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Review Article

BRCA1 and miRNAs: An Emerging Therapeutic Target and Intervention Tool in Breast Cancer

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Abstract

Reduced BRCA1 activity, either by germ-line mutations in inherited breast cancer or by epigenetic down-regulation in sporadic cancers, represents a key pathway in tumour development and progression. Although best known for its role in the maintenance of chromosome integrity, BRCA1 has recently been found to play a role in chromatin remodelling and transcriptional regulation, as well as in mammary epithelial stem cell differentiation or mammary stem cell fate decision. While BRCA1 potentially plays a significant role in both mammary tumour development and malignant progression, its function connection to tumor development is poorly understood. Recent studies have uncovered a new role of BRCA1 in the regulation of small (~19-25 nucleotides) non-coding microRNA (miRNA) expression in breast cancer cells. Several studies have also shown that aggressive breast cancers and breast cancer stem cells exhibit distinctive profiles of miRNA expression, suggesting that BRCA1 associated differential expression of miRNAs can regulate important cellular functions facilitating the maintenance of breast cancer stem cells and/or promoting breast cancer aggression. In this context, we will review recent progress in the understanding of the BRCA1 function, with emphasis on the implication of the development and progression of breast cancer via differential expression of miRNAs and discuss how these studies can improve our understanding of breast cancer pathogenesis. We will also discuss the perspectives of BRCA1 function through miRNAs and the role of miRNAs in regulating BRCA1 in breast cancer, more specifically tumor suppressor, miR-125 and oncogene, mir-155 as diagnostic and prognostic tools in clinical practice, and as new avenues for therapeutic interventions.

Keywords: Breast cancer, BRCA1, miRNA, biomarkers

Introduction

One of the main challenges for medicine in the current century is to integrate knowledge of the human genome into the medical management of patients, thereby yielding more precise diagnosis and mechanism-based deployment of therapy. Breast cancer is the second leading cause of cancer deaths in the developed world, after skin cancer, and the most commonly diagnosed cancer in women.[1] In United States, one in eight women will develop breast cancer in her lifetime. Worldwide, breast cancer accounts for almost 23% of all cancers in women, excluding non-melanoma skin cancers.[2] Due to lack of precise markers of the disease, many women receive unnecessary treatment with its attendant effects, and others die of disease despite aggressive therapy. Therefore, there remains an urgent need for more accurate biomarkers to diagnose and more importantly make prognosis of aggressive breast cancer. Hence, we discuss to identify more precise new molecular markers/targets for breast cancer in order to improve early detection of this aggressive disease and to develop new therapeutic regimens.

Breast cancer 1 (BRCA1) is a human tumor suppressor gene that plays critical roles in maintenance of genomic stability.[3] This gene is expressed in breast and other tissues, and helps to repair damaged genomes and disrupts cells when the genome cannot be repaired.[4] Recently reported that loss of BRCA1 is not prerequisite for the development of malignant breast cancer progression, but genetically inherited mutations in BRCA1 greatly increase the risk of breast cancer.[5] Although, it is a statistically rare event for all the mutations to occur at the right genes, at right places at right time, it still remains to be an open question how the joint probability of these rare events is related to the fraction of population affected by cancer. Indirectly speaking, the proportion of population affected by cancer is positively correlated to the probability of relevant mutations. Tumors arising in mutation carriers have generally lost the wild-type BRCA1 allele. In addition to being critically involved in DNA repair and maintenance of chromosome integrity,[6] recent studies have uncovered new functions of BRCA1 in chromatin remodelling and transcriptional regulation,[7] as well as in mammary epithelial stem cell differentiation or mammary stem cell fate decision.[8] Although poorly understood, these functions of BRCA1 can potentially play a significant role in both mammary tumour

development and malignant progression. Recent studies have also shown an important role of BRCA1 in small (19-25 nucleotides) non-coding microRNA (miRNA) associated regulatory mechanism involved in progression of breast cancer. miRNAs are differentially expressed when compared with the corresponding normal tissue, and some have tumor suppressor properties whereas others are oncogenic in breast cancer. The objective of this review is to give an insight into the role of BRCA1 and miRNAs as therapeutic target and intervention tool in breast cancer.

