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Review Article

Potential Role of miR-21 in Breast Cancer Diagnosis and Therapy

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Abstract

MicroRNAs are a large family of short non-coding RNA molecules involved in the regulation of gene expression. MIRN21 gene residing on chromosome 17 is linked to cancer initiation, progression and therapeutic response.

The mature miRNA is 22 nucleotides long, forms one strand of the RNA duplex which is incorporated into a protein complex, targeting a partially complementary target mRNA. miRNAs act not only within cells of origin but are transported into the bloodstream and is taken up by recipient cells and processed into mature miRNA.

miRNA expression signatures are associated not only with specific tumor subtypes but in clinical outcomes as well. Deregulation of miRNA in cancer takes place by transcriptional deregulation, epigenetic alterations or mutation.

MiR-21 are considered an 'oncomir' since it could suppress the actions of several apoptotic and tumor suppressor genes, leading to tumor cell proliferation, inhibition of apoptosis, migration, invasion, angiogenesis, and metastasis. The reduction or deletion of a miRNA, because of defects of its biogenesis, leads to tumor formation. The amplification or over-expression of a miRNA that has an oncogenic role would also lead to tumor formation. Clinical characteristics of breast cancer associated with increased miR-21 expression level were significantly correlated with higher tumor grade, increased tumor size, lymph node involvement, lympho-vascular invasion and in patients with poor prognosis.

Quantification of microRNAs can be used to predict the prognosis, clinical behavior of the tumor, and monitor the response to treatment. Altered serum or tissue microRNAs expression has served as a useful potential non-invasive biomarker for cancer detection, evaluation, and follow-up. The level of miR-21 expression is significantly associated with clinicopathological factors and the prognosis of tumor patients.

Modulation of miR-21 expression as potential cancer therapy was investigated in various cancer types. The inhibition of miRNAs, using antisense oligonucleotides (ASOs) and artificial oligonucleotides constructed on a peptide-like backbone are effective techniques for investigating miRNA functions and targets. Therapeutic delivery, using specific antisense oligonucleotide of miR-21 may still be beneficial for a large number of cancers for which no cure is available. Inhibitors of miR-21 may also function as effective approaches for reversing drug resistance in cancer cells.

INTRODUCTION

MicroRNAs are a large family of short non-coding RNA molecules involved in the regulation of gene expression [1]. It is estimated that the human genome may encode more than 1000 microRNAs, which may target up to 30% of all genes in the human genome [2].

Several important genes are associated with breast cancer, including oncogenic genes HER2, TOP2A and TAU, tumor suppressive genes p53, BRCA1, HIC-1, DNA double-strand break repair, recombination gene RDM1 and MIRN21 gene [3]. Recently, many studies suggested that several genes residing on chromosome 17 are linked to cancer initiation, progression and therapeutic response [4-6].

Genomics of MicroRNA-21

MIRN21 gene that is located along the long arm of chromosome 17 (17q23.1) in an intergenic region (Figure1), starts at 57918627 and ends at 57918698 bp from pter residing within the tenth intron of the TMEM49 (Transmembrane Protein-49) gene in the direction of transcription, [7].

The length of MIRN21 gene is reported as 3433 nucleotides long. It overlaps with the 3' UTR end of the Transmembrane Protein 49 (TMEM 49) (also known as Human Vacuole Membrane Protein 1, VMP-1).

MIRN21 gene has two transcription start sites, T1 (the minor transcription site) and T2 (the major transcription site); both

are utilized for initiation of transcription. The gene harbors its own promoter regions (5' promoter element; "CCAAT" box transcription control element, located approximately about 200-nt upstream of the T1 transcription site) that is located within the intron of the overlapping protein coding gene.

RNA Pol II is suggested to be the most likely enzyme involved in miRNA transcription due to the presence of 5' cap and 3' poly (A) tail of the pri-MIRN21. Chromatin immunoprecipitation (ChIP) analysis of upstream sequences of MIRN21 showed enrichment for Pol II but not Pol III. The maturation of miRNA involves sequential processes. The miRNA genes are first transcribed in the nucleus as long primary transcripts 3433-nt long called pri-miRNA.

