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Review

MicroRNAs: Potential biomarkers for cancer diagnosis, prognosis and targets for therapy

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ABSTRACT

MicroRNAs have a revolutionary impact on cancer research over recent years. They emerge as important players in tumorigenesis, leading to a paradigm shift in oncology. The widespread and comprehensive use of microRNA microarrays has enabled the identification of a number of microRNAs as potential biomarkers for cancer. It is encouraging to report that microRNAs have remarkable stability in both formalin-fixed tissue and blood. Many microRNAs have been identified to act as oncogenes, tumor suppressors, or even modulators of cancer stem cells and metastasis. Some studies not only reported the identified microRNA biomarkers, but also deciphered their target genes and the underlying mechanisms. The rapid discovery of many microRNA targets and their relevant pathways has contributed to the development of microRNA-based therapeutics, but the developing progress of antisense or siRNA drugs has been hampered by stability, specificity and delivery problems. This review summarizes the most significant and latest findings of original researches on microRNAs involvement in cancer, focusing on the potential of cancer-related microRNAs as biomarkers for diagnosis, prognosis and targets for therapy.
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Contents

1. Introduction

Rapid findings linking microRNAs (miRNAs) to various diseases have propelled the miRNA field. The discovery of novel miRNAs and the identification of potential miRNA target genes continue at a fast pace (Cho, 2010a). Comparing the Release 13.0 and Release 14.0 of the miRBase Sequence Database, 1,367 new hairpin sequences and 1,580 novel mature miR and miR* products have been added from

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March 2009 to September 2009 (http://www.mirbase.org/). In the last few years, researchers have discovered a particularly important role for miRNAs in tumorigenesis (Cho, 2007, 2008a, 2008b). A large number of experimental data has been published over the past year (Cho, 2009a). This review summarizes the most significant and up-to-date findings of original researches on miRNAs involvement in cancer, focusing on the potential of cancer-related miRNAs (oncomiRs) as biomarkers for diagnosis, prognosis and therapy (Table 1).

2. Potential biomarkers for diagnosis

2.1. MicroRNA markers for detection

Using research prototype real-time transcription-mediated amplification assays, specific capture and detection of mature *miR-221* from complex samples is demonstrated in the total RNA isolated from human prostate cancer cells and xenografts. These assays provide a high-throughput method of miRNA profiling in clinical specimens with high analytical sensitivity and specificity (Siva et al., 2009).

A study of clear cell renal cell cancer has identified a robust signature to define renal malignancy, with 5 significantly overexpressed and 6 significantly downregulated miRNAs in cancer samples. A combination of upregulated *miR-155* and downregulated *miR-141* is found to result in a 97% overall correct classification of the matched malignant and non-malignant tissue samples (Jung et al., 2009).

Integrative molecular-bioinformatics can be used to identify the predicted miRNA-mRNA interactions retrieved from PicTar, TargetScan and miRBase. By calculating the difference between delta cycle threshold (ΔCt) *miR-503* and ΔCt *miR-511*, adrenocortical carcinomas is significantly distinguished from benign adenomas with high sensitivity and specificity. These miRNA biomarkers may be helpful for the diagnosis of adrenocortical malignancy (Tömböl et al., 2009).

2.2. MicroRNA markers from formalin-fixed tissue and blood

Formalin fixation is the standard and routine histological practice for optimal preservation of cellular morphology. Comparing with normal breast samples, a panel of miRNAs is consistently dysregulated in breast cancer, including upregulated *miR-21*, *miR-155*, *miR-191*, *miR-196a* and downregulated *miR-125b*, *miR-221*. These results show that miRNA analysis of formalin-fixed tissue is feasible, thereby offering enormous opportunities to evaluate the clinically relevant role for miRNAs in human malignancies (Hui et al., 2009).

A recent study reported that high expression of *miR-92* significantly differentiates the plasma of colorectal cancer (CRC) from gastric cancer, inflammatory bowel disease and normal subjects. Yielding a receiver operating characteristic curve area of 88.5%, *miR-92* can be a potential non-invasive molecular marker for CRC screening (Ng et al., 2009a).

