

Role of MiRNAs and it's single nucleotide polymorphism in breast cancer

¹Debarshi Roy, ^{1,3}Ramesh Bandla, ²Praveen Boddana, ³Rajesh Medisetty, *¹Raghu Gogada

¹Department of Biochemistry and Plant Physiology; ²Department of Plant Pathology, M.S. Swaminathan School of Agriculture (MSSSoA), Centurion University of Technology and Management (CUTM), Parlakhemundi-761211, Odisha, INDIA.

³Analytical Division, Biological E. Limited, Hyderabad, Telangana, INDIA.

*Correspondence may be addressed to email: raghu.gogada@cutm.ac.in

Abstract: MiRNAs are 20-22 nucleotide long single-stranded non-coding RNA sequences, which can regulate post transcriptional activity of mRNA by binding with it at 3'UTR region (untranslated region). Thus deregulation of miRNA expression is responsible for dysregulating mRNA function which contributes in developing various diseases as well as cancerous phenotypes. Alteration of single nucleotide in miRNA sequence is one of the reasons behind deregulation of miRNA expression. The most frequent carcinoma in current day is breast cancer which causes a high mortality among women around the world as well as India. Despite of the advancement of diagnostic tools, strategies and treatment, the cases of breast cancer is increasing every year. There are plenty of biomarkers like ER, PR, Her2, Ki-67, etc available which are frequently used in diagnosis and treatment of breast cancer. After the discovery of MiRNA in 1993 in *Caenorhabditis elegans*, it is attracting all the limelight in diagnosis and treatment of different carcinomas as well as breast cancer. In this review we will discuss on involvement of different types of MiRNAs and miR SNPs in breast cancer occurrence and susceptibility in a detailed manner.

Keywords: microRNA, SNP's, breast cancer, RNA induced silencing complex.

Introduction: Breast Cancer is one of the leading and alarming prevalent cancers and it is the second most common cancer across the globe. According to a study performed by Ferlay et al. (1) an estimated 1.67 million new breast cancer cases were diagnosed in the year of 2012, which described breast cancer as ‘most frequent cancer among women’. It is also accounted as most frequent cause of cancer related mortality among women (2). The breast cancer in India scenario is also showing the similarity with global trend. According to National Cancer registry Programme cervical and breast carcinomas are two leading cancers among Indian women. Different published reports from different cancer surveys are also indicating towards rising trends of breast cancer in India (3,4). Breast Cancer prevalence among Indian women is three times higher in urban areas specially metropolitan cities like Delhi, Kolkata, Chennai, Mumbai than rural parts (5). Many life style factors such as later age marriage, late pregnancy, reduced breast feeding, age at first birth, westernization of diet, physical activity patterns may play important role in the early prognosis of breast cancer (6). Beside these, genetic factors are also crucial for developing BC in women. Although researchers are trying to focus on many known genetic factors (ex: BRCA1, BRCA2, HER2, ER, PR, etc), epigenetics and gene regulations for better understanding the prognosis and treatment of BC, recent discovery of MiRNA in 1993 has become a milestone in progression of understanding the gene regulation in many diseases as well as breast cancer (7).

MicroRNA: MicroRNAs (MiRNA) are small group of non-coding RNAs which are known for regulating gene expression through a post transcriptional mechanism, including mRNA degradation and translational repression, by binding to 3’ untranslated region (UTR) of target mRNA and cleaving the mRNA with the help of Ago2 RNAase of RISC complex (RNA induced silencing complex) (8). 22 nucleotide long these small RNAs are generally found in many biological fluids like semen, saliva, vaginal fluids and menstrual secretions and frequently used as diagnostic and prognostic biomarkers for various diseases including cancer (9,10). Many emerging evidences have shown involvement of miRNAs in cancer classification, global repression of maturation induced cellular transformation and tumorigenesis (11).

MiRNA synthesis: MiRNAs are transcribed from the noncoding portion of the gene by RNA polymerase-II or III in the form of primary mRNA (100-120 nt long) followed by synthesis of Drosha or DGCR8 cleaved hairpin like structured precursor miRNA (70-80 nt long) (12). The hairpin portion of pre-miRNA is cleaved by a protein called Dicer after it’s transportation into cytoplasm by Exportin V and a double stranded miRNA duplex with 3’ overhangs in both sides is formed. (13). This MiRNA duplex binds with RiSC complex (RNA interference Silencing Complex) which consists of Slicer, Argonout, TRNC6 etc proteins and it gets unwound by

helicase into two single-stranded miRNAs named Guide strand and passenger strand. Later RISC complex releases passenger strand and directs guide strand which is miRNA, towards target mRNA. This mature single-stranded guide strand binds with the target mRNA, exerting its inhibitory activity either by blocking the mRNA translation or mRNA degradation.

MiRNAs and Global Diseases: Many studies have proved importance of Micro RNAs in different developmental processes metabolism, cell proliferation, apoptosis, developmental timing, and neuronal cell fate (14-18) along with other regulatory roles including neuronal gene expression (19), brain morphogenesis (20), muscle differentiation (21), and stem cell division (22). MiRNAs have pivotal role in controlling several cellular growth and differentiation processes and also altered patterns of MiRNAs in cells can induce malignancy in cells, which shows influence of MiRNAs in developing cancer (23-25). MiRNA deficiencies or excesses or changes in MiRNA functions due to single point mutations or its target or epigenetic silencing of of MiRNA transcription units have found to be linked with many diseases such as myocardial infraction, autoimmune disease, etc (26). Rapid progress in MiRNA research in past few years have opened new horizon in diagnosing and treating of many diseases (27). Here we will discuss about occurrence of few diseases due to dysregulation of MiRNA structure and expression.

Cardiovascular Diseases and cardiac failure: In spite of necessity of more research in precise mechanism involved in cardiovascular biological functions, an increasing number of studies show Micro RNAs have pivotal role in regulating mammalian cardiovascular growth, proliferation, cell differentiation and apoptosis and changes in MiRNA expression level can influence developmental process and disease states like cardiac hypertrophy and failure (28). Few studies claim that abundant expressions of miR-1, miR-16, miR-27b, miR-30d, miR-126, miR-133, miR-143, and the let-7 have been found in adult cardiac tissues (29). Generally in the heart three MiRNAs, miR-1, miR-133 and miR-208 are highly expressed (30,31) and have been found to regulate mostly heart development and myocyte differentiation, whereas deregulated expression of miR-1 and miR-133 have been found to be involved in human heart failure (32-35). In case of cardiac hypertrophy miR-23a, miR-23b, miR-24, miR-195, miR-199a, and miR-214 were found upregulated and their overexpression in cardiomyocytes in vitro may be responsible behind it (36).

Inflammatory Diseases: Recent days a number of studies have investigated miRNA's role in vascular inflammation and leukocyte activation and their infiltration into the vascular wall. The study which is thought to be the first evidence of miRNA regulation demonstrated the that miR-

126 inhibits vascular cell adhesion molecule 1 (VCAM-1) expression where VCAM-1 is necessary for mediating leukocyte adherence to endothelial cells (37, 38, 39). Some studies have shown cytokines like $\text{TNF}\alpha$ and $\text{IFN-}\beta$ can induce miRNA-155 in macrophages, contribute to physiological granulocyte/monocyte expansion during inflammation (40). Few miRNAs such as miR-17-92 cluster, miR-150 in regulating B-cell differentiation and miR-181 in regulating haematopoietic lineage differentiation have been found in many reports (41-44). Besides this involvement of miR-424 in regulating translation of transcription factor NFI-A during monocyte or macrophage differentiation, induction of miR-146 in macrophages in by several microbial components and proinflammatory cytokines, moreover regulation of granulocyte differentiation and activation during inflammation by myeloid specific miR-223 strengthen the claim of importance of miRNA in regulation of human immune system and different inflammatory diseases (45-48).