miRNA: Characterization and Biogenesis

The biogenesis of miRNA is a complex process, which is different from the small interfering RNA (siRNA). In contrast to siRNAs which are produced from long double-stranded RNAs or long hairpins and often of exogenous origin, miRNAs are endogenous and encoded within the genome and come from endogenous short hairpin precursors.[9] Therefore, miRNAs may be more important than siRNAs because of endogenous regulators of gene expression. In spite of some different or novel pathways for miRNA biogenesis, the broadly accepted classic biogenesis cascade of miRNAs has been elucidated as follows: miRNA gene → pri-miRNA → pre-miRNA →miRNA:miRNA duplex → mature miRNA[10-13] as shown in Fig. 1. In general, mature miRNAs are a class of endogenous, evolutionarily conserved, small non-protein coding RNA molecules, which are now recognized as crucial post-transcriptional regulators of gene expression involved in development and progression of tumors.[11]

Small non-coding miRNAs have been discovered from C. elegans in 1993, and initially it was not attracted much interest from the scientific community.[14] However, recently, it has emerged because of highly conserved and ubiquitously expressed miRNAs are of paramount importance for the regulation of gene expression in humans.[15] Subsequently, to date, it is predicted that the human genome encodes >1600 miRNAs have been described in the miRBase database, version 19, and each miRNA is predicted to regulate several hundreds of target genes, leading to the conservative estimate of >60% of human protein-coding genes being regulated by miRNAs.[16-17]

miRNA as a novel arm of gene expressional regulation tool has been widely used in gene functional studies in a variety of fields. More importantly, it has the great potential to be employed in drug development. Recent studies have clearly shown that miRNAs modulate and fine-tune almost all biological processes such as cellular proliferation, differentiation, cell cycle regulation, apoptosis, tumor invasion and metastasis[18] and consequently implicated in various human diseases, including heart diseases,[19-21] diabetes,[22] hypertension,[23] acquired immune deficiency syndrome (AIDS),[24] obesity,[25] and cancer.[26] In general, it is suggested that up to 30% of human protein-coding genes may be regulated by miRNAs[18] analysed by computational predictions of miRNA targets, indicating that miRNAs are one of the most abundant classes of post-transcriptional regulators of gene expression. Considering their remarkable regulatory potential in context of tissue- and disease-specific expression patterns, de-regulated or altered individual/global miRNA(s) expression profiles could be indicative of disease risks and burdens; therefore, miRNAs are currently being considered as possible biomarkers to support diagnosis and prediction of different types and stages of cancers.[15] However, the precise mechanisms and implications of miRNA actions are currently debated. Emerging evidence suggests that miRNAs play important roles in the carcinogenesis of various human cancers. Some miRNAs may be involved in cancers as oncogenes and/or tumor suppressors. More specifically, we will discuss here the implication of tumor suppressor miR-125, and tumor promoting miR-155 in breast cancer, focusing on the molecular basis on new biomarkers for cancer diagnoses, and prognosis evaluation.

