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Review Article

BREAST CANCER; A REVIEW ON THE ROLE OF MiRNAs IN DISEASE PROGRESSION AND DRUG RESISTANCE

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Abstract:
Breast cancer is one among the most common types of cancer in women and is a leading cause of death. Early diagnosis and management of breast cancer has decreased the death rates due to breast cancer. The current treatment strategy for breast cancer combines surgery with radiotherapy, chemotherapy, targeted therapy and hormonal therapy. However, factors like relapse and drug resistance serve as major challenges in the successful management of this disease. . The recent studies identify the involvement of miRNAs in breast cancer development and drug resistance. MiRNAs are non-coding, single stranded RNAs that are composed of 20-25 nucleotide sequences. MiRNAs binds to the 3' untranslated areas of the target mRNA and mediate the gene expression at post transcriptional level. The aberrant expression of miRNAs leads to deregulation of gene expression and may result in drug resistance. The altered miRNA plays a vital role in metastasis, drug resistance and tumorigenesis. MiRNAs are involved in most of the major signaling mechanisms of our body and has a pivotal role in the development of neurological disorders, cardiovascular disorders, autoimmune disorders as well as various types of cancers like breast cancer. Recent studies also explore the potential of miRNAs as drug targets, biomarkers and therapeutic agents. In this review, we describe the role of miRNAs in chemotherapy resistance and disease development with special emphasis to the mechanisms involved. MiRNAs associated with the development of resistance to hormonal therapy is also being discussed here.
Keywords: Breast cancer , microRNAs, drug resistance

Introduction:

Breast cancer is one among the most common types of cancer in women and is a leading cause of death.[1] Breast cancer can be defined as the uncontrollable and continuous growth of breast cells that eventually leads to a tumor. Breast cancer mainly spreads through lymphatic system. Breast cancer may originate from lobules, ducts and less commonly from stromal tissues. All tumors that develop in breast need not be cancerous. Most of the tumors are non-cancerous and occur as fibrosis.[2,3]

The major risk factors for the development of breast cancer are gender, increased age, starting menopause at late ages, lack of breast feeding, having a first child at late age, being obese after menopause, early onset of menarche, being physically inactive, alcohol consumption, exposure to combination hormone therapy, use of oral contraceptives, familial history of breast cancer, and a history of breast cancer or non-cancerous breast diseases.[4]

Breast cancer is manifested with features like a lump in the breast region, nipple inversion, changes in the size or shape of breast, discharge from nipple, breast tenderness, skin dimpling and pain in the breast.[2]

Various screening tests like clinical breast examination, X-ray mammography, and breast self-examination has improved the early detection and diagnosis of breast cancer. Through breast self examination, one can easily recognize any possible changes in the breast anatomy.[5]

Early diagnosis and management of breast cancer has decreased the death rates due to breast cancer.[6] The

current treatment strategy for breast cancer combines surgery with radiotherapy, chemotherapy, targeted therapy and hormonal therapy.[7] However, factors like relapse and drug resistance serve as major challenges in the successful management of this disease. Even though there are various mechanisms for drug resistance and progression of breast cancer, the involvement of miRNAs gain more importance in recent studies. The aberrant expression of miRNAs leads to deregulation of gene expression and may result in drug resistance. The altered miRNA plays a vital role in metastasis ,drug resistance and tumorigenesis.[8,9]

Micro RNAs

MiRNAs are non-coding,single stranded RNAs that are composed of 20-25 nucleotide sequences. MiRNAs binds to the 3' untranslated areas of the target mRNA and mediate the gene expression at post transcriptional level.[10]