Neurodevelopmental Disease: Near about 1000 MiRNAs should be expressed in all human brains according to high throughput sequencing experiments whether current studies suggest this number is around 550, which shows the high expression of MiRNAs in human brains (49). Changes of MiRNA expression levels in early or later brain development may be representative of biochemical signals for determining cellular fate, different cell division programming or/and apoptosis in brain (50). Therefore it can be speculated that the pathogenesis of neurodevelopmental disorders such as intellectual disability, autism, Attention Deficit Hyperactivity Disorder (ADHD) and epilepsy are linked with miRNA expression changes (51). Fragile X syndrome (FXS), a genetic disorder which was first found to be linked with miRNA pathway occurs due to interaction between FMRP (Fragile X Mental Retardation Protein, which is a product of FMR-1 gene) and Dicer-derived miRNAs. This interaction can regulate target mRNA translation by binding non coding miRNA structures within UTRs of target mRNAs in inducing the genetic Fragile X syndrome (52-64). Another neurodevelopmental syndrome is Rett syndrome which occurs due to de novo mutations in MECP2 gene which causes aberrations in the DNA methyl-CpG-binding protein, MeCP2. Postnatally cultured rat neurons have shown direct repression of MeCP2 expression by miR-132, which indicates the importance of miRNA role in regulating MeCP2 by which postnatal neuronal development and synaptic maturation are maintained (52,65,66). Potential evidence of MiRNA role in Down syndrome individuals also have been found in many studies. Few bioinformatics analyses have revealed that five miRNAs; miR-99a,let-7c, miR-125b-2, miR-155 and miR-802 are encoded in chromosome 21, triplication of all or part of which is responsible for developing Down Syndrome. These all above mentioned miRNAs have been found to be overexpressed in fetal

brain and heart tissues of DS individuals, which may be responsible for developing cognitive and cardiac defects in Down syndromic individuals (52,67). According to Sethupathy P et al. miR-155 downregulates angiotensin II type 1 receptor (AGTR1) gene, associated with hypertension. The AGTR1 protein generally is also found in lower levels among DS patients than individuals without DS (68). These all findings indicates towards the importance of miRNA role in Down Syndromic individuals. Dysregulation of specific miRNA expressions has been elucidated to be linked also with Alzheimer Disease. Loss of miR-29 cluster associated with increased (beta-amyloid precursor protein-converting enzyme) BACE1/beta-secretase expression in sporadic AD patients, direct interaction of miR-298 and miR-328 with 30-UTR of BACE1 transcript involved in b-amyloid production, regulation of the expression of Amyloid Precursor Protein (APP) by miR-20a family (e.g. miR-20a, miR-17-5p and miR-106b) or elevated expressions of miR-9, miR-128a and miR-125b in AD hippocampus, there are plenty of evidences of involvement of micro RNAs in AD development have been found (69-71). In case of Schizophrenia, researchers have found association between miRNA and BDNF (Brain-derived Neurotrophic Factor), which plays important role in regulating development and synaptic maintenance of a variety of neurons in the CNS including GABA and glutamatergic neurons. Few bioinformatics studies suggest that newly described miRNAs, has-mir-1 and has-mir-206 can regulate BDNF protein synthesis by interfering in BDNF mRNA translation during brain development which indicates towards importance of miRNA roles in Schizophrenic patients (72-74).

Autoimmune Diseases: Many studies have already shown some possible roles of miRNAs regulating two most significant autoimmune diseases rheumatoid arthritis (RA) and Systemic Lupus Erythematosus (SLE). Two miRNAs, miR-155 and miR-146 were found significantly overexpressed in synovial tissues and synovial fibroblasts of RA patients than healthy individuals. Later Stanczyk J et al. and Tili E et al. found significant elevated expression of both these miRNAs in synovial fibroblasts of RA individuals following TNF/ interleukin (IL)-1 β stimulation (75-77). Few studies suggest as pathogenesis of RA is linked with many viral infections such as *Epstein-Barr Virus (EBV)*, chronic *Hepatitis C Virus (HCV)*, *HIV* and Kaposi's-sarcoma associated herpes, which have the ability to encode their own miRNAs which can control viral transcripts' expressions and suppress the host immune response during infection (78-80). miR-UL112-1 expressed by the human cytomegalovirus targeting MHC class 1-related chain B and miR-K12-11 encoded by the Kaposi's-sarcoma-associated herpes virus for downregulating numerous similar cellular target mRNAs expression can be two ideal examples of it (80,81). In a microarray analysis for studying miRNA expressions in Systemic

Lupus Erythematosus seven miRNAs (miR-196a, miR-17-5p, miR-409-3p, miR-141, miR-383, miR-112, and miR-184) were found downregulated and nine miRNAs (miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR-342, miR-299-3p, miR-198, and miR-298) were found upregulated compared to healthy controls (82). Still more research is necessary for confirming association of miRNA function with autoimmune diseases.

Liver Diseases: Understanding the miRNA regulation in liver physiology and different liver diseases like Viral Hepatitis, polycystic liver diseases have gained a lot of attention. As previously discussed, viral protein coding genes have ability of encoding their own miRNAs which can regulate their own protein coding genes. Hepatitis B Virus can be a good example in this case. The pre-miRNA transcribed from HBV gene can control its own gene expression (83,84). Even miRNA from host cell also can regulate viral genes. Regulating the replication of HCV (Hepatitis C Virus) by miR-122 has already been shown. claim. Studies also have shown eight miRNAs (miR-1, miR-30, miR-128, miR-196, miR-296, miR-351, miR-431 and miR-448) among 30 cellular miRNAs, influenced by IFN- α/β or IFN- γ , were upregulated who have an almost perfect complementarity with HCV RNA genomes. This suggests the capability of these miRNAs in HCV replication and infection inhibition (85). According to Lee et al, 2008, miR-15a levels were decreased in livers of patients suffering from Autosomal Recessive Polycystic Kidney Disease (ARPKD), indicates that miRNA expression changes may be responsible in phenotypic changes found in cystic liver disease (86).

Other Diseases: In regulation of muscle development along with hair follicle morphogenesis, autoimmune and chronic inflammatory diseases which affect skin, involvement of miRNAs have been noticed in many studies (87-92). Having signature role of Muscle-specific miR-1, miR-133 and miR-20 in myogenesis, significant up-regulation of miRNAs-100, 103 and 107 in certain myopathies, diagnosing Facio scapula humeral muscular dystrophy (FSHD) distinguished from Duchenne muscular dystrophy (DMD) based on the level of miRNAs-381 and miRNAs-382 expressions prove the importance of miRNAs in muscular development (93-95). Similarly, many studies claim involvement of a cluster of 33 miRNAs in regulation of expression of target genes required for the entry of fibroblasts into the cell cycle and proliferation. In context dermal fibroblasts are important cells in wound healing process. Another review also has outlined potential significance of involvement of miRNAs in wound angiogenesis and abnormal healing sequence in chronic wounds (96-99). These show miRNAs play important role in developing skin disease.

miRNAs in cancer: It has already been well established by many studies that overexpression or down-regulation of miRNAs which have oncogenic as well as tumor suppressor activity,

play crucial role in human cancers (100-102). In reproductive cancers such as breast, ovary, and endometrioid adenocarcinoma along with colon and haematological cancer (ALL,AML,CLL,CML), esophagus, gastrointestinal, lung, bladder, and thyroid tumors, miRNA play crucial role. (103) (Table 2,3)

Table 1: miRNAs in human diseases (127)