Breast Cancer Associated miRNAs

Recent studies on miRNA profiling have revealed differential expression of a list of miRNAs in breast carcinoma compared to their normal tissue counterparts as shown in Table 1. Iorio and colleagues with others found a few numbers of miRNAs differentially expressed between tumor and normal tissues from a miRNA expression profile study on breast cancer research: more specifically, upregulated oncogenic miR-155, miR-21, miR-27; while tumor suppressor miR-125, miR-10b, let-7, miR-145 and miR-205 were found downregulated.[27] Current progression also revealed a number of the miR-125 family target genes and their regulation pathways involved in normal cell homeostasis, cell metastasis and different diseases, which could supply the feasibility of using miR-125 as a therapeutic strategy to suppress diseases like breast cancer.[28] In a recent report, Chang and colleagues identified a novel role for BRCA1 as an important mediator of epigenetic repression of an oncomir; miR-155.[29] Yan *et al*., 2008 has shown miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis, which is associated with enhanced metastatic potential.[30] Indeed,enforced downregulation of miR-21 has been shown to increase levels of PTEN and caspase-3, which are associated with an increased number of apoptotic cells and reduced invasiveness leading to drug sensitivity.[31-32] Given that the role of adipogenic inhibitors,[25] miR-[27]

is thought to be an oncomir that promotes tumor growth and metastasis by downregulating ZBTB10.[33] In addition, Heyn and co-workers identified miR-335 as a tumor-suppressor gene which controls different factors of the upstream BRCA1 regulatory pathway (such as ERa, IGF1R, SP1), inducing an upregulation of the tumor suppressor gene BRCA1.[34] Evidence of miRNA-mediated reversal of multidrug resistance in human cancer[35] warrants further studies of miRNA-based approaches for treating drug-resistant tumors. As dysregulated expression of specific miRNAs is a common phenomenon observed in human cancers, unraveling the underlying mechanisms misguided at each step of miRNA biogenesis is crucial to our knowledge on how these miRNAs are altered. Accumulating evidence in both transcriptional and post-transcriptional regulation has enabled us to understand the novel functions of classical transcription factors, and more interestingly, in controlling cancer-specific miRNAs. Here, we review in details the role played by two miRNAs, miR-125 and miR-155, in breast cancer development and progression.

miRNA-125: The Regulatory Network in Breast Cancer Progression

miR-125 family is composed of three homologs miR-125a, miR-125b-1 and miR-125b-2. Although miR-125 family members have been reported controversial properties in different types of cancer; they may contribute to the initiation and progression of cancers by acting as either tumor suppressors or oncogenes. Recently reported its tumor-suppressor functions in several cancers such as ovarian cancer,[36] bladder cancer,[37] hepatocellular carcinoma,[38] cutaneous squamous cell carcinoma[39] and osteosarcoma,[40] including breast cancer[41] and were found to be significantly down regulated in breast cancer patients[42] in biopsy specimens. miR-125 also act as tumor suppressors[43] by mediating the ERBB2 and ERBB3 pathway[41] or by targeting the ETS1 gene.[28] Furthermore, miR-125b reduces the expression of MUC1 oncoprotein, silencing of which in breast cancer cells with siRNA promotes DNA damage induced apoptosis as reported by Rajabi and his co-workers (2010).[44] Surprisingly, in contrast to tumor-suppressive function in breast cancer mentioned above, a very recent study by Tang *et al.* has verified that miR-125b also induces metastasis of human breast cancer cells through targeting STARD13.[45] Several studies have also shown its property to increase resistance of cancer cells, to anticancer drug,[46] resulting in subsequent recurrence and metastasis. Previously reported that miRNA-125a is inversely correlated with HuR expression in various breast carcinoma cell lines. HuR is an RNA binding protein (RBP) that is upregulated in several different cancers. It was found that miR-125a can potentially aid in tumor suppression in breast cancer by utilizing HuR as a direct and functional target. HER2, the human epidermal growth factor receptor 2, has no ligand-binding domain and thus cannot bind growth factors but it binds to other ligand-bound epidermal growth factor receptor family members to create a heterodimer.[47] The miR-125a and miR-125b function as tumor suppressors in SKBR3 cells, a HER2-overexpressing human breast cancer cell line, by suppressing HER2 mRNA and protein levels. The c-Raf has also been proposed to be regulated by miR-125b leading to its antiproliferative effect.[48]

In contrast to the tumor-suppressive properties mentioned above, the members of miR-125 family, especially miR-125b, also act as oncogene in several cancers such as pancreatic cancer,[49] prostate cancer,[50] oligodendroglial cancer.[51] The controversial properties of the miR-125 family in different solid tumors suggest that miR-125 plays diverse functions in cancer pathogenesis and progression, while the underlying mechanisms on different cell context need further investigation.

