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Modulatory role of miRNAs in thyroid and breast cancer progression and insights into their therapeutic manipulation



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ABSTRACT

Over the past few decades, thyroid cancer has become one of the most common types of endocrine cancer, contributing to an increase in prevalence. In the year 2020, there were 586,202 newly diagnosed cases of thyroid cancer around the world. This constituted approximately 3.0% of all patients diagnosed with cancer. The World Health Organization reported that there will be 2.3 million women receiving treatment for breast cancer in 2020, with 685,000. Despite the fact that carcinoma is one of the world's leading causes of death, there is still a paucity of information about its biology. MicroRNAs (miRNAs; miRs) are non-coding RNAs that can reduce gene expression by cleaving the 3' untranslated regions of mRNA. These factors make them a potential protein translation inhibitor. Diverse biological mechanisms implicated in the genesis of cancer are modulated by miRNA. The investigation of global miRNA expression in cancer showed regulatory activity through up regulation and down-regulation in several cancers, including thyroid cancer and breast cancer. In thyroid cancer, miRNA influences several cancers related signaling pathways through modulating MAPK, PI3K, and the RAS pathway. In breast cancer, the regulatory activity of miRNA was played through the cyclin protein family, protein kinases and their inhibitors, and other growth promoters or suppressors, which modulated cell proliferation and cell cycle progression. This article's goal is to discuss key miRNA expressions that are involved in the development of thyroid and breast cancer as well as their therapeutic manipulation for these two specific cancer types.

1. Introduction

The study of cancer initiation and progression based on molecular pathways has become a cornerstone of cancer research, providing a solid platform for developing potential cancer therapeutics. The malfunction of several types of regulators, among which microRNAs have attracted a lot of attention in recent decades, causes changes in gene expression linked to cancer progression (Condrat et al., 2020). MicroRNAs, also known as miRNAs or miRs, are single-stranded non-coding RNAs that control the expression of genes by cleaving messenger RNA (mRNA) or preventing translation. They range in length from 19 to 23 nucleotides and are normally produced from nascent primary miRNA (pri-miRNA) transcripts by means of two distinct cleavage events that take place in sequential order (O'Brien et al., 2018; Ling et al., 2013; Bartel, 2004). The pri-miRNA is first subjected to processing by DROSHA (the DROSHA gene, which was originally known as RNASEN, is responsible for

encoding this class 2 ribonuclease III enzyme in humans) in the nucleus, which results in the release of a precursor form of a hairpin. When DICER cleaves pre-miRNA, exportin 5 (XPO5) takes it out of the nucleus (an RNase III enzyme) (O'Brien et al., 2018). The tiny RNA duplex that is produced and then loaded onto the Argonaute (AGO) protein, selectively removes other fragments of immature miRNA while preferentially retaining only one strand of mature miRNA (Medley et al., 2021). The RNA-induced silencing complex is an effector complex that is composed of the miRNA-loaded Argonaute (Ago) family proteins along with other cofactors, [one of which is GW182 (also known as TNRC6A)], essential for forming the RISC (RNA-induced silencing complex) (Catalanotto et al., 2016). The miRISC (miRNA-induced silencing complex) potentially damages mRNA and delays translation by binding with complementary bases in the 3'-untranslated region (3'-UTR) of target gene mRNA (Akgül et al., 2018; O'Brien et al., 2018). This allows the miRNAs to play a significant function in a wide range of physiological and developmental processes. Environmental stresses, including hunger,