Disease type	miRNA	Up/Down Regulation	References
Cardiac hypertrophy	miR-23a, miR-23b, miR-24, miR-195, miR-199a, and miR-214	Up	74
Down syndrome	miR-99a, let-7c, miR-125b-2, miR-155 and miR-802	Up	133
Alzheimer	miR-9, miR-128a, miR-125b	Up	140
Rheumatic arthritis	miR-155, miR-146	Up	156
Systemic lupus erythematosus	miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR 342, miR-299-3p, miR-198 and miR-298 miR-196a, miR-17-5p, miR- 409-3p, miR-141, miR-383, miR- 112, and miR-184	Up Down	165
Psoriasis	miR-203	Up	183

Table 2: MiRNAs in reproductive cancers. (126)

Cancer type	miRNA	Up/Down Regulation
Breast	miR-21, miR-155, miR-23, and miR-191 miR-205, miR- 145, miR-10b, and miR-125b	Up Down
Ovary	miR-200a, miR-200c, and miR-141 miR-199a, miR-140, miR-145, and miR125bl	Up Down
Endometrioid adenocarcinoma	miR-205, miR155 miR 200a, 200b, 200c miR-193a, 193b	Up Down

Table 3: miRNAS in cancer. (126)

Cancer type	miRNA	Up/Down Regulation
Colon		
	miR-let 7g, miR-21, miR-20a, miR-17- 19 family, miR 31, miR 135, miR-181b, and miR 200c	Up
	miR-34, miR-let7, miR 143, miR 145, miR-133b, and miR- 126	Down
AML		
	Has- miR- 191, 199a, miR 155	Up
CML		
	miR-17-5p, miR-173p, miR- 18a, miR-19a, miR-19b-1, miR- 20a and miR- 92a-1	Up
CLL		
	miR-21, miR 150, miR-155	Up
	miR- 15a, miR16, miR-29, miR143, miR-45, miR-30d, miR- let 7a, miR-181a	Down

Recent studies have shown importance of miRNAs also in angiogenesis as let-7b, miR-16, miR-21, miR-23a, miR-29, miR-100, miR-221, and miR-222 expressions were found to be associated with endothelial cells (104-106). Role of miRNAs in vascular cells has been elucidated by miRNA regulation during pathophysiological process. Researchers have conducted studies where downregulation and overexpression of miR-130 in quiescent HUVEC and in response to foetal bovine serum were shown respectively (107,108). Some research studies show induction of miR-210 expression in hypoxia, which also was reported to be overexpressed in the enhanced formation of capillary-like structures inhibited in decreased tube formation and migration (108). miR-221 and miR-222 who have anti-angiogenic effects are highly expressed in HUVEC as well as endothelial cells and reduction of endothelial Nitric Oxide Synthase's (eNOS) expression is occurred due to same reason (109,110). eNOS is known for modulating endothelial cell growth, migration, vascular remodelling , and angiogenesis, which are linked with various tumour tissues including bladder, colon, pancreatic cancers, etc. (111,112,113,114)

Breast Cancer subtypes: On basis of gene expression profile and the phenotype the breast cancer be divided into six subtypes luminal A, luminal B, tumour enriched with human

epidermal growth factor receptor 2 (Her2), basal-like, normal-like and claudin-low subtype (115-118).

Luminal A subtype: This is the most common subtype among all breast cancer subtypes, which accounts for 50%-60% of the total breast cancer cases. It is characterized by ER (Estrogen Receptor), PR (Progesterone Receptor), Bcl-2 expressions and absence of Her2 (116,117).

Luminal B subtype: Luminal B subtype can be characterized by the expressions of ER,PR and absence of Her2 and can be differentiated from the Luminal A subtype based on high Ki67 staining which is an indicator of high proliferation rate (119).

Her2 Positive subtype: Almost 15-20% breast cancers are of this subtype, which is characterized by high expression of the Her2 gene and high proliferation rate. Although the survival rate of this subtype has been increased in last decade, still the prognosis remains poor.

Basal-like subtype: This subtype constitutes 10-20% of all breast carcinomas and often shows poor prognosis. Among all of the three markers (ER, PR, Her2) none is expressed in Basal like subtype breast cancer cases. Instead of having controversial chemotherapeutic approaches, promising strategies are being developed for treating this type of breast cancer (118,120).

Normal-like subtype: Poorly characterized this subtype constitutes 5-10% of all breast cancers, where ER, PR and Her2 are expressed and it's clinical outcome is in between basal like and luminal-A subtype. Few researchers doubt regarding this subtype's existence as it can not be confirmed by microarray approach and it has the possibility to contaminate surrounding normal tissues.

Claudin-low subtype: Being triple negative in nature this subtype is characterized by low expression of claudin-3, 4, 7, occludin and E-cadherin, where claudin is a tight junction protein and E-cadherin is a calcium dependent cell-cell adhesion glycoprotein. Having stem like features this breast cancer subtype constitutes 10-14% of all cancers and has a poor long term prognosis (118,121,122).

miRNA expression pattern specificity in certain cancer subtype: Expression of miRNAs are specific to specific cancer subtypes. miR-21, miR-210 and miR-221, who have been correlated with worse patient disease-free and overall survival, play a crucial role in triple negative breast cancer and also have been noticed to be significantly overexpressed, whereas miR-10b, miR-145, miR-205 and miR-122a have been found significantly downregulated in these cancer types (120). Comprehensive miRNA profiling in normal basal and luminal breast epithelium cells isolated from plastic surgery showed 116 out of 664 miRNAs were expressed in normal breast epithelium, whereas among them 8 miRNAs let7c, miR-125b, miR-126, miR-

127-3p, miR-143, miR-145, miR-146-5p and miR-199a-3p were significantly overexpressed in normal basal cells and miR-200c and miR-429 were mostly luminal. In some studies, higher expression of miR-126, miR-127, miR-143, miR-145 and miR-199 and downregulation of miR-200c and miR-429 were noticed in malignant myoepithelioma compared with luminal and basal-like subtypes (123). According to an artificial network analysis conducted for miRNA profiling of 29 early stage breast cancer patients for determining ER, PR and Her2 status by Lowrey et al., miR-342, miR-299, miR-217, miR-190, miR-135b, miR-218 were ER specific, miR-520 g, miR-377, miR-527-518a, miR-520f-520c were PR specific and miR-520d, miR-181c, miR-302c, miR-376b and miR-30e were Her2 specific. Furthermore, highest expression of miR-342 in ER and Her2 positive luminal B tumours and lowest expression of miR-520g in ER and PR-positive tumours were revealed by further analysis (124).

Classification of MiRNAs involved in breast cancer: Researchers have shown around 50% of the human miRNA-encoding genes are present in such regions of fragile chromosomal site which are linked with cancer (125). After the first study related to miRNA measurement in serum, conducted by Lawrie et al, where miR-21 were found to be associated with relapse free survival of the patients having diffuse large B-cell lymphoma (128). Several studies have shown the use of miRNAs as potential biomarkers in different type of cancers like prostate cancer (129), lung cancer, colorectal cancer (130,131), ovarian cancer (132), renal cell carcinoma (133), squamous cell carcinoma of the tongue (134), and glioblastoma (135). The first study on miRNA dysregulation in breast cancer was reported in 2005 (136). Since then several studies have shown altered expression of miRNAs in breast carcinoma. These breast cancer related miRNAs can be subdivided into two types: oncogenic miRNAs (oncomiRs) and tumor suppressor miRNAs (tsmiRs) (137).

