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Review

miRNA: A Potential Breast Cancer Treatment? How did we get here?

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Abstract

Objective

The purpose of this research was to summarize what is currently known about the role of microRNAs in breast cancer and their possible clinical use based on articles published in peer-reviewed publications up to March 2014.

Results

MicroRNAs (miRNAs) are a kind of tiny RNA that typically range in length from 21 to 25 nucleotides. It is already common knowledge that microRNAs (miRNAs) play a crucial role in almost every cellular activity in the body, from development to tumorigenesis. MiRNAs in the bloodstream have been demonstrated to be appealing, readily detectable tumor biomarkers in a number of investigations. Breast cancer is among the most frequent forms of the disease. Different subtypes have been shown to have varying therapeutic responses, metastatic potential, and medication resistance in clinical trials. MicroRNAs may be useful in several aspects of breast cancer care, including diagnosis, prognosis, and treatment.

Conclusion

To choose the most appropriate treatment for each patient, molecular understanding is essential. MicroRNAs have promising use in cancer treatment.

Keywords: Tumorigenesis, miRNA, Breast Cancer, and Biomarkers

1. Why is it so difficult to find a cure for breast cancer?

Breast cancer is one of the most common cancers in the world with more than 1,300,000 cases worldwide.1 This very heterogeneous disease is clinically divided by histological types based on expression of specific receptors: estrogen receptor (ER) positive (the most numerous and diverse), progesterone receptor (PR) and HER2 (ERBB2) receptor or the absence of all of them, named triple negative breast cancer (TNBC).1, 2, 3, 5, 26 Another classification of breast cancer distinguished luminal A, luminal B, basal and HER2 enriched groups.4 It is clinically established that different subtypes may respond differently to therapies, give metastases and present drug resistance.1, 6 For example, TNBC is associated with high risk of recurrence and distant metastases to the brain, compared to other, receptor positive tumours,7 and responses only to chemotherapy.1 Molecular knowledge is crucial for choosing the most suitable therapy for individual patients combined with cost-effectiveness of the treatment.98 Conventional treatment for breast cancer includes wide local excision, sentinel lymph node biopsy or axillary lymph node dissection, adjuvant medical treatment and radiotherapy to the whole breast.25, 99

2. MicroRNAs: A Quick Overview of Their Origin, Mechanism, and Function

MicroRNAs (miRNAs) are a class of short RNA molecules that range in length from 21 to 25 nucleotides8.9 No one anticipated the significant role that this class of molecules would play in gene regulation until it was discovered in 1993 by Victor Ambros et al.10 that the gene lin-4 did not code for a protein. It should come as no surprise that miRNA currently plays a role in tumour initiation and progression given its centrality in all known cellular processes of the organism, including but not limited to development, proliferation, apoptosis, differentiation, and organogenesis8, 9, 10, 11, 12. The biogenesis of miRNAs has been extensively studied.13 miRNAs can be intergenic, intronic, or exonic (in exons of coding or non-coding genes) and can be transcribed as a single miRNA from its own promoter (approximately 50% of the time) or as a cluster of miRNAs from a shared promoter.8, 14, 15 The transcription of miRNA is driven primarily by RNase III. The 5′-cap structure and the 3′-poly(A) tail of the long primary transcript (pri-miRNA) may be larger than 1 kb8, 16. Secondary hairpin structure formed by a region of imperfect complementarity is identified and processed by an RNAse complex. Stem-loop shaped pre-miRNAs are exported from the nucleus into the cytosol by exportin 5.17 The RNase III endonuclease DICER1 cleaves the pre-form, generating a double-stranded miRNA of 18-25 nucleotides in length.16 The double-strand is unwound and the single strands are incorporated into the RNA-Induced Silencing Complex - RISC. MicroRNAs, which are a part of this complex, can regulate gene expression post-transcriptionally by binding partial complementarity to target mRNA, typically leading to mRNA degradation or translation inhibition.19 These interactions typically occur near the 5′ terminus of miRNA molecules, contrary to previous beliefs. Computational methods are used to predict mRNA-miRNA interactions, and a number of algorithms are currently available.20 It is known that 3′-UTR mRNA may contain multiple miRNA-binding sites for different miRNAs, and a single miRNA may bind multiple targets.21, 22 The "many targets" hypothesis suggests that 60% of the mRNAs have one or more evolutionarily conserved sequences and that they are able to interact with miRNA.