The primary transcripts of microRNAs are processed by the enzymatic microprocessor Drosha (RNase III enzyme) and DGCR8 (dsRNA binding protein) from their 3' and 5' cleavage sites into an intermediate stem-loop precursor or pre-miRNA in the nucleus. The precursor of MIRN21 is 72 bases long (pre-MIRN21), forms a secondary structure, and contains the mature miRNA sequence, stem and terminal loop structures with 2-nt 3' overhang. The precursor is then transferred from the nucleus to the cytoplasm by the enzyme Exportin 5. In the cytoplasm, a second RNase III enzyme, Dicer, removes the terminal loop generating about 20-bp RNA duplex (Figure 2).

The mature miRNA is 22 nucleotides long, forms one strand of the MicroRNA duplex. One strand is degraded and the other is incorporated into a protein complex. miRNAs are not translated into amino acids, [7,8]. RNA induced silencing complex (RISC), targeting a partially complementary target mRNA. MicroRNA targeting is mostly achieved through specific base-pairing interactions between the 5' end ('seed' region) of the miRNA recognition elements (MREs) in the mRNA targets (typically the 3' untranslated region - (3' UTR).

MicroRNA-dependent regulation of gene expression relies on the degree of complementarity between the mRNA and miRNA. In the case of perfect base pairing, the mRNA is degraded in