Oncogenic miRNA: Oncogenic miRNAs have been observed to be frequently upregulated and repress the expression of tumour suppressor gene/s, generally which remain involved in apoptosis, cell proliferation, cell migration and invasion and metastasis (138). Here we will discuss about some miRNAs or miRNA families which have already been studied and established as oncomiRs in breast cancer and their involvement in this cancer type.

miRNA-10 family: This miR family consists of two miRNAs: miR-10a and miR-10b, and as they can regulate HOX transcripts, they have crucial role in developmental process (139). Retaining within the HOX cluster of developmental regulators these miRNAs also have been reported to be involved in various cancers such as glioblastoma (140), colon cancer (141), acute myeloid leukemia (142), melanoma (143), pancreatic cancer (144) and hepatocellular carcinoma (145) including breast cancer. In case of breast carcinoma miR-10 family has been

found to be involved both in metastasis and development. According to reports miR-10b potentially targets E-cadherin and miR-10b expression level is positively correlated with tumour size, pathological grading, clinical staging, lymph node metastasis, Her2-positivity and tumour proliferation, whereas negative correlation was found with ER+, PR+ and E-cadherin levels (146,147,148). Researchers are claiming that miR-10b may modulate breast cancer metastasis by suppressing HOXD10, which results in elevation of pro-metastatic gene, RHOC, a Rho-GTPase family member, known for regulating actin dynamics, hence cell shape and motility. E-cadherin, which has pivotal role during inhibition of Tiam1 (T lymphoma invasion and metastasis)-mediated Rac activation and controlling cell-cell adhesion and EMT is suppressed by miR-10b, hence the ability of breast cancer cells to invade and migrate is suppressed. These indicate miR-10b can be used as biomarker for advanced progression and breast cancer metastasis (148,149).

miRNA-21 family: Chan et al. first reported aberrant expression of miR-21, showing significant elevation in human glioblastoma tumour tissues along with established glioblastoma cell lines compared with non-neoplastic fetal and adult brain tissues and in the same year Iorio et al. noticed elevated expression of few miRNAs (miR-125b, miR-145 and miR-155) including miR-21 in breast tumours compared with normal breast tissues (150,151). Two important molecules, PDCD4 (programmed cell death 4) and maspin (mammary serine protease inhibitor), involved in invasion and metastasis in breast cancer have been identified as miR-21 targets (152). It has been observed that miR-21 expression is negatively correlated with PTEN (phosphatase and tensin homologue) expression and upregulated by transforming growth factor- β (TGF- β) in breast cancer. Despite of poor prognosis, samples from 344 patients with primary breast cancer showed elevated level of miR-21 expression (associated with aggressive disease status including high tumour grade, negative hormone receptor status and ductal carcinoma), which was found to be associated with poor disease-free survival in early stage breast cancer patients (153,154,155).

miRNA-17-92 cluster: Locating in such region of DNA, which is amplified in human B-cell lymphomas, this miR cluster comprises of six mature miRNAs: miR-18b, miR-19b, miR-20a, miR-92, miR-93 and miR-106 (156,157). Along with having role in lymphoma, these miRNAs are markedly overexpressed in lung cancers, especially in small-cell lung cancer (158). In case of invasive MDA-MB-231 breast cancer cells, miR-17-5p was found to be highly expressed but in MCF-7 breast cancer cells similar result was not found. Furthermore, researchers have reported that ectopic expression of this miRNA in MCF-7 breast cancer cells led to more invasiveness and migratory phenotypes by targeting HBP1/ β -catenin pathway whereas

downregulation of miR-17-5p suppressed the migration and invasion of MDA-MB-231 breast cancer cells *in vitro* (159).

miRNA 155: Having an important role in suppressing apoptosis by affecting caspase 3 most important caspase involved in the execution phase of apoptosis, miR-155 is found overexpressed in many carcinomas along with breast cancer (160,161). Suppressor of cytokine signalling 1 (*SOCS1*), *RhoA* and FOXO3a are identified as some gene targets for miR-155 in breast cancer (162,163,164). Inverse correlation between SOCS1 and miR155 expression along with enhancement of breast cancer cell proliferation and tumour development due to ectopic expression of miR-155 *in vivo* establish the oncogenic effect of miR-155 (162,163). miR-155 inhibits *RhoA* gene expression, which regulates cell adhesion, motility and polarity. Reestablishment of the miR-155 induced phenotypes by expressing a miR-155 insensitive version of *RhoA* in miR-155 overexpressing cells, indicates that miR-155 downregulates the *RhoA* protein expression to enhance the acquisition of EMT phenotype (165). miR-155 can regulate cell survival by downregulating its direct target FOXO3a gene in breast cancer. Studies have shown the inverse correlation between miR-155 and FOXO3a in breast cancer cell lines, suggesting that miR-155 is an essential therapeutic target in breast cancer (166). Therefore miR-155 has an essential role in breast cancer metastasis as it is implicated in the acquisition of EMT and increases potential for invasion and metastasis.

miRNA-373/520c: miR373 and 520c are two premetastatic miRNAs which were found to be involved in promoting migration and invasion *in vivo* and *in vitro* in many studies (170, 171). These miRNAs are also found to show migratory phenotype by inhibiting the CD44 expression, which is known as a metastatic repressor. MCF-7 cells migration, expressing miR-373 and miR-520c was reduced by ectopic overexpression of CD44 which indicates downregulation of CD44 is essential to the migration of these cells. Also upregulation of miR-373 has been noticed during reduced expression of CD44 in metastatic breast cancer (167,168,169).

miRNA-375: miR-375 has both oncogenic and tumour suppressor roles. Investigation of miR-375 levels in estrogen receptor (ER α)-positive breast cancer cell lines showed that miR-375 overexpression was associated with proliferation. On the other hand, inhibition of miR-375 expression in ER α -positive MCF-7 breast cells resulted in reduced proliferation and ER α activation also has been reported. This study also suggested that RASD1 is a potential target for miR-375 and RASD1 has an important role in cell proliferation by negatively regulating ER α expression, hence miR-375 has an oncogenic role in breast cancer (172). In contrary tumour suppressive role of miR-375 also has been noticed. Investigation, where MCF-7 breast cells were exposed to continuous tamoxifen to understand the miRNA's role in tamoxifen

resistance, showing invasiveness and mesenchymal characteristics of cancer cells, showed miR-375 as one of the top downregulated miRNAs in resistant. Also increased sensitivity of tamoxifen-resistant cells, and partly reversed EMT phenotype (tumour cell invasion and metastasis) by reexpression of miR-375 were reported in that study. This study also revealed metadherin (MTDH) as miR-375 target and showed inverse correlation between miR-375 and MTDH expression in primary breast cancer cell lines (173).

miRNA-221 and miRNA-222: Both of these basal-like subtype-specific miRNAs can regulate EMT and have roles in increased cell migration and invasion along with promotion of clinically aggressive basal-like breast cancer (174). Researchers have identified few targets of these miRNAs such as tricho-rhino-phalangeal syndrome type 1 protein (TRPS1), estrogen receptor alpha (ER α), p27/Kip1 and p57. By repressing TRPS1 they can increase the EMT-promoting protein zinc finger E-box-binding homeobox 2 (ZEB2). On the other hand, overexpression of both the miRNAs in breast cancer promotes in the progression of the more aggressive basal-like breast cancer while directly targeting estrogen receptor alpha (ER α). They also repress proteins p27/Kip1 and p57, responsible for cell cycle inhibition, resulting in increased proliferation (174,175,176).

