E16. Clinical implications of microRNAs in breast cancer

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MicroRNAs (miRNAs) comprise a class of small endogenous non-coding RNA molecules that play critical roles in modulating numerous biological pathways by regulating gene expression. High throughput and expression profile studies have shown that miRNAs are commonly dysregulated in human cancer. The study of the mechanisms of action of miRNAs has uncovered an entirely new repertoire of potential biomarkers and gene-regulated pathways. MiRNAs may function as oncogenes or tumour suppressor genes and are characterised by unique properties such as stability, tissue specificity, ease of detection and manipulation. Additionally, miRNAs are differentially expressed in the blood of cancer patients versus healthy donors, providing a rationale for the detection of miRNAs as diagnostic and prognostic circulating biomarkers. Recent studies have shown that specific expression patterns of miRNAs could be used as potential predictors of response to treatments in clinical trials. Finally, manipulation of miRNA expression in cancer could be used for future molecular therapies.

Introduction

MicroRNAs (miRNAs) comprise a class of small non-coding RNA molecules of 18–25 nucleotides that regulate gene expression at the post-transcriptional level and influence basic biological processes such as cell differentiation, proliferation, survival and death. These properties have made miRNAs interesting candidates as cancer biomarkers; several studies have confirmed the involvement of miRNAs in oncogenesis, in cancer progression, and more recently as modulators of response to treatments [1]. Recent research has identified several tumour miRNAs that could represent potential therapeutic targets. Accordingly, researchers' efforts are being directed towards achieving a deeper knowledge of dysregulated miRNAs driving oncogenic transformation and progression, and towards developing new anticancer agents to modulate their expression. Because of their potential clinical implications, miRNA studies represent a remarkable field of translational research.

Biological roles of microRNAs

MiRNAs bind to untranslated regions of mRNA molecules, interrupting ribosomal synthesis of the proteins they encode, making adjustments in translation, and targeting mRNAs for degradation. MiRNAs usually complement the 3′-untranslated regions of their target mRNA, impairing translation or altering message stability in order to reduce the amount of the corresponding protein [2]. Each miRNA potentially has a pleiotropic effect on as many as a few hundred target genes; conversely, the same mRNA could in turn be regulated by several miRNAs.

MicroRNAs and cancer: potential diagnostic and prognostic implications

Several reports have shown a differential miRNA expression profile between tumours and normal tissue. Dysfunctions of the miRNA pathway affect many cellular processes that are routinely altered in cancer, such as differentiation, proliferation, apoptosis, and metastasis. Genome-wide studies have shown that in many cases miRNA genes are located at cancer-associated genomic regions.

Cancer-associated miRNAs have been described as promoting or suppressing metastasis, generally classified as oncogenes and tumour suppressors' miRNAs, respectively. MiRNAs have recently been implicated in cell migration and metastasis, since some of their targets are crucial proteins for cell motility, cell-cell adhesion, and cell-matrix interactions [3].

MiRNAs have several features that could make them useful as clinically relevant biomarkers: (1) the miRNA expression pattern in human cancer is tissue-specific and is able to indicate the origin of a tumour mass; (2) the miRNA expression signature discriminates normal from neoplastic tissue and pre-malignant from normal and malignant lesions; (3) miRNAs are stable molecules and can be extracted from different types of samples, including formalin-fixed, paraffin-embedded and plasma samples; and (4) miRNAs may have downstream effects and regulate the expression of many mRNAs simultaneously.

MicroRNAs and breast cancer

Several studies have demonstrated a pattern of dysregulated miRNAs associated with breast cancer. There are growing data suggesting abnormal expression of

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miRNAs whose functions are correlated with different biological characteristics of breast cancers. A recent review has reported important dysregulated miRNAs associated with breast cancer oncogenesis and progression [4]. The overexpression of *miR-21* has been associated with advanced breast tumour stage, spread to lymph node, disease progression, and poor survival, whereas the abnormal expression of the *miR-200* family has been demonstrated to regulate several genes involved in epithelial-to-mesenchymal transition status of breast cancer cells and in the maintenance of breast stem-cell properties.

MiR-9 and *miR10b* have been reported as potential markers of breast cancer progression. Loss of *miR-126*, *miR-335* and *miR-31* in primary breast cancer has been retrospectively associated with a worse prognosis in terms of metastatic relapse. Many other miRNAs – such as *miR-373*, *miR-520c*, and *miR-146a/b* – seem to play a crucial role in control of breast cancer spread, with preclinical studies *in vivo* and *in vitro* suggesting a promoting or a suppressing effect on tumour invasion and metastasis [4].

It is noteworthy that a recent study has demonstrated an important role for HIF1-induced *miR-210* in breast cancer progression [4]. Furthermore, recent evidence has shown that miRNA expression can classify molecular breast tumour subtypes as defined by mRNA microarray: in primary human breast tumour samples many miRNAs are differentially expressed in basal-like, luminal A, luminal B, HER2+ and normal-like cancers [5].

Circulating microRNAs and breast cancer

Circulating miRNAs have been shown to be capable of distinguishing between patients with malignancies and healthy controls in various tumour entities, including breast cancer. Recently researchers have turned their efforts to investigating the potential prognostic and predictive value of circulating miRNAs. Some recent studies have shown that circulating miRNA profile could vary according to stage of disease and other variables.

Interesting data have been reported for breast cancer [6]. Heneghan and colleagues used whole blood for detection of miRNAs. They found that preoperative *miR-195* and *let-7a* expression was significantly higher in 148 breast cancer patients than in the age-matched healthy controls; they also reported that the level of these two miRNAs dramatically decreased after surgery. The potential role of miRNAs as non-invasive biomarkers for early detection of breast cancer is supported by a subsequent study by Zhao et al. who identified a panel of circulating miRNAs differentially expressed in serum samples from breast cancer patients and matched healthy controls. Another study, conducted by Roth et al. on 89 blood serum samples from patients with primary and metastatic breast cancer, has added evidence for the potential role of circulating miRNAs as non-invasive cancer biomarkers [6].

Of note, our group has recently demonstrated that circulating levels of miRNAs can be used as potential predictors of response to systemic therapies. Our data have demonstrated that high levels of *miR-210* in plasma of HER2+ breast cancer patients correlated with resistance to trastuzumab-based regimens [7].

MicroRNA and therapeutics

Preclinical studies have established antitumour effects of specific miRNAs in animal models of human cancers. Research tools already in place, engendered by the relatively mature siRNA (small interfering RNA) industry, will facilitate and abbreviate up-front discovery and development timelines for miRNA therapeutics. MiRNAs may provide an entirely new approach to potential treatments for a variety of cancers. However, miRNA-based therapies are entirely new techniques, and efforts should be directed towards achieving reliability, specificity and safety of these technologies.

Conclusions

MiRNAs play key roles in controlling gene expression, and each miRNA is thought to regulate several genes, influencing fundamental biological processes from cell development to cell death. Several studies have confirmed miRNA involvement in breast cancer oncogenesis and progression. Along with their diagnostic potential, miRNAs have also reportedly proved to be of prognostic and predictive value. Notably, regulation of the expression of miRNA in different cancer systems seems to affect response to current pharmacological treatments. Future studies will need to focus on the identification of miRNAs as predictors of response to systemic treatments and on feasible approaches to regulate their expression in cancer tissues in a most selective and specific manner.

Conflict of interest statement

None declared.

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