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The Role of MiRNA in Breast Cancer

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Abstract

MicroRNAs (MiRNAs) constitute 19-25 nucleotide, non-coding RNA that regulate the expression of target genes, mainly at the post-transcriptional level. Breast cancer (BC) is most common cause of death in women accounting for 522,000 in 2012. It has got poor prognosis. In this review, we aim to provide a comprehensive story on miRNA signatures of cancers specially breast cancer.

Keywords: microRNA; therapeutic; diagnostic; breast cancer.

Introduction

Breast cancer (BC) is leading cause of cancer related mortality in women worldwide [1].

Although breast cancer has been detected at early stage as compared to earlier years, there is still many cases resulting into death .The chance of a woman having invasive breast cancer during her lifetime is about 1in 8.The chance of dying from breast cancer is about 1in 36 .BC is poor prognosis disease that alter molecular features, tumor characteristics, expression patterns and response to therapy. One of its feature of drug resistance specially triple negative receptor (TNRC) which is difficult to manage .In the past, there has been many research done at molecular level and some genes are found to be responsible for disease process but most of the molecular mechanism underlying its progression remain poorly understood. This has led to a significant interest in the quest for novel predictive marker for BC. Therefore advance therapeutic strategy needed to treat breast cancer.

Biosynthesis of miRNA

So there comes miRNAs which are 19-25 nucleotides, non coding negatively regulated gene expression mainly at post transcriptional level. They play significant role in tumor initiation .The dysregulation of miRNA results from mutation, and methylation of miRNA gene. MiRNA regulates gene expression making it a diagnostic and therapeutic biomarker in breast cancer. As there are many experiments done using miRNA as tool for different cancer ,it is essential to know about it Most miRNA genes are transcribed by RNA polymerase II as primary miRNA transcript. The primary miRNAs are further cleaved into 22^{nt} mature miRNA by RNAase III Drosha – DGCR8 (DiGeorge critical region 8) in nucleus and Dicer in cytoplasm.Mature miRNA recognizes its complimentary sequences in the 3' untranslated regions of an mRNA. MiRNAs bind the 3'untranslated regions (UTRs) of mRNA and suppress the mRNA translation. As a part of this complex, miRNA is able to regulate gene expression at a post-transcriptional level.

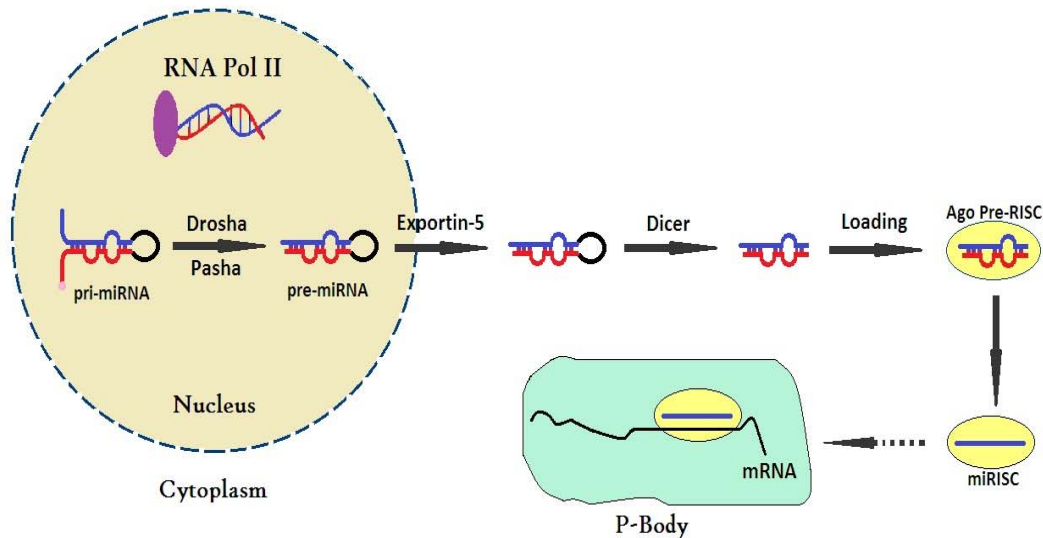


Figure 1: It shows biosynthesis of miRNA

MiRNA role in cellular processing

MiRNA are involved in various cell processes for determination and maintenance of cell lineage. It involves development, proliferation, apoptosis, differentiation, and organogenesis. Luo Q et al. showed that miR-497 regulates cell growth and invasion by targeting cyclin E1 in breast cancer. It act as a tumor suppressor gene inhibiting cellular growth, suppressing cellular migration as well as invasion and arresting G1cell cycle [2]. Korner C et al. showed that miR-31 sensitizes human breast cells to apoptosis by direct targeting of protein kinase C epsilon [3]

MiRNA as angiogenesis

Angiogenesis or vasculogenesis is the de novo formation of endothelial cells from mesoderm cell precursors which is essential for growth and development ,wound healing. However, it is also major step in the transition of tumors from benign state to

malignant .Angiogenesis and invasion are essential processes for solid tumor growth and dissemination. MicroRNA miR-98 regulates tumor growth, invasion, and angiogenesis using a highly aggressive breast cancer model in vitro and in vitro. MicroRNA miR-98 inhibits tumor angiogenesis and invasion by targeting active receptor-like kinase-4 and matrix metalloproteinase-11 [4].

