo et al. detected the aberrant levels of 46 miRNAs in ESCC patients. They observed 7 miRNAs which were dysregulated in the tumor tissue [34], suggesting their values to distinguish malignant ESCC lesions from adjacent normal tissue. In particular, miR-181d, miR-335, miR-7 miR-25, and miR-495 were correlated with clinical information of patients [34]. Additionally miR-25 and miR-130b were correlated with the degree of differentiation, while miR-103/107 level was negatively associated with survival rates. Furthermore Feber and colleagues showed important role of miR-21, miR-203 and miR-205 in EC [35], suggesting their values as prognostic biomarkers. In addition to prognostic markers, several other studies showed the value of miR-141, miR-200b/200c/429, which were involved with resistance to cisplatin [36]. In particular Imanaka et al., showed high levels of

miR-141 in the cisplatin-resistant ESCC cell lines [36], while Wu and colleagues illustrated the overexpression of miR-200b/200c/429 in endometrial cancer and EC, which was associated with resistance to cisplatin [37].

MiRNAs and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common type of liver cancer with poor prognosis. Accumulating data have shown the association of some miRNAs with HCC development or their values as new targets for HCC therapy [38-41]. Circulating levels of some potential miRNAs, including, miR-21, [42] miR-222 [43], miR-1, miR-25, miR-92a, miR-206, miR-375 and let-7f [44] and miR-223 [44] have reported in serum/plasma of HCC patients. Of note, appropriate controls are warranted to investigate their values, since HCC is often accompanied by viral hepatitis, or other underlying liver conditions.

Recently, the first miRNA-targeting agent, miravirsen (a locked nucleic acid modified DNA phosphorothioate antisense oligonucleotide) against miR-122, received permission for clinical test. This suggests their value as new approach for the treatment of HCC patients [45].

MiRNAs and Cholangiocarcinoma

Cholangiocarcinoma (CCA) is among the most lethal malignancies derived from bile duct epithelial cells. This poor prognosis can be explained at least in part by its slow growth, late metastasis, and lack of efficient screening tools. Several miRNAs have been found in preclinical studies to predict gemcitabine resistance such as miR-21 and miR-200b [46]. Moreover, abnormal expression of miR-22, miR-125a, miR-127, miR-199a/a0, miR-214, miR-376a, miR-424, miR-200a/b, miR-146a, miR-155, miR-221, miR-31, and miR-223, miR-122, miR-145, miR-200c, miR-221, and miR-222 [47-48]. Another study by Okamoto et al. [49] showed that overexpression of miR-29B, miR-205 and miR-221 restore gemcitabine sensitivity in the resistant cell line.

MiRNAs and Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is a fourth leading cause of death with poor outcome. The expression levels of four miRNAs in plasma, including miR-21, miR-210, miR-155 and miR-196a were found to be increased PDAC patients [50]. Li and colleagues evaluated the level of 735 circulating miRNAs in PDAC patients. This study showed the diagnostic value of miR-1290 [51]. In addition, Kawaguchi et al. [52] detected the high level of plasma miR-221 in PDAC patients, compared to those with benign pancreatic tumors and controls [53]. Moreover, we previously [54-55] explored the expression pattern of more than 1200 human miRNAs using High-resolution miRNA profiles in 19 stage-pT3N1 homogeneously treated patients (adjuvant gemcitabine 1000 mg/m²/day, days-1/8/15, every 28 days). Our findings showed that miR-211 was a prognostic factor in resected PDAC [53]. Several other studies revealed that PDAC cells with high expression of miR-21 were chemoresistant to gemcitabine [54].

Perspective

Gastrointestinal cancers are among the most lethal malignancies with devastating outcome. This poor prognosis can be explained by several factors, e.g., invasive characteristics of tumor cells and resistance to chemotherapies and/or targeted agents. Moreover, most of patients are diagnosed at advance stages, supporting on the

identification of novel biomarkers in detection and management of patients during the therapy. It has recently been shown that the aberrant activation of some microRNAs are associated with the development and progression of UGI cancers or can be changed in response to therapy, suggesting their values as prognostic and/or predictive biomarkers in the management of GI cancers. In addition, they can circulate through body via blood circulation or other body fluids. Although several microRNAs have been found from preclinical and clinical studies, these findings have not been translated into routine clinical practices. This could be in part due to the fact that the reported alterations of circulating miRNAs are not consistent across different studies. Therefore the potential value of circulating miRNAs for serving as diagnostic or prognostic molecular markers remains to be further investigated in patient's samples, in retrospective and prospective setting. MiRNA profiling of free circulated miRNAs or circulating exosomes in the body fluids using high throughput technologies and validation by qRT-PCR in an independent cohort may help in the detection of novel biomarker involved in tumor progression and/or response to treatment. Additionally large-scale and multi-center studies are warranted to explore the value of candidate markers.

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