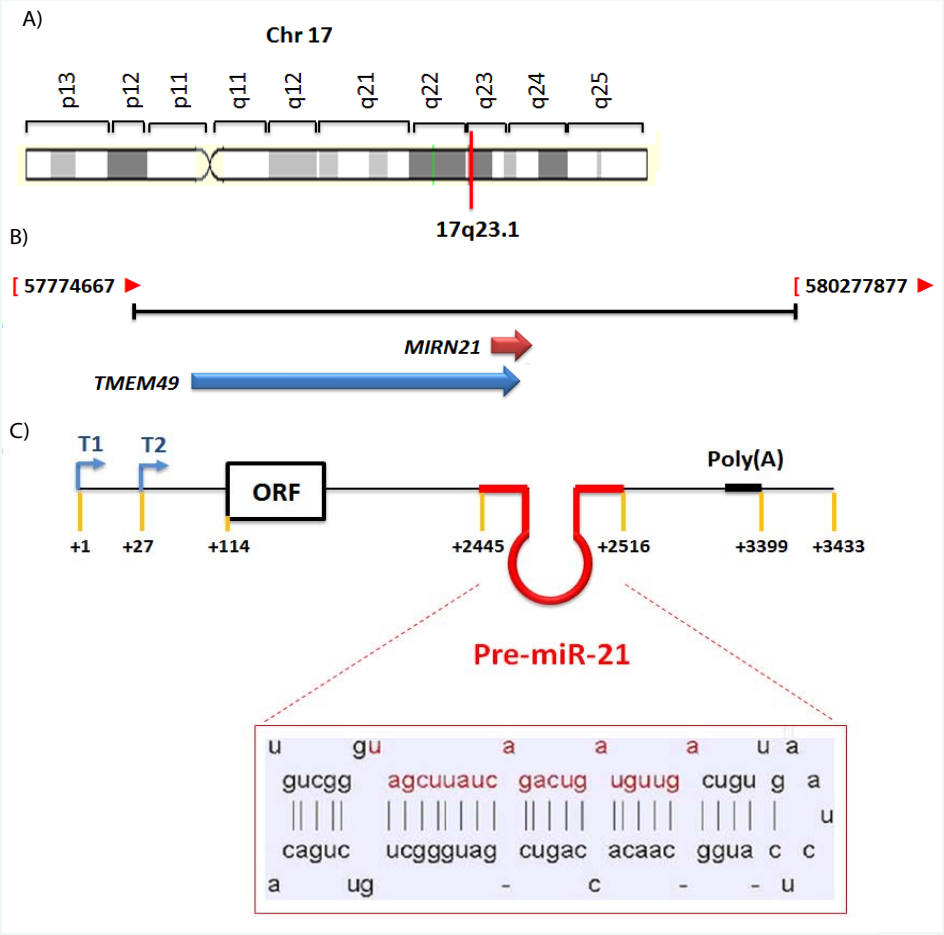

Figure 1 Location of microRNA-21 gene on chromosome 17.
(A) *MIRN21* gene lies within an intergenic region along the long arm of chromosome 17 region 2 band 3.1 (55273409-55273480, + strand).
(B) *MIRN21* gene overlaps with the 3' UTR end of the *TMEM49* gene (ncbi.nlm.nih.gov/gene/406991).
(C) Structure of full length microRNA-21 gene and Stem-loop structure of *MIRN21*
MIRN21 gene has two transcription start sites, T1 (the minor transcription site) and T2 (the major transcription site). An Open Reading frame (ORF) analysis within the 3433-nt identified a potential peptide sequence, located near the transcription start site (+114), encoding 124 amino acids long peptide with unknown function. The red loop resides the MIRN21 stem-loop precursor between nucleotides +2445 and +2516 of pri-miR-21. Poly (A) is the poly adenylation signal between nucleotides +3394 and +3399 [7].

specialized cytoplasmic regions called the processing-bodies (p-bodies), whereas imperfect match leads to translational inhibition without influencing mRNA integrity [9-11].

miRNA acts not within cells of origin but acts at other sites within the body. Pre-miRNA, packaged into exosomes and/or multivesicular bodies, are transported into the bloodstream and taken up by recipient cells and processed into mature miRNA to inhibit the expression of target protein-coding genes in the recipient cell (Figure 2) [12,13].

The regulatory mechanism of miR-21 expression is highly complex as it involves the unique miR-21 promoter, multiple transcription factors, hormones and signaling events that activate miR-21 transcription machinery [14].

The expression is driven by its own promoter, which contains binding sites for multiple transcription factors such as NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), AP-1 (activation protein-1), STAT3 (Signal transducer and activator of transcription 3), and NFIB (Nuclear factor-I/B protein). MiR-21 transcription is induced by transcription factors STAT-3, AP-1, and NF-κB, but repressed by NFIB. The microRNA itself participates in feedback loops with these transcription factors that regulate their transcription [14].

Although the majority of miRNAs are intracellular, some have been detected outside cells, including various body fluids. Extracellular miRNAs are not only passive released outside the necrotic or injured cells, but are strictly regulated with significant concentrations. However, the biological stimuli that trigger miRNA secretion in vesicles or in a non-membrane bound form and factors that modulate circulating miRNA levels are still unclear [1].

MicroRNA as tumor suppressor genes and oncogenes

Cancer is a disease involving multi-step changes in the genome [15]. Increasing evidence has shown that expression of miRNAs is involved in the initiation and progression of tumorigenesis in cancer [16,17].

Large-scale studies in human cancer have further demonstrated that miRNA expression signatures are associated not only with specific tumor subtypes but in clinical outcomes as well [18-22]. Several examples showing miRNA deregulation in cancer by transcriptional deregulation have been reported [23,24]. Other studies suggest that epigenetic alterations play a critical role in deregulating miRNA expression in human cancers [25,26]. Mutation might also contribute to down regulation of mature miRNAs [18]. Over 50% of miRNAs are aligned to genomic fragile sites or regions associated with cancers, and several groups have provided evidence that DNA copy number abnormalities are involved in miRNA deregulation [16,27]. The key proteins in the miRNA biogenesis pathway may be dysfunctional or deregulated in cancer and may enhance tumorigenesis [19,22].

Interestingly, other studies reported a tumor-specific pattern of down regulation and up regulation of miRNA genes [16,20,28].