Members of Bcl-2 family involved in apoptosis are an important group of miR-125 targets. Anti-apoptotic members of Bcl-2 family such as Bcl-w, Bcl-2, Mcl-1, and Bak-152 acting as the Bcl-2 homologous antagonist, and others involved in apoptosis like P53, TP53INP1, TNFAIP3, p38α etc have all been demonstrated to be direct targets of miR-125.[52] Aberrant expression of miR-125 leads to up-regulation of Bcl-2, Mcl-1 and down-regulation of Bak-1, TP53INP1 and consequently to protect cells from apoptosis, which in turn promotes tumorigenesis.[52] Besides, p38α expression repressed by miR-125b is required for protecting cells from UV-induced apoptosis. ERBB2, which enhances kinase-mediated activation of downstream signaling pathways such as MAPK, has been verified to be the target for both miR-125a and miR-125b.[41] Experimentally, miR-125-induced downregulation of ERBB2 and ERBB3 has been uncovered to reduce cell motility and invasiveness of numerous cancers, including breast cancer[41] and endometrial cancer.[53] Among other targets of miR-125 associated with proliferation, metastasis and migration, HuR, Rock-1, PDPN, STAT3 and STARD13 are five important genes identified, which can induce cell metastasis and migration, and in turn enhance tumorigenesis.[52] Furthermore, CBFβ, a transcriptional factor involved in hematopoiesis, which has been confirmed to be a new direct target of miR-125b, and ABTB1, an anti-proliferative factor targeted by miR-125b, also contribute to block differentiation and proliferation in leukemia, respectively.[54-55] Matrix metalloprotease MMP11, MMP13, Kurppel-like factor KLF13, c-Jun, ARID3B (AT-rich interactive domain 3B), ARID3A (AT-rich interactive domain 3A), germ layer specification and hematopoiesis regulator LIN28A, growth factors such as VEGF-A and IGF-II, and growth factor

receptors like FGFR2 are also implicated in tumor progression targeted by miR-125.[52] It is necessary to mention that the same target may have different functions in different cellular processes, cellular context, and diseases. miR-125 can act as cancer promoter or cancer repressor depends on the cell context. The down regulated miR-125 caused breast cancer but the up regulated miR-125 induced chemoresistance.

miRNA-155: The Regulatory Network in Breast Cancer Progression

miR-155 is overexpressed in several human carcinomas, including breast cancer.[56] It is an effective suppressor of apoptosis, due to its effects on caspase 3, the most important caspase that is involved in the execution-phase of apoptosis.[57] The tumor-suppressor gene suppressor of cytokine signaling 1 (*SOCS1*) has been identified as a target of miR-155 in breast cancer cell lines[58-59] and the expression of *SOCS1* was found to be inversely correlated to miR-155 expression in human breast cancer cells. Ectopic expression of miR-155 also enhanced proliferation of breast cancer cells and the development of tumors *in vivo*.[60] Furthermore, silencing of SOCS1 in breast cancer cells re-establishes the oncogenic effects of miR-155, while restoring SOCS1 expression promotes the pro-tumorigenesis function of miR-155, which indicates that miR-155 negatively regulates SOCS1.[60] Another study also showed that miR-155 is upregulated in normal mouse mammary gland epithelial cells (NMuMG cells) by the TGF-β pathway and it mediates TGF-β-induced epithelial-to-mesenchymal transition (EMT) and cell invasion.[61] The ectopic expression of miR-155 in NMuMG cells disturbs proper tight junction formation between cell walls and promotes cell migration and invasion.[62] In addition, miR-155 directly inhibits the expression of RhoA, which regulates various cellular processes, including cell adhesion, motility, and polarity.[63] Overall these studies demonstrate that miR-155 is regulated by the TGF-β pathway and also downregulates the RhoA protein expression to enhance the acquisition of EMT phentype. miR-155 is highly expressed in invasive tumors but not in noninvasive cancer samples.[64] Therefore, the miR-155 appears to play an essential role in breast cancer metastasis due to its implications in the acquisition of EMT and increased potential for invasion and metastasis. Another role of miR-155 in the regulation of cell survival is seen through the downregulation of its direct target FOXO3a in breast cancer. Ectopic expression of miR-155 induced cell survival and chemoresistance to several agents led to repressed FOXO3a protein with consistent mRNA levels, while the knock-down of miR-155 resulted in increased FOXO3a involved in apoptosis and increased chemosensitivity.[61] Overall it revealed that there is an inverse correlation between miR-155 and FOXO3a in breast cancer cell lines, suggests that miR-155 might be an essential therapeutic target in breast cancer.