The biogenesis of miRNAs starts from nucleus and further maturation processes occur in the cytoplasm.[11] miRNAs can be classified as intergenic or intragenic. Intergenic miRNAs occur as independent units and have specific promoter, transcript and terminator regions . [11,12] Inside the nucleus, miRNA genes are transcribed to primary miRNA (pri-miRNA) by RNA polymerase II .[13] Pri-miRNAs are then cleaved to precursor miRNAs (pre-miRNA) with the microprocessor complex Drosha-DGCR8. [14] The pre-miRNAs are then delivered to cytoplasm with the help of exportin -5.[15] With the help of DICER ,which is a RNAase III enzyme and TRBP(transactivation response RNA binding protein), the pre-miRNA is further modified to mature miRNA duplex.RNA induced silencing complex (RISC) is formed from miRNA duplex by combining with Argonaute protiens with the aid of Dicer-TRBP complex.With the aid of RNA helicase,the duplex is unwound and converted into two single stranded miRNAs, the mature miRNA and the passenger strand.The mature miRNA remains attached to the RISC and undergoes base pairing with the target mRNA at the 3' untranslated region. This may result in translational repression or inhibition and in some cases, mRNA degradation occurs.[16] It is the degree of complementarity that determines the process to take place. A perfect base pairing of the miRNA with the mRNA can cause degradation of the mRNA and a partial complementarity can cause translational repression.[17]

Thus, miRNAs are involved in most of the major signaling mechanisms of our body and has a pivotal role in the development of neurological disorders, cardiovascular disorders, autoimmune disorders as well as various types of cancers like breast cancer. Recent studies also explores the potential of miRNAs as drug targets, biomarkers and therapeutic agents.[18]

MicroRNAs ASSOCIATED WITH THE PROGRESSION OF BREAST CANCER AND DRUG RESISTANCE

The abnormal expression of miRNAs related to breast cancer plays an inevitable role in the cancer progression and drug resistance.[9] The miRNAs involved breast cancer has been divided into two subtypes. They are oncogenic miRNAs (oncomiRs) and tumor suppressor miRNAs (tsmiRs). [19]

The upregulation of oncogenic miRNAs leads to expression of oncogenic genes and is associated with breast cancer progression. On the other hand, the downregulation of tumor suppressor miRNAs are involved in breast cancer progression.[19,20] The over expression of oncogenic miRNAs thus inhibits the action of tumor suppressor genes. This may further potentiate the action of oncogenes. Thus both the tsmiRNA and oncogenic miRNA re involved in angiogenesis, `metastasis and cell proliferation of breast cancer.[21]

Different screening procedures like miRNA microarray and high-through-put sequencing of the resistant cells discovered that various miRNAs were involved in breast cancer resistance. Subsequently, the evaluation of the selected miRNAs using clinical samples could identify the therapeutic targets for improved management of breast cancer.[22]

MiRNAs IN CHEMOTHERAPY RESISTANCE

Doxorubicin (Adriamycin)

Doxorubicin is an anthracycline antibiotic used as anti-neoplastic agent. It inhibits the growth of cancer cells by blocking topoisomerase II. Various miRNAs are involved in doxorubicin resistant breast cancer cell lines. The levels of tumor suppressor miRNAs

like miR-145, miR-128 and miR-505 is decreased in doxorubicin resistant breast cancer cell lines. These miRNAs are downregulated and is followed by an increase in the levels of MRP1.The enhanced expression of Multidrug resistance-associated protein 1(MRP1) leads to drug resistance in breast cancer. The upregulation of the above mentioned miRNAs sensitized the doxorubicin resistant cell lines and thus caused the reversal of doxorubicin drug resistance .Conversely, the downregulation of oncogenic miRNAs like miR-181a, miR-663 and miR-106b could sensitize the doxorubicin cell lines.

- MRP 1 act as targets for miR-145 and acts by inducing the intracellular accumulation of doxorubicin. The downregulation of miR-145 leads to doxorubicin resistance.
- MiR-128 is found to be decreased in breast cancer cell lines that are resistant to doxorubicin. The over expression of these miRNAs decreased the levels of Bmi-1 and ABCC5 which act as the targets and acts by increasing the apoptosis.
- Apoptosis is associated with sensitization to breast cancer treatment. In doxorubicin resistant breast cancer, miR-181a is upregulated and acts by inhibiting apoptosis.miR-663 also works by similar mechanisms.[18,23,24]

Paclitaxel and Docetaxel

These are cytotoxic drugs that are used to treat various types of cancer. They act by stabilizing microtubules and thereby enhancing cell death. Studies suggest that miR-100, miR-34a and miR-30c are downregulated in breast cancer cell lines resistant to paclitaxel. Whereas, miR-129-3p are upregulated in docetaxel resistant cell lines.