3. Potential biomarkers for prognosis

3.1. MicroRNA markers of treatment response

Evaluating the potential association of miRNA expressions with clinical outcomes in gastric cancer patients, downregulation of *miR-451* is revealed to be associated with worse prognosis. Overexpression of this miRNA in gastric cancer cells regulates the oncogene *MIF* (macrophage migration inhibitory factor) production, reduces cell proliferation and increases sensitivity to radiotherapy. These findings support the role of *miR-451* as a prognosis marker for gastric cancer (Bandres et al., 2009a).

Chronic lymphocytic leukemia (CLL) with *TP53* (tumor protein 53) mutation and 17p deletion is resistant to chemotherapy. Low expression of *miR-34a* in CLL is found to be associated with p53 inactivation, chemotherapy-refractory disease, impaired DNA damage response and apoptosis resistance irrespective of *TP53* mutation or 17p deletion. *miR-34a* is shown to have a role in chemotherapy resistance and thus may serve as a marker for poor prognosis for CLL (Zenz et al., 2009).

3.2. MicroRNA markers for predicting progression and metastasis

A recent study has observed that the expression of *miR-196a* is higher in esophageal adenocarcinoma, Barrett's esophagus and dysplastic lesions comparing with normal squamous mucosa, and in high-grade dysplasia comparing with Barrett's esophagus and low-grade dysplasia. It is confirmed that *miR-196a* specifically targets *KRT5* (keratin 5), *SPRR2C* (small proline-rich protein 2C) and *S100A9* (S100 calcium-binding protein A9) three prime untranslated region (3′ UTR). This miRNA is identified as a potential marker of progression during Barrett's metaplasia-dysplasia-invasive adenocarcinoma sequence in esophagus (Maru et al., 2009).

A study of hepatocellular carcinoma (HCC) has shown that the loss of *miR-122* expression in tumor cells segregates with specific gene expression profiles linking to HCC progression. This miRNA is specifically repressed in a subset of primary HCCs that are characterized by poor prognosis. *miR-122* is shown to be a potential diagnostic and prognostic marker for HCC progression (Coulouarn et al., 2009).

A study group has identified *miR-129* with prognostic potential for predicting disease progression in bladder cancer. Transfection with *miR-129* precursor exerts significant growth inhibition and induces cell death. A direct link between *miR-129* and their two putative targets *GALNT1* (UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1) and *SOX4* (sex determining region Y-box 4) are established using luciferase assays (Dyrskjøt et al., 2009).

In a large cohort study, prostate-specific oncomiR *miR-221* is found to be progressively downregulated in aggressive forms of prostate cancer. Downregulation of this oncomiR is linked to cancer progression and recurrence in a high risk prostate cancer cohort. It is shown that progressive *miR-221* downregulation hallmarks metastasis and this oncomiR is a prognostic marker in high risk prostate cancer (Spahn et al., 2009).

Measuring by methylation-specific polymerase chain reaction and bisulphate sequencing, it has been observed that expression of *miR-9* in CRC is inversely correlated with the methylation of its promoter regions. Aberrant DNA methylation and histone modifications may work together to induce silencing of miRNAs in CRC. While methylation of the *miR-129-2* and *miR-137* CpG islands is frequently observed in CRC, methylation of *miR-9-1* is associated with the presence of lymph node metastasis (Bandres et al., 2009b).

3.3. MicroRNA markers of survival

MicroRNA *lin-28* is considered to be a highly specific embryonic stem cell marker. As one of the stemness factors involved in reprogramming adult fibroblasts into induced pluripotent stem cells, this miRNA is oncogenic in HCC (Nimmo and Slack, 2009). Another study group has demonstrated that epithelial ovarian cancer patients with high expressions of *lin-28*'s homologue (*lin-28b*) have shorter progression-free and overall survival. *lin-28b* may promote ovarian cancer progression and serve as an unfavorable prognostic marker for the disease (Lu et al., 2009).

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