miRNAs Regulated by BRCA1

BRCA1 is a large protein with multiple functional domains and interacts with numerous proteins including BACH1, BARD1, and p53 to regulate many important biological processes.[65] It regulates many target genes including a few listed miRNAs involved in tumor progression as shown in Table 2. Most importantly, it has been shown elevated miR-155 levels are consistently found in aggressive human breast cancers.[66] In a recent report, BRCA1-mediated epigenetic repression at the promoter region of miRNA-155 was identified as a novel mechanism by which BRCA1 carries out its tumor suppressor functions and indicates miR-155 to be a model of miR-155 mediated regulation of BRCA1 and its functional consequences in breast cells and its deregulation.[29] Cancer cell model systems supported the effect of the miR-155 on the equilibration between cancer cell proliferation and cell death. The significance of this regulation was underlined in primary sporadic breast cancers demonstrating an altered expression of miR-155. Therefore, it is described one major miR-155 supervising signal cascades crucial for breast tissue homeostasis, represents another example of a superior function of miRNAs in the regulation of entire pathways, which may reflect a common mechanism, defining single miRNAs as gatekeepers by simultaneously regulating molecules of a network, important for crucial cellular functions. Deregulation of such individual miR-155 can thus have a dramatic impact on the cell and tissue homeostasis, directly offering a promising diagnostic tool and therapeutic target.

BRCA1 Regulated by miRNAs

Studies have shown that BRCA1 expression is often down-regulated in aggressive breast cancers,[67] and breast cancer stem cells exhibit distinctive profiles of miRNA expression,[35] suggesting that miRNAs can regulate important cellular functions facilitating the maintenance of breast cancer stem cells and/or promoting breast cancer aggression, although the underlying mechanisms remain poorly understood. Most importantly, it is reported that miRNAs such as miR-146a, miR-15, miR16, miR17, miR182 regulate BRCA1 by interacting with its 3'UTR. A recent report revealed that several tumor-suppressor miRNAs are induced by EZH2, including miR-146a, let-7a-d, miR-26a, miR-101, and miR-200b and c. EZH2 is a histone methyltransferase involved in epigenetic regulation of many genes.[68] The increased level of EZH2 is likely to increasing the expression level of miR-146a, which in turn will down-regulate BRCA1. Conversely, knockdown of EZH2 was shown to increase BRCA1.[69] Interestingly, a report showed EZH2 is up-regulated in BRCA1-deficient tumors and tumor cell