Studies on chronic lymphocytic leukemia (CLL) have demonstrated that miR-15a and miR-16-1 are knocked down or knocked out in around 69% of CLLs (deletion of chromosome 13q14). This is the first evidence of the involvement of microRNAs in human cancer and was documented in 2002 by Calin and et al.27. The findings prompted the researchers to map all microRNA genes,28 many of which are found at highly variable chromosomal regions that are susceptible to deletions or amplifications. When a transcript encoding a tumor suppressor gene is amplified, it may lead to increased production of the miRNA and, in turn, the silence of the tumour suppressor gene if the miRNA is engaged in the negative regulation of the transcript. However, miRNAs that act to silence oncogenes are often found in regions of the genome called fragile foci, where they are particularly vulnerable to damage from events like deletions or mutations. This means that changes in microRNA expression are the norm rather than the exception in human cancer. Below we provide a few instances of how microRNA is engaged in the cancerogenesis process, as outlined by Hanahan and Weinberg in 2000.

Cancer cells are distinguished by their unchecked capacity to multiply. Multiple studies have shown that miR-34 regulates p53 and Notch pathways, consistent with its tumour suppressor activity. It is well known that Notch signalling maintains the balance between cell proliferation, differentiation, and apoptosis.65 Therefore, alterations in this signalling pathway are linked to tumourigenesis. Notch-1 and Notch-2 are downstream genes of miR-34 in pancreatic cancer cells,67 and Ji et al. reported that miR-34 restoration in human gastric cancer cells decreased expression of target gene Notch66. It is worth noting that pancreatic cancer stem cells are enriched with tumor-initiating cells or cancer stem cells with high levels of Notch-1/2 and loss of miR-34, suggesting the engagement of miR-34 in pancreatic stem cell self-renew

MiR-199 is another miRNA that has a role in controlling the Notch pathway. miR-199b-5p adversely influenced the proliferation of medulloblastoma (MB) cells by inhibiting Hes-1 (a transcription factor). Moreover, over-expression of miR-199b-5p reduces the number of cells with a stem-like phenotype (CD133+) and inhibits the expression of multiple cancer stem-cell genes.68 It is interesting that the level of miR-199b-5p was much greater in the non-metastatic cases

than in the metastatic ones. Patients from first group (high level) have exhibited a greater overall survival. MiR-290 cluster may directly target the Retinoblastoma-like 2 protein (Rbl2), alter telomere integrity and telomere-length homeostasis.69 Small, non-coding RNA plays also a key function in angiogenesis. Some microRNAs, including as let7-f, miR-27b, and miR-130a, have been shown to promote angiogenesis in vitro70, 71. Furthermore, Lee et al. discovered that miR-378 acts as an oncogene by suppressing the expression of tumor suppressors Sufu and Fus-1 to promote tumor cell survival and angiogenesis.

Some microRNAs were shown to have higher expression in BC tumor relative to surrounding tissues, as found in a research by Mojdeh Mahmoudian and colleagues. There was an upregulation of hsa-miR-25-3p, -29a-5p, -105-3p, and -181b1-5p and a downregulation of hsa-miR-335-5p and -339-5p. Except for hsa-miR-339-5p, these putative microRNAs were shown to have an up or downregulation related with TNM stages. All potential microRNAs linked with HER-2 status, with the exception of hsa-miR-105-3p. Further, ROC analysis indicated that the combination of these six microRNAs has the potential to act as a biomarker to distinguish between tumor and non-tumor breast tissue samples.

In human tumors, metastasis is the leading cause of death. There is currently strong evidence that microRNAs coordinate and play important roles in tumour invasion and metastasis.74, 75 Si et al. found that miR-21 was highly overexpressed in breast tumors compared to the matched normal breast tissues among 157 human miRNAs analyzed. MiR-21 has been demonstrated to inhibit tumor cell invasion and decrease expression of Pdcd4 in cultured colon cancer cells, according to research by Asangani et al.

4. Clinical methods for miRNA detection

Biomarkers must be used in clinical practice for detection and early diagnosis. Because of their compact size, miRNAs are very stable, making them an ideal diagnostic tool. It is important to further investigate the miRNA topic because of its potential use in tumor diagnosis, prognosis, and cure.29 Numerous studies have been developed on the global expression of miRNAs, and they can be detected and isolated from frozen and paraffin-embedded tissues, blood,37, 38 and various biologic fluids like urine,39 sputum40 or saliva41. MiRNA expression profiles (miRNome) have been shown to be superior than global mRNA profiling in discriminating between cancer types32, 35. It's also important to note that miRNA expression profile is tissue-specific, which might be useful in clinical diagnosis and treatment.36