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Abbreviation	
miRNA	MicroRNA
XPO5	Exportin 5
AGO	Argonaute
RISC	RNA-induced silencing complex
miRISC	miRNA-induced silencing complex
BRAF	Serine/threonine – protein kinase B-Raf
TC	Thyroid cancer
PTC	Papillary thyroid cancer
FTC	Follicular thyroid cancer
MTC	Medullary thyroid cancer
ATC	Anaplastic thyroid cancer
PDTC	Poorly differentiated thyroid cancer
DTC	Differentiated thyroid carcinoma
RET	Rearranged during transfection
SEER	Surveillance, Epidemiology, and End Results
COL4A1	Collagen alpha-1(IV) chain
TGFB1	Transforming growth factor beta 1
PDCD4	Programmed cell death protein 4
FOXO1	Forkhead box protein O1
TNM	Tumor node metastases
ROCK1	Rho-associated, coiled-coil-containing protein kinase 1
ERK	Extracellular-signal-regulated kinase
MAPK	Mitogen-activated protein kinase
SphK1	Sphingosine kinase 1
Era	Estrogen receptor alfa
FGF2	Fibroblast Growth Factor 2
SOS1	Son of sevenless homolog 1
MSI2	Musashi RNA Binding Protein 2
MET	MET Proto-Oncogene, Receptor Tyrosine Kinase
RTK	Receptor tyrosine kinases
PI3K	phosphoinositide 3-kinase
PPAR γ	peroxisome proliferated or activated receptor γ
EFEMP2	EGF containing fibulin extracellular matrix protein 2
FFPE	Formalin-fixed paraffin-embedded
MI-FTC	Minimally invasive follicular thyroid cancer
sMTC	Sporadic Medullary Thyroid Cancer
hMTC	Hereditary Medullary Thyroid Carcinoma
EZH2	Enhancer of zeste homolog 2
hTERT	Human telomerase reverse transcriptase
VEGF	Vascular endothelial growth factor
MADD	MAP Kinase Activating Death Domain
ER	Estrogen receptor
NIS	Na ⁺ /I-symporter
SMAD2	S Mothers against decapentaplegic homolog 2
TGFBR1	Transforming growth factor beta receptor 1
EMT	Epithelial-mesenchymal transition
PPAR	Peroxisome proliferator-activated receptors
mTOR	Mammalian target of rapamycin
IARC	International Agency for Research on Cancer
CCNE1	Cyclin E1
GGH	Gamma glutamyl hydrolase
NSEP1	Nuclease sensitive element binding protein 1
LAPTMB4	Lysosome-associated transmembrane protein 4-beta
v-MYB	Avian myeloblastosis viral oncogene homolog
HER2	Human epidermal growth factor receptor-2
CK5	Cytokeratin 5
STAT3	Signal transducer and activator of transcription 3
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
SOCS1	Suppressor Of Cytokine Signaling 1
ER	Estrogen receptor
PR	Progesterone receptor
TGF-beta	Transforming growth factor beta
qPCR	Quantitative polymerase chain reaction
EGFR	Epidermal growth factor receptor
CK5/6	Cytokeratin 5/6
BRCA1	BReast CAncer gene 1
EMT	Epithelial-mesenchymal transition
Bcl-2	B-cell lymphoma 2
ER β 1	Estrogen receptor beta

hypoxia, oxidative stress, and DNA damage because of miRNA-mediated gene expression, are linked to the causes of cancer (Ali Syeda et al., 2020). Numerous miRNAs can operate as tumor-inducing or tumor-inhibiting genes (oncomiRs), and the dysregulation of their expression is linked to cancer initiation, development, and metastasis in a substantial way. In numerous human tissues, alterations of such miRNAs are regarded as a crucial step in the development and progression of tumors. Oncogenes are genes that control cell survival, division, and death (apoptosis). Over-expression of certain miRNAs can turn off tumor suppressor genes, while down-regulation of miRNAs can make more oncogenes expressed (Otmani and Lewalle, 2021).

Tumors of the thyroid gland accumulate mutations that drive carcinogenesis through a process known as dedifferentiation, and this is widely regarded as the progression model for thyroid cancer. Redesigning the stepwise replica of thyroid cancer development has been made possible by analysis of the genome sequences of these tumors (Ramírez-Moya et al., 2019). Thus, identifying genetic processes for thyroid cancer evolution is critical, mainly for the therapy of histological subtypes that are less responsive to the standard curative approaches. Thyroid cancer (TC) may now be considered an epidemic, according to growing diagnostic evidence, and various reasons may contribute to its development (Cao et al., 2021; Ghafouri-Fard et al., 2020). In terms of how BRAF and RAS signaling support tumorigenesis and proliferation, the capacity to distinguish between two genetic types is a critical component of the future research of genomic investigations in thyroid cancer. BRAF-driven cancers have a lot of MEK-ERK activity, whereas

RAS-driven tumors have a lot of PI3K activity. Cancers that are driven by BRAF mutations are highly different in terms of gene expression, miRNA profiles, and epigenetic changes (Hussen et al., 2021; Ramírez-Moya et al., 2019).

Breast cancer is caused by abnormal proliferation of cells or tissues in the mammary glands and ducts. The vast majority of malignant breast lesions are carcinomas, which are more specifically referred to as adenocarcinomas (Feng et al., 2018). Breast cancer is a very heterogeneous disease with a broad ranges of intertumoral and intratumoral non-uniformity, as well as a wide range of tumor types among those who are affected (Dai et al., 2017; Polyak, 2011). It is a complicated condition that includes the mechanisms of cancer instigation and development, angiogenesis, invasion, and metastasis. In addition, there is a substantial risk of cancer remission after treatment. When the mammary gland's cellular and molecular communication pathways are deregulated, it can lead to the development of malignant alterations (Karagiannis et al., 2016; Castañeda-Gill and Vishwanatha, 2016; Ahmad, 2013). Additionally, alterations in the expression of miRNAs can have a significant impact on breast cancer pathology, morphology, and treatment outcomes (Ohzawa et al., 2017; Kurozumi et al., 2017). Furthermore, investigations have shown that aberrant miRNA expression profiles are present in breast cancer cases as compared to their non-malignant counterparts (Fridrichova and Zmetakova, 2019). miRNA molecules hold enormous promise as new biological therapeutic agents, targets, or biomarkers for breast cancer patients (Teo et al., 2021).