lines,[70] suggesting a positive feedback loop that down-regulates BRCA1 by the EZH2-miR-146a pathway. miR-15a has been proposed to be a tumor-suppressor miRNA which induces apoptosis and reduces tumorigenicity in chronic lymphocytic leukemia through the regulation of antiapoptotic Bcl-2 expression.[71] This implication is further supported by Yang et al. who showed curcumin, an anti-cancer agent, up-regulates miR-15a and miR-16, which can down-regulate Bcl-2 in MCF7 cells.[72] Since miR-15a and miR-16 were shown to target BRCA1, these miRNAs appear to have a dual role. miR-17 is transcribed from a miRNA cluster gene, miR-17-92. Castellano *et al.*[73] revealed that the miR-17-92 is transactivated by Myc in an ER-alpha-dependent manner and targets BRCA1, indicates a mechanism by which the oncogene Myc may repress tumor-suppressor BRCA1. On the other hand, Yu *et al.*[74] showed that Cyclin D1 induces miR-17-92, and miR-17/20a represses Cyclin D1 levels, forming a negative feedback loop. Because BRCA1 is dynamically regulated during cell cycle progression, the feedback loop suggests a possible mechanism of cell cycle-associated change in the BRCA1 level. miR-182 has also shown to regulate the expression of BRCA1. A recent study showed miR-182 to be regulated by RNA helicase DDX5 in basal breast cancer cells.[75] Interestingly, another study found that p53 interacts with the Drosha processing complex through its association with DDX5, which facilitates the processing of primary miRNAs, including miR-16-1 and miR-143.[76]

BRCA1, miRNA and Stemness

Recent findings suggest a role for tumor progenitors, known as cancer-initiating or cancer stem cells (CSCs), in the propagation of a drug-resistant phenotype in numerous malignancies, including breast cancer.[77-78] The cancer stem cell hypothesis posits that conventional chemotherapies, targeted to highly mitotic cells, fail to destroy quiescent or slowly dividing CSCs, which then re-grow the tumor.[79-80] Because epigenetic therapies are well-established differentiating agents,[81-83] may also target poorly differentiated CSCs, could allow for the establishment of epigenetic breast cancer diagnostic, prognostic, and pharmacodynamic biomarkers[84-86] for improved interventions against this devastating malignancy. Current studies also reported that exploitation of EMT-related miRNAs as a form of differentiation therapy may represent a novel therapeutic strategy for the treatment of advanced breast cancer, unlike traditional gene therapy, because the fact is miRNA can simultaneously target many key genes/proteins involved in the process of EMT. Therefore, it remains to be determined how miRNAs introduced to prevent or reverse EMT in breast carcinoma cells will affect normal differentiated epithelium or normal stem cells. Furthermore, recent findings raise the question as to whether it will be detrimental to drive an MET in cancer.

Recent studies reported that loss of BRCA1 blocks differentiation of mammary progenitor cells and facilitates the development of "basal-like" mammary tumors.[87] BRCA1 expression increases during differentiation of mouse mammary epithelial cells; loss of BRCA1 impairs mouse epithelial differentiation and increases the population of mammary progenitor cells,[88] suggesting a critical role of BRCA1 in the regulation of mammary progenitor cells. However, how BRCA1 regulates mammary epithelial differentiation remains poorly understood. Based on recent studies, it is reported that BRCA1 promotes mammary epithelial differentiation by repressing miR-155 expression.[29] "Basal-like" breast cancer cells are aggressive and show increased stem cell resemblance.[29,78] Interestingly, loss of BRCA1 facilitates the development of "basal-like" mammary tumors[87] and enhances self-renewal of breast cancer cells, suggesting that the BRCA1-miR-155 pathway may constitute a new mechanism underlying the role of BRCA1 in breast cancer development and malignant progression. The schematic diagram showing the regulation of miRNAs involved in progression of invasive breast cancer from its normal tissues (Fig. 2).