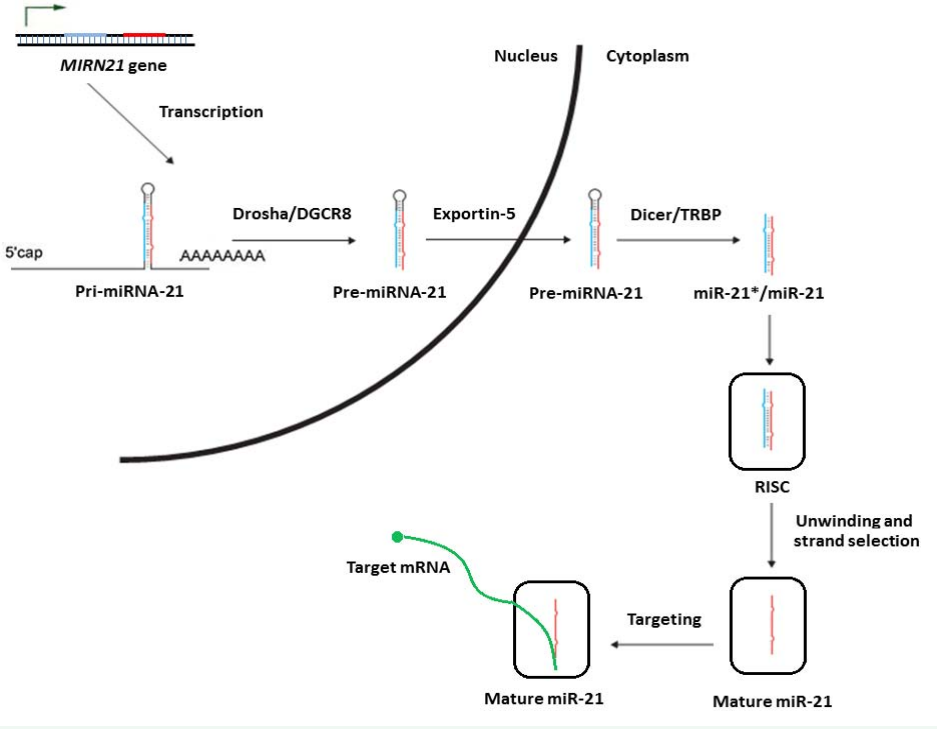

Figure 2 The miRNA-21 biogenesis pathway.
A 3433-nt long pri-miR-21 with a 5'cap and 3'poly (A) tail, is cleaved by nuclear RNase III Drosha and DGCR8 into a 72-nt long pre-miR-21. Dicer, and its RNA binding partner TRBP cleave the pre-miRNA into the mature miR-21/miR-21* duplex, which assembles into the RISC (RNA-induced silencing complex). The target mRNA and the mature miR-21 strand ('guide' strand) are brought together within RISC, while the 'passenger' strand is removed [8].

The role of miR-21 in cancer

The oncogenic role of miR-21 in various types of cancer is reported in several studies. MiR-21 is considered an 'oncomir' since it could suppress the actions of several apoptotic and tumor suppressor genes, including the programmed cell death 4 (*PDCD4*), tropomyosin 1 (*TPM1*), phosphatase and tensin homolog (*PTEN*) tumor suppressor, cell division cycle 25 homolog A (Cdc25a), reversion-inducing cysteine-rich protein with kazal motifs (*RECK*), mammary serine protease inhibitor (*MASPIN*) genes, and tissue inhibitor of metalloproteinase 3 (*TIMP3*), leading to tumor cell proliferation, inhibition of apoptosis, migration, invasion, angiogenesis, and metastasis [29-31].

MiR-21 resides in particular genomic region that are prone to alterations in cancer. This region (17q23) is frequently amplified in breast cancer, neuroblastoma, colon, prostate and lung cancer, and 50% of medulloblastoma.