Tumour Suppressor miRNA: Like oncogenic miRNAs Tumour suppressor miRNAs also have crucial role in breast cancer.

miRNA 200 family: miR-200 family consists of five miRNAs: miR-200a, miR-200b, miR-200c, miR-141 and miR-429 which are generally known to suppress EMT, which is partly mediated through regulating E-cadherin transcriptional repressors ZEB1 and ZEB2 (also known as SIP1). Significant E-cadherin expression and alteration of cell morphology to an epithelial phenotype are responsible for ectopic expression of miR200 family. In this regard, miR-200c has been noticed to regulate breast cancer cell migration, stress fibre formation, migration, invasion and elongation, along with metastasis by targeting FHOD1 and PPM1F, direct regulators of the actin cytoskeleton (177-180). Downregulation of miR-200c is also have been found to be associated with drug resistance in human breast cancer (181). Also this miRNA family is involved in regulating PLCG1, BMI1, TGF- β 2, FAP-1, ZEB and Suz12 and hence acts as tumour suppressor (179, 182-190). As earlier discussed, miR-200 family is involved in regulating transcription factor ZEB, an activator of EMT, overexpression of this miRNA in mouse breast cancer cells is associated with macroscopic metastasis (191). Later Korpál et al. strengthened this notion in clinical aspects. More research is needed to define this miRNAs' role in breast cancer metastasis (192).

miRNA 205: Like miR-200 family, significant downregulation has been noticed also in miR-205 in cells, who have undergone EMT in response to TGF- β and in the triple-negative primary breast cancers (193,194). In many studies this miRNA expression has been reported to be restricted in basal epithelium of mammary ducts and lobules while compared with reduced or lost expression in matching tumour specimens and breast tumours while compared with the matched normal breast tissue (195). Ectopic expression of miR-205 while directly targeting Her3 and VEGF-A can inhibit invasion, proliferation and anchorage independent growth (196). In triple negative breast cancer, p53-induced miR-205 has tumour suppressive role and it's re-expression is strongly responsible for reduction of cell proliferation, cell cycle progression and clonogenic potential in vitro and inhibition of tumour growth in vivo. This miRNA also targets E2F1 and LAMC1, who have ability to regulate cell cycle progression and cell adhesion, proliferation and migration, respectively (197).

miRNA-145: miR-145 also is significantly downregulated in breast cancer like miR-205, while compared with normal breast tissue, where N-RAS and VEGF-A were post transcriptionally targeted and regulated by miR-145 leading to inhibition of tumour angiogenesis, tumour growth and invasion, also supports this claim. N-RAS and VEGF-A are required for the above mentioned phenotypes (198). Studies suggest that this miRNA may also be used as novel cancer biomarker for early cancer detection due to its early manifestation altered expression. miR-145 has shown pro-apoptotic as well as tumour suppression functions (195). According to Spizzo et al. miR-145 has tumour suppression function along with TP53 activation dependent pro apoptotic potential in breast cancer cell lines. Also this miRNA can directly interact with estrogen receptor- α (ER- α) expression and promote apoptosis in both ER- α positive and wild type TP53-expressing breast cancer cells (199). A well-known oncogene c-Myc, having potential of regulating cell growth and proliferation, which can inhibit tumour cell growth both *in vivo* and *in vitro* can be silenced by miR-145 (200). Inhibition of invasion property of breast cancer cells, while having no significant involvement in cell growth, shows that miR-145 also can suppress breast cancer metastasis. Silencing of metastasis gene mucin 1 (MUC1) is partially responsible for this breast tumour suppression (201). Furthermore, miR-145 also has observed to suppress cell-cell adhesion protein JAM-A and fascine in breast tumour cell lines, which is responsible for drastically decreasing cell motility (202).

Let-7 family: In let-7 family there are total 10 members: let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-98 and miR-202, which are basically involved in muscle formation, cell adhesion and gene expression and development regulation (203,204). Let-7 is generally downregulated in many cancers such as lung cancer (205), gastric cancer (206), colon cancer

(207) and Burkitt lymphoma (208), whereas in breast cancer it is lost at an early stage of disease progression (209). Yu et al. found reduced expression of let-7 family miRNAs in breast tumour initiating cells (BT-IC) and increase with differentiation. On the other hand overexpressed let7 miRNAs can reduce proliferation, mammosphere formation of BT-IC in vitro and tumour formation and metastasis in NOD/SCID mice. Let-7 miRNAs target H-RAS and HMGA2, which suggests that let-7 can regulate BT-IC stem cell-like properties by silencing multiple targets (210).

miRNA-125: Both isoforms of miR-125, miR-125a and miR-125b have been found to be significantly downregulated in breast cancer patients (214,215). In a study conducted by Guo et al. decreased expression of miRNA-125 was observed where, miR-125a was inversely correlated with HUR expression (an RNA binding protein overexpressed in several different cancers) in various breast cancer cell lines. Overexpression of 125a was associated with decreased HUR levels, which is responsible for cell growth, and reduced cell migration and proliferation, suggests that HUR is a potential target of miR-125a for suppressing breast tumour (210,211,212). miR-125a and miR-125b both were downregulated also in breast cancer cases where HER2 (human epidermal growth factor receptor 2) which is common in most of the cancers including breast cancer patients, is over expressed (212). Researchers have proposed c-Raf as target of miR-125b for exerting its antiproliferative effect (213).

miRNA-206: miR-206 has been observed to be upregulated in estrogen receptor negative (ER-) breast cancers and play a crucial role in inhibiting the expression of the estrogen receptor gene *ERα* (*ESR1*) (216). A study conducted by showed reduced expression of miR-206 in ERα-positive human breast cancer tissues. That miR-206 was found to suppress ESR1 expression along with MCF-7 breast cancer cells' growth inhibition (217). Another study which demonstrated downregulation of miR-206 in metastatic breast cancer cells in comparison to normal parental cells, also supports the tumour suppressive role of miR-206 (218). These findings support the potential role of miR-206 in suppressing breast cancer migration.

miRNA-31: Having pleotropic effects on breast cancer metastasis, miR-31 has been observed to inhibit metastasis in multiple steps by inhibiting premetastatic genes expression. Ectopic overexpression of miR-31 in MDA-MB-231 and SUM-159 breast cancer cells in vitro and in vivo, showed encapsulated and less invasive cancer instead of larger tumours formation and increased proliferation. Also, miR-31 can reduce cell survival and secondary tumours formation ability (219). In a study where miR-31 regulation of six identified gene targets, rizzled3 (*Fzd3*), integrin α-5 (*ITGA5*), myosin phosphatase-Rho interacting protein (*M-RIP*),

matrix metalloproteinase 16 (*MMP16*), radixin (*RDX*) and *RhoA* were investigated, showed only *ITGA5*, *RDX*, and *RhoA* had the ability to reverse the motility defects and impaired invasion. This suggests these three genes as important targets of miR-31 (220). These studies indicate miR-31 as inhibitor of metastasis and increased invasiveness.

miRNA-34a : p53 regulated this miRNA, which remains downregulated in several cancers, has been found in lower levels in triple negative and mesenchymal-type breast cancer cell lines when compared to the normal epithelial cell lines. This study suggests that p53 mutation may be responsible for the reduced miR-34 expression (211,221). Furthermore, study on effect of miR-34a on breast cancer development reporting downregulation of this miRNA in five different breast cancer cell lines compared to the normal epithelial cell line 184A1 and inhibition of breast cancer cell proliferation and migration through downregulation of its targets, Bcl-2 and SIRT1, strengthen the claim of miR-34a having tumour suppressive role in breast carcinoma (222).

miRNA-342: miR-342 has tumour suppressive role in tamoxifen resistant breast cancer cells. Tamoxifen resistance is a major problem in clinical applications today, where inspite of being one of the most prescribed endocrine therapies, about 30%–40% of patients fail adjuvant tamoxifen therapy and almost all of these patients having metastatic cancer, develop tamoxifen resistance as well. Tamoxifen is a selective estrogen receptor (ER α) modulator and has effects in breast cancer patients particularly where HER2 receptor tyrosine kinase overexpresses (223). Studies suggest HER2 which is a significant tamoxifen resistant factor has a splice oncogenic isoform HER2 Δ 16 associated with metastatic breast cancer and resistance to endocrine therapy (224). Another study revealed contribution of miR-342 to tamoxifen resistance in several models, including cell lines that overexpress HER2 Δ 16. Furthermore, miR-342 is found to be downregulated in tamoxifen resistant breast cancer cell lines along with tamoxifen refractory breast cancers (225).