- MiR-100 works by enhancing cell cycle arrest and apoptosis using mTOR as targets. These are downregulated in chemo resistant cells.
- MiR-30c acts by reversal of EMT. However, the downregulation of these may activate EMT and leads to chemotherapy resistance by promoting tumour metastasis.
- MiR-129-3p is upregulated I docetaxel-resistance and acts by reducing apoptosis and cell cycle arrest.[18,25]

Cisplatin

Cisplatin is a chemotherapeutic agent used to treat solid tumors .It inhibits DNA synthesis and thus arrest the proliferation of cancer cells. Numerous miRNAs are involved in cisplatin-resistant breast cancer.About 46 miRNAs are upregulated and about 57 are downregulated in cancer cells resistant to cisplatin.[18,26]

MiRNAs IN HORMONE THERAPY RESISTANCE

Hormonal therapy showed promising potentials to fight with breast cancer. The identification of oestrogen receptor alpha in most of the breast cancer patients led to the use of oestrogen receptor modulators. Binding of tamoxifen to ER alpha receptors prevented the interaction of oestrogen with its receptor. Unfortunately, the altered expression of miRNAs were found to be associated with the development of resistance to hormonal therapy.

MiR-45 1a, miR-342, miR-320a,miR-873 were found to be downregulated in Tamoxifen resistant breast cancer cells. In contrast, miR-101 and miR-301 were upregulated.

- MiR-342 acts by enhancing apoptosis and downregulation of these miRNA leads to decreased apoptosis and increased resistance.
- MiR-873 inhibits the activity of ER alpha receptor and thereby decree se proliferation of cells. Downregulation of these miRNAs leads to reversal of the mechanisms and cause tamoxifen resistance.
- Upregulation of miR-101 potentiate P13K pathway and promotes the synthesis of growth factor s which is involved in drug resistance.[18]

CIRCULATING miRNAs- SOURCES

Circulating miRNAs are found in milk, saliva, plasma as well as serum. These are secreted to the body fluids by:

- Passive secretion from injured or inflamed cells
- Active secretion from membrane bound vesicles like exosomes or micro particles.
- Active secretion from miRNA-protein complex.

Both exosome derived and non- exosomal miRNA plays crucial role in breast cancer metastasis and drug resistance.[27] Exosomes act as intercellular vehicles

that helps in cell to cell communication by binding with cell membrane. Exosome mediated transfer of miRNA can thus contribute to cancer progression as well as drug resistance. Recent studies revealed the ability of exosome derived miRNAs to transfer drug resistance to sensitive cells.[17]

Besides breast cancer, exosome derived miRNAs also conferred drug resistance in other types of cancers like neuroblastoma. prostate cancer, pancreatic carcinoma etc. Along with miRNAs, other exosomal contents like P-gp are also involved in drug resistance.[17,28]

Conclusion

Even though advanced therapies are available in the management of breast cancer, relapse and resistance are major challenges. The recent studies identifies the involvement of miRNAs in breast cancer development and drug resistance. The dysregulated miRNAs leads to the altered expression of genes thus leading to metastasis and cell proliferation. The upregulation and downregulation of various miRNAs are involved in resistance to drugs like doxorubicin, cisplatin, tamoxifen etc.The property of miRNA to vary the expression of target genes can thus be utilized as a novel strategy for the treatment of breast cancer. Thus, miRNA based therapeutics has a very wide range of potential in the effective management of breast cancer disease. But in order to put these methods into practice, more knowledge has to be gathered regarding the mechanisms and consequences of miRNA based therapy.

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