Some studies have revealed that varied miRNA expression profiles are

important for pathogenesis in individuals, potentially promoting the lack of distinction and cancer metastasis. This review provides a concise explanation of how numerous transcripts may be implicated in the etiology of thyroid cancer and breast cancer as well as how they may be exploited as potential biomarkers for both type of cancer therapy.

Numerous studies have shown that during the past few decades, both breast cancer and thyroid cancer rates have increased globally. One of the most common malignancies to be diagnosed worldwide is breast cancer. According to the statistical analysis, lung cancer is the top cause of mortality in the USA, followed by breast cancer (Guo et al., 2018; Rossi et al., 2021). Approximately 2,76,480 cases of invasive breast cancer and 48,530 cases of ductal carcinoma were diagnosed in the United States in 2020, with 42,170 predicted breast cancer-related fatalities. However, 4%–5% of instances of invasive breast cancer occur in women under the age of 40, despite the fact that women >40 years account for the majority of cases (Hendrick et al., 2021). Along with the incidence rate of breast cancer, the relative risk of thyroid cancer is also steadily growing. Thyroid cancer is the most prevalent endocrine cancer type in the world. Over a period of less than ten years, the incidence rates of thyroid cancer increased by about 93%. This endocrine carcinoma accounts for one out of every ten cancer diagnoses in Thiruvananthapuram, India and a significant portion of patients were over 40 years of age (Deng et al., 2020; Furuya-Kanamori et al., 2018; Lim et al., 2017; Pellegriti et al., 2013; Mathew and Mathew, 2017; SekkathVeedu et al., 2018). In India, the number of women with thyroid cancer went from 2.4 to 3.9 in the last ten years, and the number of men with thyroid cancer went from 0.9 to 1.3. Overall, there was a relative growth of about 62% and 48%, respectively. Considering these alarming incidence of thyroid and breast cancer cases in India as well as in global scenario, the present review focus on how numerous transcripts may be implicated in the etiology of thyroid cancer and breast cancer, as well as how they may be exploited as potential biomarkers for both types of cancer therapy.

2. miRNA as biomarkers in cancer

The term “biomarker” refers to several forms of measurable health indicators or disorder. These indicators have become increasingly exact and trustworthy throughout time, owing to human technology developments. The assumption that RNA molecules could not be utilized as biomarkers from blood samples due to the elevated amounts of nucleases found in plasma was debated for a while (Kamm and Smith, 1972a,b), but it was eventually abandoned following the revealed as miRNAs remained resilient in samples of fixed tissues (Xi et al., 2007). In 2008, Lawrie et al. (2008) used miRNAs to analyze the serum of patients with diffuse large B-cell lymphoma as biomarkers for cancer; since then, potential major applications of miRNAs as biomarkers for several diseases has been discussed in the scientific literature. This innovative class of compounds contains a wide variety of benefits, which may transform them into excellent prospects for the role of biomarkers in a number of diseases. The perfect biomarker should be simple to obtain. This is a requirement that is satisfied by miRNAs, which are readily available for extraction using liquid biopsies taken from blood, urine, and other physiological fluids. Several studies have utilized it to distinguish between cancer stages and even to test medication responsiveness because of its great specificity for the tissue or cell type of provenance and its sensitivity in the way it evolves according to disease development (Lan et al., 2015; Acunzo et al., 2015). A further advantage of miRNAs is the possibility that they can be employed as multimarker frameworks for the purposes of definitive diagnosis, directed treatment, and determining whether or not a patient is receptive to treatment. The use of multimarker panels that are constituted of several miRNAs may give a non-invasive way for diagnosis and the prediction of illness progression. This is in contrast to the practice of testing many protein markers, which may be both time-consuming and costly (Condrat et al., 2020). This can be of utmost significance in cancer, which is an extremely heterogeneous disease. Because of this, a multimarker strategy is strongly

recommended. Unfortunately, research into miRNAs as potential biomarkers remain in its preliminary phases, and as a result, the findings are not generally reproducible at this time point.