Role of miRNA polymorphisms in breast cancer occurrence or susceptibility: One of the most famous and discussible genetic variations in current day is Single nucleotide polymorphism (SNP) which found almost in every 100-300 bases and plays crucial role in developing several cancers including breast cancer (231,232). SNPs found in miRNA coding genes or in the miRNA binding target genes either form new miRNA or alter target mRNA function due to overexpression of the target gene, which describes miRNAs as potential biomarkers for cancer/breast cancer prognosis and clinical management. (233-236). Here role of miRSNPs in breast cancer occurrence and susceptibility will be discussed on the basis of three criteria.

1. SNPs in target genes affecting micro RNA-mRNA interaction.
2. SNPs in miRNA Biogenesis Genes.
3. SNPs in genes that encode microRNAs.

SNPs in miR target genes affecting micro RNA-mRNA interaction: SNPs found in the 3' Untranslated region (UTR) of miRNA target gene can play an important role in altering the mRNA-miRNA interaction, which may increase the risk of cancer including breast cancer, if the target gene is oncogene or tumour suppressor gene. (237-239). There are almost 27 SNPs which have been mentioned in the following table, which play crucial role in breast cancer. (Table 4) In MDM4 family, constitutes of MDM2 and MDM4 genes, rs4245739 SNP has been found to be involved in reduced risk of breast cancer. This gene family is found in the epithelial cells that line the lumen of milk ducts in a matured breast (240). rs4245739 SNP (A>C) in 3' UTR region of MDM4 genes, which can negatively regulate p53, a tumour suppressor protein having vital role in cancer pathogenesis, is a target of miRNA-191 (241-243). Phe191Tyr (T>A), another novel SNP found in 3' UTR region of Spleen tyrosine kinase (SYK), has been observed to play important role in increased breast cancer risk (244-246). Spleen tyrosine kinase (SYK), is a member of the nonreceptor tyrosine kinase family and normally expressed in the breast epithelial tissue (246). Studies have shown expression of this gene family in breast tissue in addition to cell lines of breast cancer (247). According to many studies increased level of SET8 expression can inhibit cell apoptosis by p53 transcriptional activation suppression; which promotes tumour migration along with invasion by enhancing the EMT (248,249). SET8 is known for catalysing the histone H4 K20 monomethylating and also non-histone proteins like p53. (250,251). Among 129 variants of SET8, rs16917496 (T>C), which is a novel SNP, has been observed to be located inside 3'-UTR region, capable of binding with miR-520, which can regulate breast cancer risk. (252,253). Palladin (PALLD) (an actin-associated protein involved in actin-rich structures colocalization) is a target gene for miR-96 and miR-182, which have controversial effect on increased risk of breast cancer and its invasion. Despite of it, rs1071738 (C>G) SNP, which is located in the target site of miR-96 and miR-182, on 3' UTR region of PALLD, is found to be associated with increased risk of breast cancer. The above mentioned miRNAs' seed regions are entirely complimented to the 3'-UTR region of PALLD, hence a mismatch, seen in the presence of G allele can abolish the antimetastasis effect of miR-182 and miR-96 in this regard (254-259). These SNPs are novel among the 27 SNPs mentioned in the table. Studies suggest C allele of rs7963551 in the 3'UTR region of RAD52 which is binding site of let-7 miRNA and AC variant allele and CC allele genotypes of same SNP have

reduced risk of breast cancer occurrence. On the other hand, in case of women having a higher number of pregnancies, the A allele of rs7963551 showed significantly higher breast cancer risk. (261,262). In the 3'UTR region of BRCA1 gene miR-SNP rs8176318, miR-SNP rs12516 and miR-SNP rs3092995 have been identified to play crucial role in breast occurrence (260). reported rs8176318 miR-SNP for predicting breast (including TNBC) and ovarian cancer risk in a population of Irish women. According to another study homozygosity for the A alleles in miR-SNPs rs12516 and rs8176318 was significant associated with familial breast and ovarian cancer in a Thai cohort (263). On the other hand, elevated breast cancer risk was observed among in African American breast cancer patients having rs3092995, with the G allele predominant as compared to control subjects (264). miR-SNP rs1042538 in the core binding region of miR-124 in IQGAP1 (encoding IQ motif-containing GTPase-activating protein 1) can be predictive for breast cancer risk and prognosis. In Chinese population, TT genotype of this SNP is associated with lower breast cancer risk when compared to the AA genotype. Whether AA genotype has been found to be linked with higher breast cancer risk (265). Brenden and colleagues found strong association of miR-SNP rs743554 in the ITGB4 3'UTR region with specific risk of developing ER-negative breast cancers and worse overall survival when compared to those with the wildtype alleles. They also showed impairment of miR-34a binding to the ITGB4 3'UTR seed region by this SNP (266). A case control study in German population, where 1223 breast cancer families and 1495 controls were compared to study the effect of rs2747648 SNP in the 3'UTR miRNA binding site of ESR1, demonstrated that the T allele variant of this miR-SNP was associated with increased breast cancer risk in premenopausal women, whereas another group of researchers reported C allele genotypes of this SNP in same categoric women with lower breast cancer risk. (267). AG genotype of SNP rs334348 in the 3'UTR of TGFBR1 has been reported to be prone to breast cancer where, G allele is targeted by miR-628-5p with higher efficacy than its A allele counterpart in vitro (268). On the other hand, in the same study, SNP rs1982073 in TGFB1 was observed to exert its effect on gene expression with miR-187 altered interaction, and CC carriers of this SNP was linked to increased risk of breast cancer (268). CT and TT variants of miR-SNP rs115160714 in the 3'UTR region of Topoisomerase IIb binding protein 1 (TOPBP1) are found to be associated with higher breast cancer risk, when compared to CC genotype in Caucasian populations, TOPBP1 is hypothesized to bind with three miRNAs (miR-3138, miR-4302, and miR-1207-5p) and reported to possess rs115160714 (269,270). Overexpression of Matrix Metalloproteinases (MMP9) in multiple cancers are associated with increased invasion and poorer prognosis. Researchers have reported that The C allele of the miR-SNP rs1056628 can

bind and affect 3'UTR region of miR-491-5p targeted MMP9 which can prevent miRNA-mediated inhibition (271,272). In an Iranian population this c allele has been observed to be linked with increased breast cancer (273).

Table 4: miRNAs in cancer. (126)

Cancer type	miRNA	Up/Down Regulation
Esophagus		
	miR-194, miR- 192, miR-200c	Up
	miR- 203	Down
Gastrointestinal		
	miR-106b- 25	Up
	miR-15b, miR- 16	Down
Lung		
	has-mir-21 and has-mir- 205, miR- 17-92	Up
	has-mir-126*, miR-let 7, hsa-let-7a-2, let-7f-1	Down
Bladder		
	miR-2 23, miR- 26b, miR- 221, miR- 103-1, miR-185, miR-23 b, miR- 203,miR 17-5p, miR-23, miR- 205	Up
	miR-29c, miR-26a, miR-30c, miR- 30e-5p	Down
Thyroid tumors		
PC	miR- 146 b, miR- 221, miR- 222, miR- 181b, miR- 155, miR- 224	Up
AC	miR-30d, miR-125b, miR- 26a, miR- 30a- 5p	Down