Therapeutic Implications of BRCA1 Associated miRNAs in Breast Cancer

Recent advances in the miRNA research have provided us more insights and improved understanding towards miRNA biogenesis, function and particularly their association with molecular pathogenesis of a variety of complex diseases including cancer, heart diseases, chronic viral infections, immune disorders, neurodegenerative disease and metabolic diseases. Moreover, understanding the miR-125 and miR-155 signatures in susceptible individuals including their expression profiles, dynamics, may eventually enable the miRNA-based individual-specific therapy, as well as disease diagnosis and prognosis. In addition, miR-125 and miR-155 specific delivery, an invaluable tool for various areas of basic and applied research and, more importantly, for therapeutic intervention in different aspects of human carcinogenesis, such as cell proliferation, apoptosis, differentiation, angiogenesis, motility and metastasis, to target cell populations using approaches of nanobiotechnology looks promising. Re-expression of miRNAs down-regulated in cancer e.g. miR-125 and/or silencing of miRNAs up-regulated in the tumor e.g. miR-155 may lead to cancer cell apoptosis and are the ideal targets for developing therapeutics.

Conclusion

The involvement of BRCA1 associated miRNAs, most specifically miR-125a/b and miR-155 as the promising molecular targets for breast cancer treatment. Other aspects such as their role as

molecular biomarkers, the identification of the full spectrum of targets of a given miR-125/miR-155 need to be elucidated in light of the specific genome. Since miR-125 and miR-155 play key roles in human cancer, identifying the underlying pathways and ways to regulate them will provide a more complete understanding of their functions and regulations during cancer progression and may have clinical applications in the future.

Based on the evidence discussed above, the question arises of whether miR-125 and miR-155 can be used as a biomarker to guide treatment selection with respect to DNA-damaging agents. Further, there have been considerable efforts in determining whether circulating miRNAs in blood-stream can be used as biomarkers for early detection of cancer based on its potential early involvement, miRNA-155 could represent a candidate marker in this respect. Therefore, early detection, prognosis of breast cancer-specific miR-125 and miR-155 in plasma provides a relatively non-invasive method for monitoring predictive markers, with the expectation that they will exhibit a greater degree of specificity and sensitivity over the current biomarkers. In the future, miRNA-based treatments, in combination with traditional cancer therapies, may be a new strategy for the clinical management and especially for drug-resistant breast cancers. However, more robust quantitative understanding between BRCA1 associated miRNAs (specifically miR 125 and miR 155) and breast cancer development is still lacking. Quantification of this association would play a critical in development of technology driven tools. Before this becomes a reality in patients though, several issues need to be addressed. First, there is a need to know the full spectrum of targets and effects that a given miR 125 and miR 155 have on a given genome to fully characterize this aspect before any clinical application can even be taken into consideration. Due to time sensitive nature of cancer propagation, highly efficient characterization would play a critical role for preventive actions. Second, how miR 125 and miR 155 participate in fine tuning of breast cancer stem cell maintenance. Third, it needs to be established how can we reach a tumor-specific delivery of the miRNAs of interest? The advent of nanoparticles, able to target tumor-specific antigens hopefully will address this concern and allow tumor specificity. Another aspect of relevance consists in determining how the modulation of miRNA expression can integrate the existing anti-cancer therapies. Overall, this implies that miRNAs have great potential to be developed as a novel class of therapeutic targets. Although researches are presently at the bench level, they are promising to be translated into therapeutic agents in the future for tackling diseases on the cellular miRNA level.

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Conflicts of Interest

The author(s) declared no potential conflicts of interest.

Table 1. List of Breast Cancer associated miRNAs

miRNA	Potential Target	Illustration	References
miR-21	Bcl-2, TPM1, PDCD4	Oncogenic	[89-91]
miR-27	ZBTB10, RYBP, MYT1	Oncogenic	[92-93]
miR-10b	RHOC	Invasion and metastasis	[94]
miR-17-5p	AIB1	Tumor suppressor	[95]
miR-335, miR-126	SOX4, TNC	Metastasis suppressor	[96]
miR-27b	CYP1B1	MCF-7 cells (+), Jurkat cells (-)	[97]
miR-125a, b	ERBB2, ERBB3	Coordinate suppression	[41]
miR-155	SOCS1, APC	Related to biopathologic features	[27]
miR-206	ER-α	Represses mRNA and protein	[98]
miR-9	REST	Epigenetic inactivation	[99-100]
let-7	Ras, HMGA2	Self-renewal, tumorigenicity	[101]
miR-145, miR-205	PTEN, ZEB1, ZEB2	Biomarkers	[102-103]
miR-373, miR-520c	Cd44	Invasion and metastasis	[104]
miR-146	IL-1, TRAF6	Suppresses NF-κB	[105]
miR-200 family	ZEB1, ZEB2	Regulate EMT	[106-108]
miR-210	Efna3, Ptp1b	Prognostic factor	[109-110]