3. Insights into thyroid cancer

The American Cancer Society estimates that there were 62,000 new instances of TC detected in men and women in 2014. This makes thyroid cancer the fifth most common form of cancer in women in the United States (American Cancer Society, 2014). TC incidence is increasing globally as a result of enhanced diagnostic imaging and surveillance. There is consistency between new instances of thyroid cancer and a declining mortality rate. Clinical features of TC are quite diverse, ranging from indolent tumors with low mortality to highly aggressive malignancies. Despite a steady rise in incidence, TC mortality has not altered significantly over the past five decades. TC is divided into various histological kinds and subtypes, each having its own cellular origins, features, and prognoses (Lloyd et al., 2004). Follicular thyroid cells and parafollicular (C) cells are the two types of endocrine thyroid cells that can differentiate into a tumor of the thyroid gland. PTC (Papillary thyroid cancer), FTC (follicular thyroid cancer), PDC (poorly differentiated thyroid cancer), and ATC (anaplastic thyroid cancer) are the types of follicular thyroid cell-derived carcinoma that make up the bulk of thyroid malignancies. Both follicular and papillary thyroid cancers are included together under the umbrella term known as ‘differentiated thyroid carcinoma’ (DTC). Only a small percentage of thyroid cancer cases are found to be parafollicular C cell-derived MTC (medullary thyroid carcinoma) (Sites, 2014). The abnormal activation of RET signaling (induced by RET mutations (Hofstra et al., 1994) is the key molecular mechanism that underlies the development of MTC tumors. Follicular thyroid cell-derived tumors do not have this molecular mechanism (Xing, 2013).

Thyroid follicular epithelial cells are the primary source of DTC, which accounts for more than 95% of TC cases. PTC, FTC, and Hurthle cell thyroid cancer fall within the category of well-distinguished TCs. PTC is extremely prevalent among all thyroid malignancies, and it has been a major contributor to the recent global increase in TC incidence. PTC is responsible for at least 80% of all thyroid malignancies in the overall population (Papaioannou et al., 2021; Hitu et al., 2020). Patient age is a significant prognostic factor in PTC, with greater survival rates for patients under the age of 45 and survival rates of around 95% at the age of 40 (Zembska et al., 2019). PTC can be caused by both radiation and long-term exposure to other chemicals that damage DNA.

PTC affects mostly middle-aged individuals, with a median presentation age of 50 years and a female-to-male ratio of 3:1. The follicular subtype of thyroid cancer represents the second most common form of the disease, popularly known as FTC. It is reported in 10% of the entire TC and has a higher frequency among women aged 40–60 years. In advanced situations, FTC is known to both spread into the bloodstream (hematogenously) and metastasis. Only about 10–15% of patients have evidence of distant metastases; bone and the lungs are the most common sites of metastasis. Metastases of FTC to the facial skeleton are highly rare and difficult to cure. The gnathic bones, paranasal sinuses, and orbit can all be affected by FTC facial bone metastases (Varadarajan et al., 2017).

MTC is a rare malignant neoplasm that starts from parafollicular C cells of the thyroid gland (5–10% of TCs). MTC induces an increase in calcitonin levels, which is a key characteristic of MTC (Chen et al., 2020). Basic changes in sporadic and hereditary MTC can be caused by genetic modifications, with prognosis and mutational status connections. Fine-needle aspiration (FNA) cytology is generally applied for the diagnosis in sporadic cases, and serum calcitonin levels are frequently evaluated in patients who have a high risk of inborn or hereditary illness (Oliveira et al., 2021). In MTC, about 25% of cases are inherited, while the rest are sporadic (Matrone et al., 2022). Patients over the age of 45 years are more likely to be diagnosed with MTC than ever before. Survival rates are lower for people who are older and have more tumors. However, patients who have a variety of surgical resections at a primary

stage do better (Gogna et al., 2020).

ATC is an infrequent disorder that affects the thyroid gland and has a poor prognosis. Local progression and distant evolution are all characteristics of this disease, which has a quick beginning and is associated with both local and distant metastases (Jannin et al., 2022). ATC is an atypical amorphous form of thyroid cancer that is practically incurable, with a six-month median survival rate. Surprisingly, only about 20% of ATC patients survive a year after diagnosis (Alobuia et al., 2020). Because of its poor prognosis, it accounts for 40–50% of all TC associated causality in the US. In terms of how aggressive it is, PDC is like ATC. However, it also has some things in common with FTC and PTC, like follicular components and the production of thyroglobulin (Saini et al., 2018). In accordance with the European Union's rare cancer surveillance programme (RARECARE), ATC is considered a rare cancer, with an incidence of <6 person/100,000 person years. In fact, the SEER (Surveillance, Epidemiology, and End Results) database (Janz et al., 2019) recorded about 0.12 per 100,000 person-years of ATC in the United States in 2014, and between 0.1 and 0.3 per 100,000 person-years in Europe, according to data from the Netherlands (de Ridder et al., 2020), Denmark (Hvilsom et al., 2018), and Wales official health register. Based on a reported study by Deeken-Draisey et al. (2018), it was found that 0.5% (11/2106) of TC was ATC (Fig. 1).