The miR-21 gene is located in the fragile site FRA17B. Fragile sites are preferential sites of sister chromatid exchange, translocation, deletion, amplification, or insertion of tumor-associated viruses such as human papilloma virus (HPV). FRA17B is one of the HPV16 integration loci causing genetic and epigenetic alterations, suggesting that the mapping of miR-21 gene at or near HPV integration sites may contribute to its elevation in cancer [32,33]. Another possible cause of miR-21 up-regulation, was provided by [32,34] who revealed the presence of a CpG island region, 2 kb upstream the mature miR-21 sequence that could be hypomethylated in breast cancer causing up-regulation of expression.

In normal tissues, proper MicroRNA (miRNA) transcription, processing and binding to complementary sequences on the target mRNA results in the repression of target-gene expression through a block in protein translation or altered mRNA stability. The overall result is normal rates of normal growth, proliferation, differentiation and cell death [35].

The reduction or deletion of a miRNA that functions as a tumor suppressor leads to tumor formation. A reduction in or elimination of mature miRNA levels can occur because of defects at any stage of its biogenesis that lead to inappropriate expression of the miRNA-target oncoprotein. The overall outcome might involve increased proliferation, invasiveness or angiogenesis decreased levels of apoptosis or undifferentiating tissue, ultimately leading to tumor formation [35].

The amplification or over-expression of a miRNA that has an oncogenic role would also lead to tumor formation. Increased amounts of miRNA, which might be produced at inappropriate time or in the wrong tissues, would eliminate the expression of a miRNA-target tumor suppressor gene and lead to cancer progression. Increased levels of mature miRNA because of amplification of a constitutively active promoter of a miRNA gene, would increase the efficacy of miRNA processing or increase its stability [35,36].