MiRNA in cancer

Breast cancer linked miRNA can be subdivided into dual nature oncogenic MiRNAs(oncomiRs) and tumor suppresser miRNAs(tsmiRs) .OncomiRs are associated with overexpression or up regulation where as tumor suppressor miRNAs are frequently lost or down regulated in cancer. MiRNAs have been involved almost in all cancer like lung cancer [5],breast cancer [6] ,gastric carcinoma [7] ,papillary thyroid carcinoma[8] and colon carcinoma [9] Calin et al. have shown that frequent deletions and down regulation of micro-RNA genes miR-15 and miR-16 at 13q14 in Chronic lymphocytic leukemia [10] .Many of microRNA genes are located in chromosomal loci prone to deletions or amplifications.in 2005 ,Lorio et al. were first to describe miRNA gene expression deregulation in human breast cancer(6).Wang zx et al. study showed miR-21 deregulations plays a significant role in doxorubicin by targeting PTEN in breast cancer [11]. Metastasis is commonest cause of mortality in human cancer. MiRNA is involved in tumor invasion and metastasis.MiR-200 can repress breast cancer metastasis through ZEB1- independent but moesin dependent pathways [12].

Almost 90% of death related to cancer is from metastasis so finding a way to inhibit this metastasis may lead to substantial reduction in death. Several miRNAs like miR-301a, miR-103, miR-21,miR-9,miR-181-b1,miR-17,miR-489,miR-373 etc. have been found to promote metastasis. And finding a therapeutic strategy to reduce the expression of these miRNAs may lead to an effective approach for treating breast cancer.

Tumor suppressor miRNAs like miR-34, miR-126 affects cell proliferation , migration

and apoptosis. However miRNA-31 enhance primary growth tumor and suppress metastasis [13]. Mi-335 is an anti-metastatic miRNA that has been shown to down regulated in most breast cancer cases [14].

MiRNA can suppress cellular proliferation and cell signaling pathway targeting receptor like HER2. MiR-199b-5p inhibits HER2 by targeting HER2 3'-UTRs [15]. MiR-203 is a tsmiR that promotes apoptosis and cell motility .Its overexpression causes cell arrest, apoptosis and suppress cell motility and invasion

Different miRNAs studied in breast cancer

MiRNA	Expression	Target gene	Function	Remarks	References
MiR-145	Up	MMP11/ALK4			[16]
MiR-200	Down	BMI-1	Inhibition of self renewal		[17]
MiR-22	Down	TET (1-3)	Suppression of miR-200 family expression		[18]
MiR-21	Up	ANKRD46	Metastasis Proliferation		[19]
MiR-9	Up	CylinD1 E-cadherin	Metastasis	Oncogene pathway Wnt/B-cathetin	[20]
MiR10b	Up	Hoxd10 Syndecan-1	Metastasis		[21]

Drug Resistance

Although majority of primary breast cancer are ER α - positive and respond to anti-estrogen therapy, around one-third of patients with BC fail to respond to anti-estrogen therapy and have a poor prognosis. Zhao et al. demonstrated that miR-221 and miR-222

are frequently up-regulated in ER α - negative breast cancer cell. The overexpression of miR-221 and miR-222 contributes to tamoxifen resistance through negative regulation of ER α , whereas knockdown of miR-221 and/or miR-222 restore ER α expression and tamoxifen sensitivity [22]. Therefore, miRNAs could serve as potential therapeutic targets for drug resistance breast cancers.

MiRNA prognostic biomarker

Biomarker indicates severity or presence of some disease state. And the outcome of the condition can better explained with the help of miRNA. There has been many studies that shows miRNA a prognostic marker in different cancer . Markou et al [23] revealed miR-21 and miR-205 were significantly associated with disease free interval and only miR-205 with overall survival.

Conclusion

All these cited literature indicates that miRNA can play a vital role in cancer biology specially breast cancer. Understanding the molecular mechanisms involved in miRNA expression and secretion can lead medical science to next step both in clinical and basic research .Thus miRNA can act as a potential diagnostic and therapeutic biomarker in breast cancer.

Conflict of Interest

None declared.

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