4. Key modulatory role of miRNA in thyroid cancer

In contrast to normal tissues, several independent studies that examined miRNA expression in various forms of thyroid carcinoma demonstrated dysregulation of miRNAs (Santiago et al., 2020). Different forms of TCs, even though they originate from the same type, differ greatly in their miRNA expression profiles (Table 1).

4.1. PTC

PTC miRNAs play a crucial function in the progression of PTC. During angiogenesis and under hypoxic conditions, miRNA-21-5p expression increased in PTC cell lines while inhibiting the expression of the COL4A1 gene and TGFB1 gene (Wu et al., 2019). The miRNA-183 and miRNA-182 enhanced the growth of PTC cells by inhibiting the PDCD4 gene and CHL1 gene expression. A report showed that miRNA-5189-3p and miRNA-92a-3p were over-expressed in PTC for nodal metastasis and also acted as biomarkers for this malignancy (Papaioannou et al., 2021). The survival and growth of PTC were observed to be influenced by miRNA-96. This miRNA inhibited FOXO1 gene expression, which further down-regulated Bim/Akt/FOXO1 axis, and as a result malignant cell proliferation occurred (Song et al., 2015). Under-expression of miRNA-150 in PTC samples is inversely or negatively connected with lymph node and tumor node metastases (TNM) stage metastasis, where it targets endogenous ROCK1 (Rho associated protein kinase 1). miRNA-152 and miRNA-20b have been linked to more aggressive PTC via the ERK/MAPK signaling pathway (Papaioannou et al., 2021). Lower-expression of miRNA-448 was linked to TNM phase and lymph node metastasis in PTC cells and tissue (Ghafouri-Fard et al., 2020). Several miRNAs act as potential influencers through different genes to develop PTC. miRNA-128 (through SphK1), miRNA-206 (through MAP4K3), miRNA-219-5p (through ERA), miRNA-29a-3p (through OTUB2), miRNA-361-5p (through ROCK1), miRNA-613 (through SphK2), miRNA-744 (through NOB1), miRNA-654-3p, miRNA-195 (through FGF2 and CCND1), miRNA-329 (through WNT1), miRNA-199a-5p (through SNAI1), miRNA-206 (through MAP4K3), miRNA-497 (through Akt3), miRNA-4500 (through PLXNC1), miRNA-101 (through RAC1), miRNA-4728 (through MAPK and SOS1 signaling pathway), miRNA143-3p (through MSI2), miRNA-758-3p (through TAB1) and miRNA-5010-3p were expressed in very low level in PTC specimens which increased invasion, cell development and migration (Papaioannou et al., 2021). According to a study, serum miRNAs-199-3p and miRNA-146a-5p were down-regulated and

miRNA-10a-5p, let-7b-5p were up-regulated in PTC compared to pathologies of benign thyroid tumor while miRNA-342-3p, miRNA-150-5p, and miRNA-146a-5p were down-regulated and let-7b-5p, miRNA-191-5p and miRNA-93-5p over-expressed in papillary thyroid cancer compared to normal thyroid (Graham et al., 2015). Down-regulated miRNAs such as miRNA-138, miRNA-363, miRNA-9-1, miRNA-195, miRNA-152, miRNA-363, and miRNA-20b aided in the early detection of PTC. Studies found that some genes like MET, CCND1 and several miRNAs named miRNA-34a, miRNA-221, miRNA-222 were also used as ideal diagnostic tools for very sensitive PTC (Cong et al., 2015). Different levels of circulating miRNAs have been linked to various types of thyroid dysfunction. miRNA precursor Let-7e, miRNA-222 and miRNA-151-5p were remarkably higher in serum of the PTC patients (Yu et al., 2012). Previous research work has revealed that miRNA-21 serum levels are notably higher in pre-operative PTC compare to the control group. The miRNA-151-5p, miRNA-222 and miRNA-221 levels were remarkably lower in the PTC patients (Yoruker et al., 2016). Exosomes of PTC patients contain an increased level of miRNA-31, which is remarkably lower after tumor removal. miRNA-151 is mostly expressed in the blood of PTC patients. miRNA-222, miRNA-146b and miRNA-221 expressions were elevated in PTC patients compared to controls. Down-regulation of thyroglobulin-encoded functional microRNA (miRNA-TG), which acts through MAP kinase signaling, is a useful biomarker for PTC (Zembska et al., 2019). According to Geraldo et al. (2012), miRNAs like let-7f and miRNA-146-5p acted as an important prognostic tool for rapidly increasing PTC. Mutation of BRAFT1799A helped in assessing miRNA expression as important molecular markers of PTC treatment. PTC is the most usual endocrine gland cancer, and the most common genetic moderation seen in this type of cancer is the RET/PTC rearrangement. Cell de-differentiation and proliferation were increased by the continuous activation of the ERK-PTC-BRAF-RAS-MAPK/RET signaling pathway (Perdas et al., 2016). By binding to TIMP3's 3' untranslated region (3'UTR), miRNA-221 was found to lower TIMP3 expression, while at the same time making PTC cells multiply and spread (Fig. 2a). It was discovered that this miRNA was part of the onco miRNA family (Diao et al., 2017).