SNPs in miRNA Biogenesis Genes : A very recent review by Poonam Malhotra et al., 2019 described more elaborately the effect of SNPs in miRNA biogenesis genes (274). SNPs rs644236 (C > T) and rs7737174 (A > G) in DROSHA (Nuclear RNase III), which is a key factor in the execution of the initiation step of miRNA processing was found to be linked with elevated risk of developing breast cancer in Korean post-menopausal women whereas rs2291109 (A > T) SNP in the same gene was found to be associated with increased breast cancer susceptibility (275,276). DGCR8 is an essential component of the pri-miRNA processing complex with Drosha. rs9606250 (A > T) and rs417309 (A > G), these two polymorphisms have been found in elevated breast cancer risk in Korean and Chinese breast cancer patients respectively (276,277). Epigenetic state of Exportin 5, known as XPO5 is responsible for exporting pre-miRNAs from the nucleus. missense SNP rs11544382 (A > G) was observed to be significantly linked with breast cancer susceptibility when compared to

homozygous controls, in Caucasian women. rs34324334 along with rs11544382 were found to be highly prone to develop breast cancer due to altered nucleocytoplasmic transport activity in post menopausal women (278). SNP rs1057035 (C > T), located in the 3'UTR of DICER1, a RNAlII protein in cytoplasm, having role in cleaving pre-miRNA to miRNA, has been observed to play significant role in disease-free survival, overall survival and elevation of breast cancer progression and breast cancer associated mortality (277,279). AGO2 a critical factor from in RISC (RNA interfering Silencing complex) complex, brings miRNA to the target site. Two SNPs rs11786030 (A > G) and rs2292779 (C > G), located in AGO2 were resulted in decreased free survival and poor overall survival. On the other hand SNP rs3864659 (A > C) in AGO2 was observed to have a protective role against breast cancer risk in a study conducted within Korean population. (275,277).

SNPs in genes that encode microRNAs: Single Nucleotide Polymorphism in miRNA coding gene sequence possibly develops new miRNA with altered function, which can regulate target mRNA due to multiple reasons including structural changes and affecting the CpG island of promoters (235,280). Studies suggest SNPs in microRNA may have crucial role in breast cancer occurrence (281). Around 13 SNPs have been demonstrated in (Table 5). Very recently few studies have observed more single nucleotide polymorphisms in miRNA encoding gene which were linked to breast cancer occurrence. miRNA 605, located on chromosome 10q21.1 plays a important role in the regulation of tumorigenesis and cancers (227). Arezu Kazemi, 2019 et al. conducted a study on 162 females affected by breast cancer from Iraian population to identify the correlation between rs2043556 in miR-605 and breast cancer. They performed the study using restriction fragment length polymorphism (RFLP) followed by Sanger sequencing and found rs2043556 to be associated with increased risk of breast cancer susceptibility. (226). A metanalysis study performed to correlate role of polymorphisms in miR-146a rs2910164, miR-196a rs11614913 and miR-499 rs3746444 with breast cancer risk showed rs11614913 CC genotype in miR-196a2 was linked with elevated level of breast cancer occurrence. This study is useful for early detection of breast cancer (229). Another metanalysis on these functional miRNAs' SNPs reported increased breast cancer risk with miR-499 rs3746444 in Asians and in the overall populations, while miR-196a rs11614913 was found in decreased association with breast cancer risk among Caucasians. They did not find any relationship between miR-146a rs2910164 with breast cancer susceptibility (230). On the other hand variant genotypes rs3746444 in miR-499 were reported to be associated with significantly increased risks of breast cancer in Chinese women (228). According to researchers The G allele of miR-SNP rs895819 (A > G) of pre-miR-27a is associated with a significantly reduced risk

of breast cancer in variant compared to controls in a German study cohort (54). Later a meta-analysis also reported the same though it showed reduced breast cancer risk in Caucasian population (55). But in another study by Feng and colleagues on Asian cohort found rs895819 SNP was linked to an elevated risk of breast cancer (56). Hence, effect of are population specific.

Table 5: (Gene Polymorphisms and their role in breast cancer susceptibility; Ref: microRNA-related single-nucleotide polymorphisms and breast cancer, Farbod Bahreini et al., 2020).

a) While the referenced articles investigated the mentioned allelic variants, the SNP database of <https://www.ncbi.nlm.nih.gov> shows the allelic variants as presented in parenthesis.

b) This SNP does not have any rs number as it is considered as a novel one and has not been submitted in any database.

Gene	Role	Single-nucleotide polymorphism	Allelic variants	Related microRNA	Breast cancer association	References
Bcl2	Prevention of normal cell apoptosis	rs1016860	C>T	miR-629	Increased risk	Hashemi Doulabi, Ghaedi, Ranji, and Khazaei Koochpar (2020)
Bmpr1-b	Phosphorylation of SMAD protein	rs1434536	C>T	miR-125b	Increased risk	Saetrom et al. (2009)
Brca1	DNA repairing	rs8176318	C>A (G>T) ^a	miR-1182 miR-149 miR-345 miR-544 miR-639	Increased risk	Ahmad, Jalil, Haq, and Shah (2019); F. Yang, Chen, Xu, and Guan (2016)
		rs12516	C>T (G>A) ^a	miR-188-5p miR-502-5p miR-557 miR-623 miR-637 miR-639	Increased risk	F. Yang et al. (2016)
Brca2	DNA repairing	rs15869	A>C	miR-548	Increased risk	Cao et al. (2016); Sanchez-Chaparro et al. (2020)
Cd44		rs13347	C>T	miR-509-3p	Increased risk	L. Jiang et al. (2012)
ErbB4	Arresting the cell cycle	rs1836724	C>T (G>A) ^a	miR-28-5p miR-708-5p miR-665	Increased risk	Bagheri, Mesrian Tanha, Mojtavai Naeini, Ghaedi, and Azadeh (2016); Zabihi et al. (2017)
	Inducing differentiation	rs1972820	G>A	miR-3144-3p	Reduced risk	Zabihi et al. (2017)
Esr1	Increasing the proliferation rate in breast tissue	rs1062577	T>A	miR-186 miR-3636 miR-3662	Increased risk	Dehghan et al. (2017)
		rs2747648	C>T	miR-453	Increased risk	Tchatchou et al. (2009)
Gata3	Embryonic	rs1058240	G>A	miR-1299- miR-182- miR-95	Increased risk	F. Yang et al. (2014)
Hpgd	Prostaglandins metabolism	rs8752	G>A (C>T) ^a	miR-485-5p	Increased risk	He et al. (2014)
Il23r	Differentiation	rs10889677	C>A	Let-7e Let-7f	Increased risk	L. Wang et al. (2012)
Iqgap1	Negative regulation of E-cadherin-mediated cell-cell adhesion	rs1042538	T>A	miR-124	Increased risk	Walch et al. (2008); Zheng et al. (2011)
Itgb4	Cell growth regulation	rs743554	G>A	miR-34a	Increased risk	Brendle et al. (2008)
Klf14	Cell proliferation	rs10800708	A>T	miR-892a miR-4252 miR-5095 miR-2114-3p	Increased risk	Shasttiri, Rostamian Delavar, Baghi, Dehghani Ashkezari, and Ghaedi (2019)
MDM4	Negative regulation of p53	rs4245739	A>C	miR-191	Reduced risk	Haupt, Maya, Kazaz, and Oren (1997); J. Liu et al. (2013); Oliner et al. (1993)
Mmp9	Collagen degradation	rs1056628	A>C	miR-491-5p	Increased risk	Pirooz et al. (2018)

Table 6: Association of breast cancer risk with SNPs in miR target genes; Gene Polymorphisms and their role in breast cancer susceptibility (Ref: microRNA-related single-nucleotide polymorphisms and breast cancer, Farbod Bahreini et al., 2020).