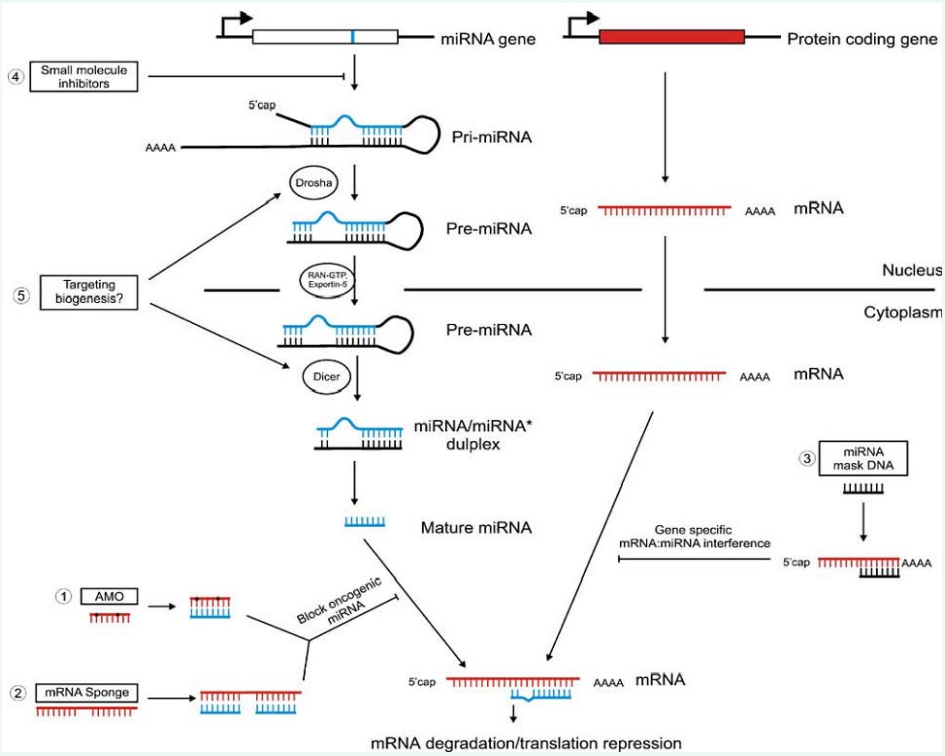

Figure 3 Therapeutic miRNA strategies in human cancer.
Schematic diagram of miRNA biogenesis and the therapeutic strategies. ① Anti-miRNA oligonucleotides (AMO) base pair with miRNA, therefore inhibit miRNA binding to target mRNAs; ② mRNA sponges contain multiple binding sites for a specific miRNA which in turn prevent the binding of this miRNA with its endogenous targets; miRNA mask DNA is complementary to miRNA binding site, resulting in gene-specific interference of miRNA:mRNA interaction; ④ small molecule inhibitor for mir-21 has been reported to inhibit the level of mature miRNA as well as pri-miRNA; ⑤ targeting miRNA biogenesis has been proposed, however, the feasibility of this approach need future evaluation [67].

Through functional suppression, miR-21 is implicated in practically every walk of oncogenic life: the promotion of cell proliferation, invasion and metastasis, genome instability and mutation, inflammation, replicative immortalization, abnormal metabolism, angiogenesis, and evading apoptosis, immune destruction, and growth suppressors. In particular, miR-21 is strongly involved in apoptosis [37].

The role of miR-21 in breast cancer

Several major breast cancer subtypes depend on the status of gene/ protein expression. The basal like, human epidermal growth factor receptor-2 estrogen positive (HER2-/ER+) /estrogen receptor negative (HER2-/ER-) and the luminal-like breast cancers [38] differ in their patterns of mRNA gene expression, phenotypes, prognosis, and sensitivity to different treatments. Clinical characteristics of breast cancer associated with miR-21 expression level revealed that increased miR-21 levels in breast tissue were significantly correlated with higher tumor grade, increased tumor size, lymph node involvement, lympho-vascular invasion. Tumors with advanced clinical stage had significantly higher levels of miR-21 in breast tissue [27,39,40]. Higher levels of miR-21 in breast tissue were observed in patients with poor prognosis according to NPI. [41,42] also showed miR-21 levels to be positively correlated with vascular invasion, visceral metastasis, and advanced clinical stage. [43] found miR-21 up-regulation to be associated with poor response to therapy, and worse survival in breast cancer. These results are consistent with the oncogenic role of miR-21 leading to tumor cell proliferation, inhibition of apoptosis, invasion, angiogenesis, and metastasis in various types of cancer [29,30].

Investigations of miR expression profiles in normal tissue and in breast tumor specimens using miR array technology revealed that miR-21 was progressively upregulated in virtually all cancer biopsies compared to normal tissue with increasing tumor stage [44,45]. Tissue localization studies showed that miR-21 was mainly localized in the cytosol of luminal epithelial cells and in fibroblasts of normal breast tissue. In tumor tissue, miR-21 was highly upregulated in carcinoma cells of epithelial origin compared to matching normal tissue. In some cases, increase of miR-21 expression was observed in tumor- associated fibroblasts but not in carcinoma cells. Additionally, miR-21 expression changes were investigated in the epithelial cell lines undergoing malignant transformation (MCF-7, BT-474 and MDA-MB-231) [34,44].

miR-21 expression was elevated in tumorigenic cell lines (compared to non-tumorigenic ones, IMECs and MCF10A). *In vitro* experiments showed that miR-21 knockdown in the breast tumor cell line MCF-7 using sequence-specific and chemically modified oligonucleotide termed anti-miR-21 led to the reduction of cell growth in a dose dependent manner. To investigate the role of miR-21 in tumor formation *in vivo*, anti-miR-21 transfected MCF-7 cells were injected into mammary pads of female nude mice. Injected cancer cells where miR-21 expression was inhibited grew substantially slower compared to controls. Reduced tumor growth is likely due to lower proliferation or increased apoptosis caused by selective miR-2 1 down regulation [46-48].

Serum miR-21 levels were significantly correlated with younger age at diagnosis, higher pathological grade, more nodal involvement, distal metastasis, lympho-vascular invasion, and advanced clinical stage [49,50]. Thus high miR-21 expression profile indicated more aggressive phenotype among women and could be a useful tool to stratify patients into prognostic groups [51]. Other studies showed that miR-21 levels are positively correlated with vascular invasion, visceral metastasis, and advanced clinical stage, [31,41,42] and associated with poor response to therapy, and worse survival in breast cancer, [43,52].