4.2. FTC

In follicular carcinomas, oncogene activation is frequent. RAS gene alterations or a paired box gene 8/peroxisome proliferator-activated receptor gamma (PAX8-PPAR) gene rearrangement are seen in around 80% of follicular carcinomas (Tuttle, 2018; Nikiforova et al., 2003). There is evidence that MAPK, RTK, and PI3K/Akt signaling pathways, which are all regulated by growth factors and oncogenes such as RAS, also have a role in FTC malignancies. Aneuploidy, RAS mutations, and PAX8-PPAR γ rearrangements are some of the most prevalent genetic abnormalities found in FTC. The genomic translocation of PAX8- peroxisome proliferated or activated receptor γ (PPAR γ) leads the formation of fusion oncogenes familiar in 30% of follicular thyroid cancer cases (Eberhardt et al., 2010). In FTC, miRNA-222, miRNA-146b and miRNA-221 are up-regulated, and miRNA-197 and miRNA-346 expression are also elevated. *In vitro* investigations with both FTC133 and K5 cell lines revealed that over-expression of miRNA-197 and miRNA-346 enhanced cell proliferation, whereas inhibition of both miRNAs stopped cell growth. In the NPA87 cell line, this miRNA had no effect. This confirms that dysregulation of miRNA-197 and miRNA-346 is a hallmark of the FTC phenotype tumor suppressor protein EFEMP2 (fbulin 4) activity inhibited by miRNA-346 (Santarpia et al., 2013, Fuziwara and Kimura, 2014). When compared to a non-metastatic group, a study based on minimally invasive FTCs (MI-FTC) showed elevated levels of miRNA-92a, miRNA-221-3p, miRNA-222-5p, miRNA-10b, and miRNA-222-3p (Jikuzono et al., 2013). CARMA1 is a scaffold protein that is essential for T and B cell antigen receptor-induced NF- κ B activation. miRNA-539 was designed to target the 3'-UTR of CARMA1 in order to reduce CARMA1 expression and