microRNA	Target gene	Allelic variants	SNP	Breast cancer association	References
miR-101	NRF2 SOX2	C>G	rs7536540	No effect	J. Chen et al. (2014); J. Wang et al. (2017); Yi, Huang, Wen, and Yi (2019)
		C>T	rs462489	Increased risk	
		G>C	rs1053872	Increased risk	
miR-145	TGFβR2	T>C	rs353291	Increased risk	Chacon-Cortes et al. (2015); Garcia-Garcia et al. (2019)
miR-146a	ERBB2	G>C	rs2910164	Controversial	Meshkat et al. (2016); Shen et al. (2008); Q. Sun et al. (2014); Venkitaraman (2001)
miR-196a2	Brca1	C>T	rs11614913	Increased risk	Morales et al. (2018); Yan, Gao, and Zhang (2017)
miR-27a	SPRY2 TMEM170B BAK	A>G (T>A, C, G) ^a	rs895819	Reduced risk	Li, Xu, Ding, and Tang (2019); Morales et al. (2016)
miR-34	ERBB2	T>C	rs4938723	Controversial	Bensen et al. (2013); Sanaei et al. (2016)
miR-423	BRMS1	A>C	rs6505162	Controversial	Pollard et al. (2018); X. Sun, Wang, Liu, and Wang (2017)
miR-499	FOXO4 PDCD4 Sox6 Rod1	A>G	rs3746444	Increased risk	X. P. Ma, Zhang, Peng, Yu, and Jiang de (2013); Morales et al. (2018); Yan et al. (2017)
miR-520f	ERBB2	G>A	rs75598818	Reduced risk	Harvey et al. (2015); Keklikoglou et al. (2012); Meshkat, Mesrian Tanha, Ghaedi, and Meshkat (2018); Yang, Zhao, Wei, Zuo, and Zhu (2017)
miR-559	ERBB2	C>T	rs58450758	Increased risk	Bahreini, Ramezani, Shahangian, Salehi, and Mashayekhi (2019); H. Chen et al. (2009); D. P. Wang et al. (2020); F. Yang et al. (2019)
miR-618	FOXP2	A>C	rs2682818	Increased risk	Feng, Ji, Liang, and Fan (2019); Morales et al. (2016)

Perspective: Since the discovery of miRNA in 1993 by Lee and colleagues, the importance of this small molecule has been growing rapidly. miRNAs have been found to be associated in various diseases including several carcinomas. Similarly in occurring breast cancer also miRNA and miRNA related SNPs have immense importance. This phenomena has opened a new horizon in cancer research as well as breast cancer study. As Breast cancer is the best

studied cancer according to pathobiology, subtypes and treatment, the role of miRNAs are well characterized. In this review we have shown many miRNAs and their SNPs who can regulate tumour metastasis, invasion, migration along with apoptotic activity in breast carcinoma. miRNAs also have ability to regulate several pathways. More importantly, miRNAs exert their silencing function through a complex process depended on cellular content, revealing tissue or cell type-specific phenotypes. (283) Expression of miR related SNPs (SNPs in miRNA synthesising genes, miRNA target genes and miRNA encoding genes) and their effect in breast cancer are population specific. Here also we have noticed many studies which support this claim. Therefore more studies on miR SNPs in different population will help researchers to understand their role in breast cancer progression. So, more understanding in miRNA and their SNPs is required in coming days, Specially interactional networks between miRNAs and the human genome, transcriptome and proteome is very important to clearly understand. These studies will help researchers to transit the previous promising laboratory results into diagnostics and prognosis of breast cancer along with efficacious therapies in clinical practice (283). In conclusion, studies on miRNAs and miRSNPs can be bring revolution in breast cancer prognosis and treatment in near future.

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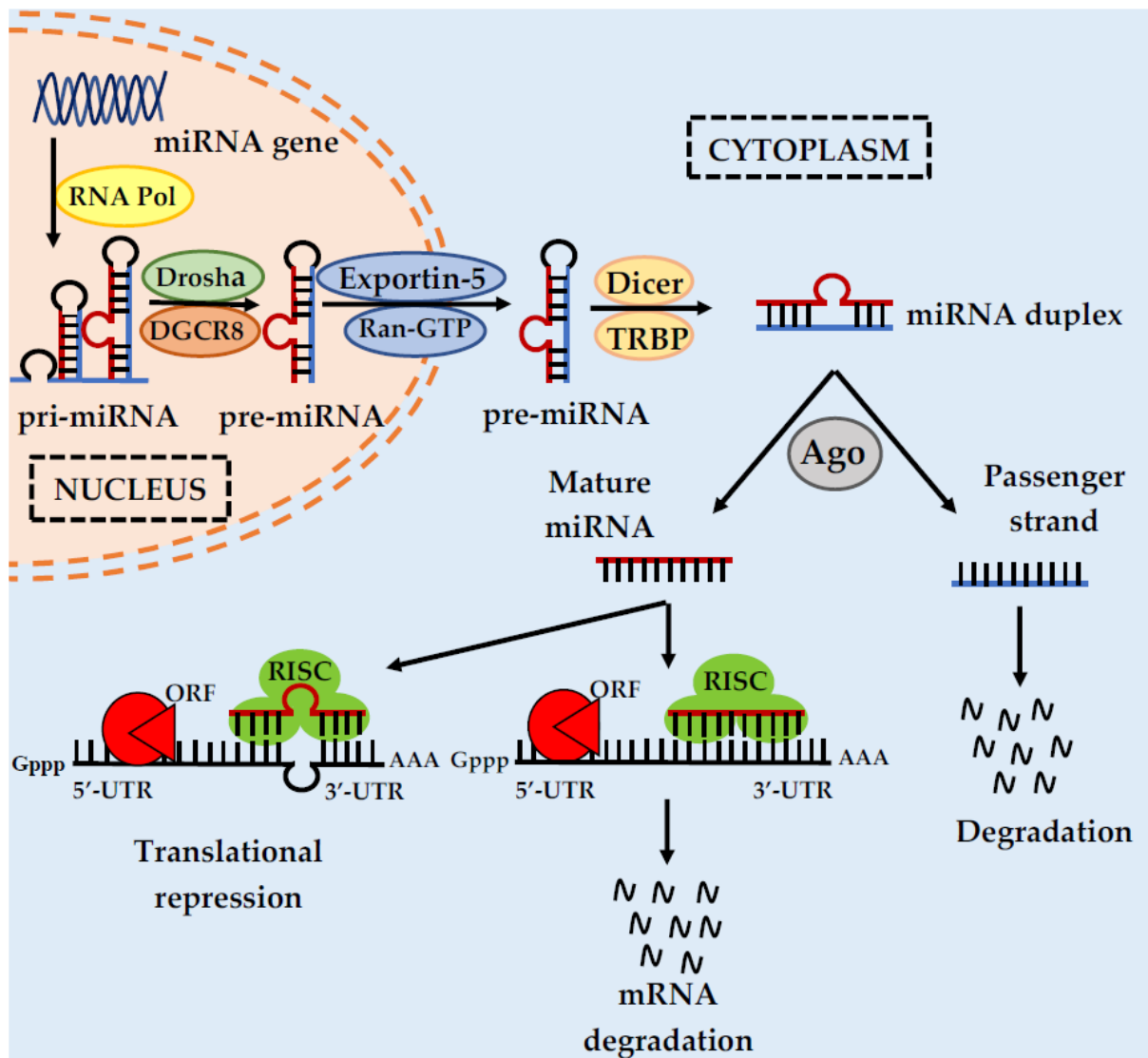


Figure 1: Hui-Yi Loh, Brendan P. Norman, Kok-Song Lai, Nik Mohd Afizan Nik Abd. Rahman, Noorjahan Banu Mohamed Alitheen and Mohd Azuraiddi Osman 1, *Int. J. Mol. Sci.* 2019, 20, 4940. The Regulatory Role of MicroRNAs in Breast Cancer. Reproduced with permission from Bhardwaj, A.; Singh, S.; Singh, A.P. MicroRNA-based cancer therapeutics: Big hope from small RNAs. *Mol. Cell Pharmacol.* 2010.