MicroRNA and cancer prognosis

Quantification of microRNAs has a crucial clinical application, because microRNAs are expressed in a tissue-specific manner and exhibit expression profiles that are different between normal and neoplastic tissues and between tumors with distinct biological properties and molecular subtypes. In addition, it can be used to predict the prognosis and clinical behavior of the tumor, as well as to monitor the response to treatment [53-55].

Currently, microRNAs have been detected in human blood in a remarkably stable form that is protected from endogenous RNase activity in both healthy individuals and cancer patients [53,56]. Altered serum microRNAs expression has been reported in various cancers. Their aberrant expression patterns are correlated to the aggressiveness of the tumor [57]. These data provide evidence that circulatory microRNAs can serve as a useful potential non-invasive biomarker for cancer detection, evaluation, and follow-up [54,58].

Receptor status of the tumor represents both prognostic and predictive markers in breast cancer. High miR-21 expression was significantly associated with HER2+ positive tumors, and that miR-21 expression is induced by HER2+ signaling via MAPK pathway [41,50,59,60].

[50] found serum miR-21 over-expressed in the circulation of breast cancer patients with metastasis (stage IV; 26.5-fold) compared to those without metastasis (stages II/III; 2.78-fold) and. 12.72-folds in BC patients compared to healthy controls. Similar over-expression levels were reported in the circulation of BC patients with different ethnic background [40,61].

Serum miR-21 expression could differentiate BC patients from cancer-free individuals with higher sensitivity and specificity than conventional biomarkers such as carbohydrate antigen 15–3 (CA15-3) and carcinoembryonic antigen (CEA), and could even distinguish patients with stage IV breast cancer from patients with earlier stages of BC, with 87.5% specificity and 92.9% sensitivity [10,42].

The level of miR-21 expression is significantly associated with clinicopathological factors and the prognosis of tumor patients, suggesting that it might serve as a diagnostic and prognostic marker for human malignancy [39, 41,62]. In breast cancer patients, expression of miR-21 is increased in breast cancer tissues compared with corresponding NATs (Normal Adjacent Tissue) [48].

miR-21 expression profile in several studies was significantly up-regulated in breast cancer tissues 10-13-folds compared to the normal adjacent tissues [27,40,44,50].

Overexpression of miR-21 in breast cancer is associated with several aggressive disease features, including high tumor grade,

ductal carcinoma, negative hormone receptors [39,41]. Increased expression of miR-21 has been related to various processes involved in carcinogenesis, including inhibition of apoptosis, promotion of cell proliferation, stimulation of tumor growth and chemo resistance [42].

Application of miR-21 in cancer therapy

[63], demonstrated the feasibility of restoring tumor suppressive miRNAs and targeting oncogenic miRNAs for cancer therapy using *in vivo* model systems. Modulation of miR-21 expression as potential cancer therapy was investigated in various cancer types, such as pancreatic cancer, lung cancer, glioblastoma and others [64-66].

The strategies used in this field (Figure 3), depend on either**:** knockdown of *miR-21* in human breast cancer cell lines to inhibit proliferation, *in vitro* migration and *in vivo* targeting miR-2, or for reversing drug resistance in cancer [67]**.**

Functional studies showed that knockdown of *miR-21* in MCF7 cells led to reduced proliferation and tumor growth [68,69]. Knockdown of *miR-21* in MDA-MB-231 cells significantly reduced invasion and lung metastasis [70]. The inhibition of miRNAs using antisense oligonucleotides (ASOs) is a unique and effective technique for investigating miRNA functions and targets. Peptide nucleic acids (PNAs) are artificial oligonucleotides constructed on a peptide-like backbone. PNAs have a stronger affinity and greater specificity for DNA or RNA than natural nucleic acids, and are resistant to nucleases [71]. PNA-based ASOs can be used without transfection reagents, and are highly effective and sequence-specific. [71] used PNA *miR-21* inhibitor for *in vivo* investigation and provided long-lasting inhibition of miRNAs that show no cytotoxicity up to 1 μM.