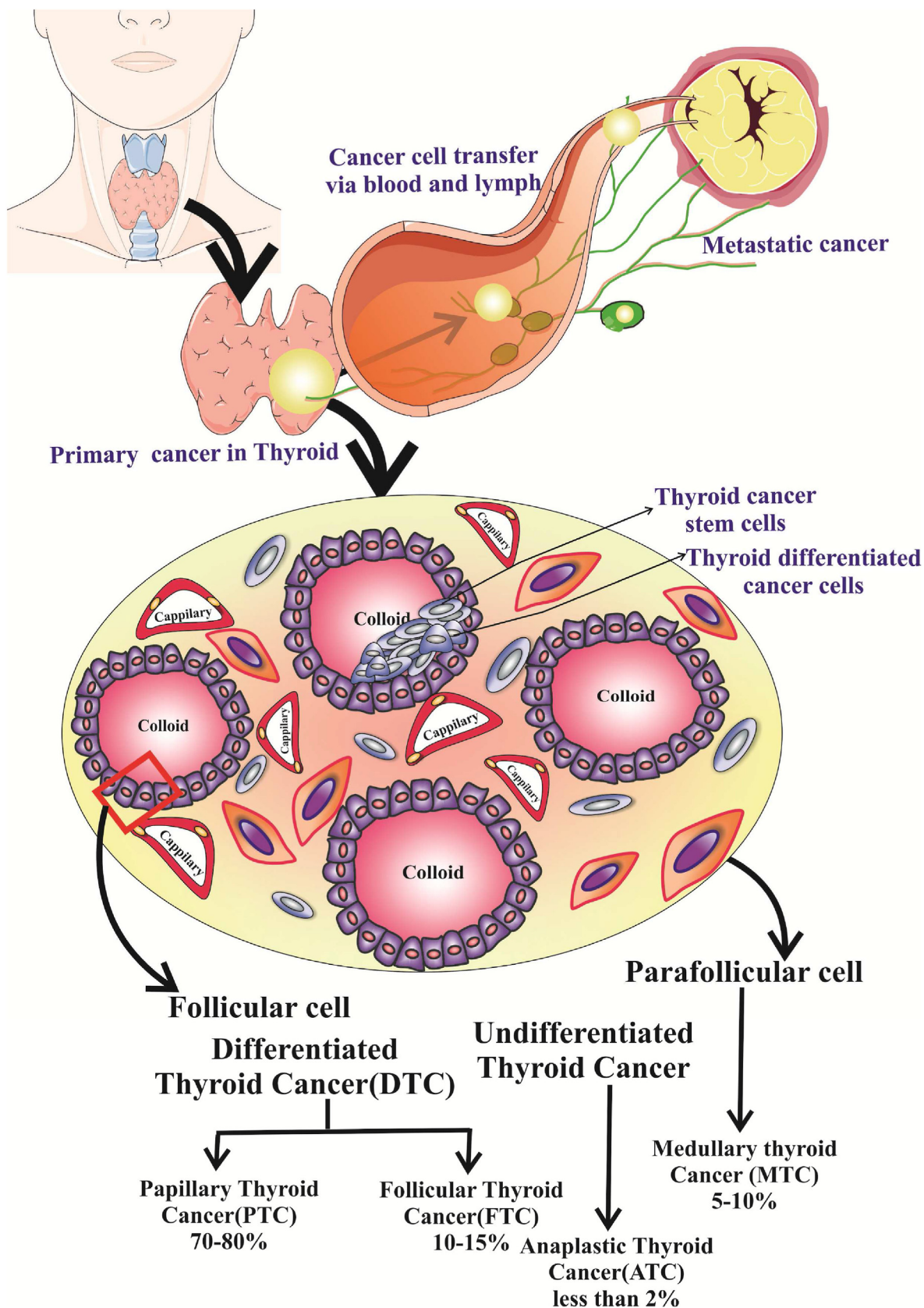


Fig. 1. A concise summary of the main molecular subtypes of thyroid cancer with their possible contribution towards worldwide thyroid cancer initiation.

Table 1

A tabular representation of some miRNA expressions seen in the numerous distinct subtypes of thyroid cancer cells.