Table 2. List of miRNAs regulated by BRCA1

miRNA	Potential Target	Illustration
miR-146a	SMAD4, TRAF6, RAK1	[111]
miR-99b	SMAD3, phosphorylation	[112]
miR-155	PU1, C-MAF, SHIP-1, SOCS-1	[112]
miR-205	ZEB1, SIP1, PKC-ε	[113]
miR-29a, 29b	MCT-1, Cyclin T2, Cdk6, NAS	[114]

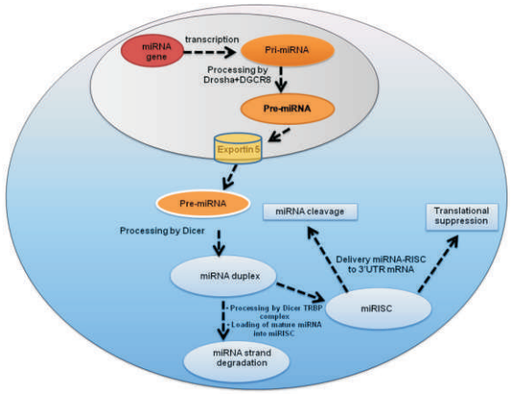

Fig. 1: Schematic overview of biogenesis and function of miRNAs. The miRNA-coding genes are transcribed by RNA polymerase II into long primary transcript of miRNA (pri-miRNA) containing the hairpin structure. These pri-miRNAs are subsequently processed into precursors of miRNAs (pre-miRNA) by nuclear RNase III Drosha with the aid of cofactor DGCR8. Following nuclear processing, the pre-miRNAs are exported to the cytoplasm by a nuclear transport receptor, Exportin-5, before being processed by the cytoplasmic RNase III Dicer into mature miRNAs. Finally, the single-stranded miRNA are incorporated into an RNA-induced silencing complex (RISC) to induce translation suppression or degradation of cellular mRNAs depending on the degree of complementary with the target mRNA.

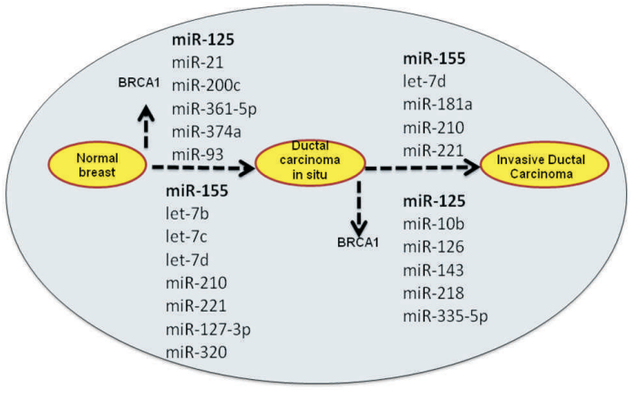

Fig. 2: The key miRNA changes along the cancer progression from normal breast to ductal carcinoma in situ (DCIS) and then to invasive ductal carcinoma (IDC). The two miRNAs (miR-125 and miR-155) with bold typeface were reversal in gene expression. Key breast cancer gene BRCA1 was inversely related to miR-155 and displayed expression reversal along the breast cancer progression path, along the DCIS/IDC progression axis.

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