Kong et al.24 provide a review of methods and strategies for profiling miRNA expression, and 46 the most pressing question is whether or not the miRNAs changing in a given disease are representative of, and unique to, that disease. Some miRNAs are already being used in clinical practice; for instance, the FDA has approved a miRNA-based diagnostic assay.47 The most widely used techniques for detecting miRNA are quantitative-reverse transcription polymerase chain reaction (qRT-PCR), hybridization-based methods, and next generation sequencing [review 47]. Using the Solexa deep-sequencing technology, Wei et al. systematically screened the miRNA expression profile of T-47D breast cancer cells treated with and without prolactin.62 They found a number of miRNAs significantly differentially expressed between these two panels and also detected several new miRNAs associated with the prolactin receptor signaling pathway in breast cancer. Several cutting-edge technological approaches have been proposed for miRNA research and analysis; these include a nanopore sensor based on the -haemolysin protein49 and an electrochemical genosensor that can readily detect miRNA in the serum or other biological samples.48 However, there are still significant limitations to use miRNA expression as routine in the clinic; thus, more clinical studies are needed.

5. The role of microRNA in breast cancer: a potential roadblock to curative treatment?

Iorio et al. (2005) were the first to report changes in miRNA expression in human breast cancer.50 They examined 76 breast tumors, 10 normal breast samples, and 14 breast cancer cell lines to determine which miRNAs are substantially

downregulated in cancerous tissues compared to normal ones. Microarray and Northern blot analysis found 29 miRNAs in this panel to have abnormal expression. The most often altered microRNAs in breast cancer were microRNA-10b, microRNA-125b, microRNA-145, and microRNA-21 and microRNA-155. This study shows that they may have a role in breast cancer tumourogenesis as either a tumour suppressor (down-regulated) or an oncogene (up-regulated). In 2007, Sempere et al. published a paper comparing the distribution of miRNas in breast tumor tissue and normal tissue from more than 100 patients using hybridization in situ.52 miR-125b expression is known to be high in differentiated cells and tissues51, so its decreased level in breast cancer suggests impaired differentiation capabilities of cancer cells. As was previously noted, miRNAs may suppress oncogenes, hence preventing tumorigenesis. In breast cancer, members of the ErbB family are frequently amplified or overexpressed (20-30%) and are significantly associated with a worse prognosis53, 54. Scott et al. examined miR-125a and miR-125b overexpression in SKBR3 cells, which decreased ErbB2 protein level by approximately 40-65% and ErbB3 level by around 60-80%.54 Wang et al.55 provided the first experimental evidence that miR-125a, miR-15b, and miR-205 collaborate to control the expression of ErbB2/ErbB3 in breast cancer cells.56 ErbB family is a promising target for selective anticancer medicines due to its involvement in tumourogenesis. There are two main types of ErbB-targeted medicines now in use in the clinic: tyrosine kinase inhibitors (such aslapatinib against EGFR and ErbB) and blocking antibodies (like transtuzumab targeting ErbB2). Antibody56 is the only known method of blocking the ErbB3 receptor, and it is now being examined in human clinical trials (http://www.clinical-trials.gov/). This is because to the poor or absent kinase activity of this receptor. Several studies have shown that ErbB2 requires ErbB3 to promote breast cancer cell proliferation57 and that ErbB3 plays an important role in ErbB2-altered breast cancers58. The same research team also found that ErbB3 contributes to ErbB2-mediated therapeutic resistance to tamoxifen59 and paclitaxel60, and they proposed a novel strategy to target ErbB2/ErbB3 by reducing their protein levels by microRNA rather than inhibiting only the

Two miRNAs, miR-10b* and miR-139-5p, were down-regulated and three, miR-425, miR-454, and miR-301a, were up-regulated for all three subtypes; they were shown to be differently expressed by Biagioni et al. Importantly, the soft agar colony formation experiment in MCF7 breast cancer cells demonstrated that lower levels of miR-10b* related to larger tumor growth, suggesting that this miRNA acts as a master regulator of breast cancer cell proliferation. Exploring the therapeutic potential of miR-10b* in breast cancer may need further in vivo research in a xenograft model, which demonstrated a vital function for miR-10b* in breast cancer cell proliferation64. Zhong et al. found that an altered miRNA expression pattern is important in gaining resistance to adriamycin and docetaxel which are two chemotherapeutic drugs routinely used in the treatment of breast cancer. Targeting PTEN.79 may be involved in this control.