microRNAs (miRNAs) have emerged as key actors in carcinogenesis. microRNA-21 (miR-21), is expressed early during pancreatic ductal adenocarcinoma (PDA), [64]. Targeting miR-21 in human PDA-derived cell lines using lentiviral vectors (LVs) may impede tumor growth. LVs-transduced human PDA, efficiently down regulated miR-21 expression, both *in vitro* and *in vivo*. Consequently, cell proliferation strongly was inhibited and PDA-derived cell lines died by apoptosis. *In vivo*, miR-21 depletion stopped the progression of a very aggressive model of PDA, through cell death by apoptosis [37]**.** Furthermore, combining miR-21 targeting and chemotherapeutic treatment provoked tumor regression. Targeting oncogenic miRNA strongly inhibited pancreatic cancer tumor growth both *in vitro* and *in vivo*. Because miR-21 is overexpressed in most human tumors; therapeutic delivery of miR-21 antagonists may still be beneficial for a large number of cancers for which no cure is available [72].

Inhibition of miR-21 using specific antisense oligonucleotide alone resulted in increased apoptosis rates, reduced cell proliferation and upregulation of PTEN and RECK proteins in pancreatic adenocarcinoma cell line HS766T. Cell treatment with antisense-miR-21 in combination with the anti-cancer drug gemcitabine sensitized HS766T cells to gemcitabine resulted in superior effects compared to gemcitabine alone [65]. Similarly, [64] demonstrated that miR-21 overexpression in multiple pancreatic cancer cell lines increased cell invasiveness, proliferation and chemoresistance to gemcitabine whereas miR-21 downregulation in the same cells resulted in decreased cell proliferation, invasiveness and increased sensitivity to gemcitabine. The question whether gemcitabine alone can modulate miR-21 expression is unclear. Another anticarcinogen, indole-3-carbinol (I3C), efficiently downregulated endogenous miR-21 expression in vinyl carbamate (VC) - induced lung tumors in mice compared to the animals treated with VC alone [64].

Drug resistance is a major clinical obstacle to the successful treatment of human cancer. The microRNAs-21 (miR-21), an oncomiR, may play an important role in the progress of drug resistance. Inhibitors of miR-21 may function as effective approaches for reversing drug resistance in cancer cells. Further understanding of miR-21-mediated signaling pathways will help to promote the therapeutic-clinical use of miR-21 in cancer [11,73].

CONCLUSION

The role of miR-21 in cancer biology, suggests that miR-21 can potentially serve as a promising non-invasive diagnostic and prognostic biomarker for Breast Cancer. MiR-21 could identify asymptomatic high-risk women for developing BC, discriminate BC patients from healthy controls, and distinguish patients with metastasis from patients with earlier stages of BC with remarkable specificity and sensitivity. Also, miR-21 could be used as a prognostic indicator for poor outcome in BC patients. In addition, miR-21 would be useful as a biomarker for disease monitoring after curative tumor resection.

miR-21 exhibited up-regulation in about 92% in breast cancer tissue compared to normal adjacent tissue of BC patients. Higher levels of miR-21 in breast tissue were observed in patients with poor prognosis. Significant correlation is evident between chromosome 17 copy number and microRNA-21 expression levels in breast cancer tissues and correlates with several clinic-pathological characteristics.

The deregulation of miRNA molecules and their accurate profiling favors its chances to be the biomarker of choice in the diagnosis and prognosis of several diseases.

The potentials of miRNA as biomarkers in the diagnosis and treatment of a variety of diseases is strongly emerging. Evidence are accumulating of the power of using miRNA inhibitory therapeutic to compete with current approaches targeting specific proteins.

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