As was previously established, miR-21 is crucial in the development of tumors. Wang et al. looked at how miR-21 expression correlated with doxorubicin sensitivity in breast cancer cells. They demonstrated that miR-21 dysregulation is crucial to doxorubicin resistance in breast cancer by using TaqMan RT-PCR and Western blot assay to identify mature miR-21 and tumour suppressor gene (PTEN) protein expression.80

Deregulation of miRNA-200c is associated with treatment resistance in breast cancer. Researchers found that miRNA-200c was down-regulated in non-responders compared to responders after analyzing miRNA expression in tumor samples from 39 breast cancer patients who had received neoadjuvant chemotherapy.81 Similarly, miRNA-30c was found to play a critical role in chemoresistance by directly targeting the actin-binding protein Twinfilin 1, which is responsible for promoting epithelial-to-mesenchymal transition.82 Both in vitro and in vivo, miR-19 inhibition sensitized MDR cells to chemotherapeutic agents.83 Although radiotherapy is a tried-and-true method of treating cancer, nothing is known about how microRNA may affect radiation resistance [revived in 85] in breast cancer at the present time. Interestingly, analyses have been performed on different cell lines that differed in their TP53 status, and the results suggest that miR-95 promotes radiation resistance independently of the TP53 function, as shown by Liu et al.85 in prostate and breast cancer. Experiments using xenograft tumor models showed that tumors overexpressing

miR-95 underwent reduced necrosis and increased proliferation while being irradiated. The production of miRNA-21 in breast cancer cells leads to radiation resistance by interfering with cell cycle progression (radiation-induced G2/M arrest).86 miRNA-21 has a function in radioresistance as a radioresistant miRNA. Antisense targeting of miR-155 by Chen et al.87 and miRNA-302 as a possible radiotherapy sensitizer by Liang et al.89 provide evidence for this hypothesis.

Important microRNAs in metastasis are called metastamiRs. It was shown in a poor prognosis phenotype, migration, and invasion. When comparing tumors with and without lymph node metastasis, the relative expression of miR-155 was significantly higher in tumors with lymph node metastasis.87 Similarly, Petrovi et al. found that miR-21 expression levels were significantly elevated in invasive with non-invasive component and pure invasive cancers compared with normal tissu. miR-21 is a major particular element to the process of invasion, since it shows the greatest difference between non-invasive and pure invasive cancer samples compared to other studied group pairs.92 Resistance to trastuzumab is a serious problem in the treatment of HER2+ breast tumors. Gong et al. looked for miRNAs that were differently expressed in the trastuzumab-resistant breast cancer cells, and observed that miRNA-21 was up-regulated among the reported PTEN-targeting miRNAs. They demonstrated that re-sensitizing resistant cells to trastuzumab's therapeutic activities—growth arrest, proliferation suppression, and G1-S cell cycle check—could be achieved by inhibiting miR-21 using antisense oligonucleotides.93

Using a polyamidoamine (PAMAM) dendrimers vector, Mei et al. showed that combining taxol chemotherapy with miR-21 inhibitor treatment reduced cell viability and invasiveness, suggesting that this may be a promising novel therapeutic approach for the treatment of breast malignancies.94 Tamoxifen (the selective oestrogen receptor modulator) resistance is a clinical issue in the treatment of HER2 positive breast cancer. Using tamoxifen-resistant MCF-7 cell models, Cittelly et al.95 investigated the role of microRNAs (miRNAs) in this phenomenon and concluded that miR-342 regulates tamoxifen response in breast tumor cell lines by modulating the expression of genes involved in apoptosis and cell cycle progression in tumor cells. Thus, restoring miR-342 expression may be a potential therapeutic strategy to sensitizing and reducing the development of tamoxifen resistant breast cancers. Another research team has linked MiR-221/222.96 to tamoxifen resistance in breast cancer. Overexpression of miR-145 reduces levels of cancer cell survival factors and inhibits cancer cell growth and metastasis, according to data published in 2011 by Kim and colleagues.97 They showed that miR-145 delivered via an adenoviral vector system significantly suppressed tumor growth in mice bearing breast tumors.

U.S. The function of microRNAs in breast cancer resistance and sensitivity is being studied in a clinical study (NCT01612871) authorized by the National Institutes of Health. Women with metastatic invasive breast cancer or locally advanced breast cancer for whom tamoxifen or anti aromatase medication is appropriate are eligible to participate in the trial. Participants are being sought for this research at this time [http://www.clinicaltrials.gov]. You may find online descriptions of several more clinical studies. Deregulation of microRNAs has a role in carcinogenesis, invasion, metastasis, and resistance to therapy. Different forms of human tumors have been linked to aberrant miRNA expression, suggesting that miRNAs may act as tumour-suppressor genes or oncogenes. Due to its various roles in cellular homeostasis and one-hit-many-target route, miRNA shows considerable promise as a therapeutic tool. MiRNA has been suggested in the literature as a possible biomarker for use in personalized medicine as a therapeutic tool.

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