Sl. No.	Name of miRNA	Sample type	Expression	Targeted gene	Oncogenic or TSG role	Type of thyroid cancer	Reference
1	miRNA-595 and miRNA-222	Tissue	Up-regulation	Functioning downstream of the RAS pathway and triggering epithelial-to-mesenchymal transition	Oncogene	PTC	Wei et al. (2019)
2	miRNA-183 and miRNA-182	Tissue	Up-regulation	Inhibiting the PDCD4 gene and the CHL1 gene expression	Oncogenic	PTC	Papaioannou et al. (2021)
3	miRNA-92a-3p	Tissue	Over-expression	VHL expression	Oncogenic	PTC	Papaioannou et al. (2021)
4	miRNA-96	Tissue	Up-regulation	Inhibited FOXO1 gene expression which further down-regulate Bim/Akt/FOXO1 axis	Oncogenic	PTC	Song et al., 2015
5	miRNA-150	Tissue	Under-expression	It targets endogenous ROCK1 (rho associated protein kinase 1)	TSG	PTC	Papaioannou et al. (2021)
6	miRNA-29a-3p	Tissue	Very lower-expression	Through OTUB2	oncogene	PTC	Papaioannou et al. (2021)
7	miRNA-361-5p	Tissue	Very lower-expression	Through ROCK1	oncogene	PTC	Papaioannou et al. (2021)
8	miRNA-613	Tissue	Very lower-expression	Through sphk2	oncogene	PTC	Papaioannou et al. (2021)
9	miRNA-195	Tissue	Very lower-expression	Through FGF2 and CCND1	oncogene	PTC	Papaioannou et al. (2021)
10	miRNA-329	Tissue	Very lower-expression	Through WNT1	oncogene	PTC	Papaioannou et al. (2021)
11	miRNA-199a-5p	Tissue	Very lower-expression	Through SNAI1	oncogene	PTC	Papaioannou et al. (2021)
12	miRNA-101	Tissue	Very lower-expression	Through RAC1	oncogene	PTC	Papaioannou et al. (2021)
13	miRNA-4728	Tissue	Very lower-expression	Through MAPK and SOS1 signaling pathway	oncogene	PTC	Papaioannou et al. (2021)
14	miRNA143-3p	Tissue	Very lower-expression	Through MSI2	oncogene	PTC	Papaioannou et al. (2021)
15	miRNA-758-3p	Tissue	Very lower-expression	Through TAB1	oncogene	PTC	Papaioannou et al. (2021)
16	miRNA -221	Tissue	Over-expression	Directly bind to the 3' un-translated region (3'UTR) of TIMP3 and inhibited its expression	oncogene	PTC	Diao et al. (2017)
17	miRNA-197 and miRNA-346	Tissue	Over-expression	EFEMP2 (fbulin 4)	oncogene	FTC	Santarpi et al. (2013); Fuziwara and Kimura, 2014
18	miRNA-885-5p	Tissue	Over-expression	Transcription factor PAX8 and its target gene NIS	Oncogene	FTC	Stokowy et al. (2016)
19	miRNA-183 and 375	Tissue	Over-expression and up-regulation	pdc4d	Oncogene	MTC	Galuppini et al. (2021);
20	miRNA-375	Serum	Higher expression	RET/RAS	Oncogene	MTC	Censi et al. (2021)
21	miRNA-21	Serum	Up-regulation	pdc4d	Oncogene	MTC	Pennelli et al. (2015)
22	miRNA-592	Tissue	Over-expression	Cyclin-dependent kinase 8	Oncogene	MTC	. Liu et al. (2021)
23	miRNA-182	Tissue	Upregulated	RET oncogene	Oncogene	MTC	Spitschak et al. (2017)
24	miRNA-154, miRNA-323, miRNA-370, miRNA-9	Tissue	Over-expressed	RET mutation	Oncogene	MTC	Mian et al. (2012)
25	miRNA-127	Tissue	Lower-expression	Somatic RET mutations	Oncogene	MTC	Mian et al. (2012)
26	miRNA-224	Tissue	Over- expression or up- regulation	Wild-type re-mutation	Oncogene	MTC	Mian et al. (2012)
27	miRNA-34b	Tissue	Exogenous over-expression	veg-f-a	TSG	ATC	Das et al. (2020)
28	miRNA-564	Tissue	Up-regulation	Astrocyte-elevated gene-1	TSG	PTC	Song et al. (2019)
29	miRNA-139	Tissue	Over-expression	Fibronectin 1	TSG	PTC	Ye et al., 2017
30	miRNA-204-5p	Tissue	Over-expression	Inhibiting IGFBP5	TSG	PTC	Liu et al. (2015)
31	miRNA-142-3p	Tissue	Down-regulation	Trithorax group proteins,	TSG	FTC	Colamaio et al. (2015)
32	miRNA-219-5p	Tissue	Dysregulation	Oestrogen receptor (ER)	TSG	PTC	Huang et al. (2015)

prevent thyroid cancer metastasis. A CRAMA1 knockdown plasmid demonstrated anti-metastatic activity in FTC cells. CRAMA1 activity was potentially inhibited by miRNA-539 (Gao et al., 2015). In comparison to healthy thyroid tissue, conventional and oncogenic variations of two histological types of FTC showed over-expression of miRNA-182/-183/-221/-222/-125a-3p and down-regulation of miRNA-542-5p/-574-3p/-455/-199a. Although in the oncogenic variant, the miRNA-885-5p was increased. The transcription factor PAX8 and its target gene NIS are both directly repressed. In a meta-analysis, researchers identified four miRNAs as being potential *de novo* follicular thyroid carcinoma biomarkers. These include miRNA-7-5p, miRNA-206, miRNA-181c-3p and miRNA-637 all of which have been shown to

distinguish between benign and cancerous thyroid tissue by various published studies. Mutation-negative FTC can be differentiated from follicular thyroid adenomas by two miRNA classifiers found by Stokowy and colleagues with a specificity and sensitivity of 87% and 89%, respectively (Stokowy et al., 2016). Stokowy et al. (2015) identified two different miRNA classifiers miRNA-7-5p and miRNA-7-2-3p for distinguishing PTCs and FTCs from benign TC. The sensitivity and specificity of two miRNA classifiers, were 82% and 49%. In addition to this, miRNA-146b, miRNA-183, and miRNA-221, all of which are observed to be dysregulated in PTC are elevated in FTC compared to normal thyroid cells, whereas miRNA-199b was found to be down-regulated (Wojtas et al., 2014) (Fig. 2b). The use of laser micro-dissection to extract

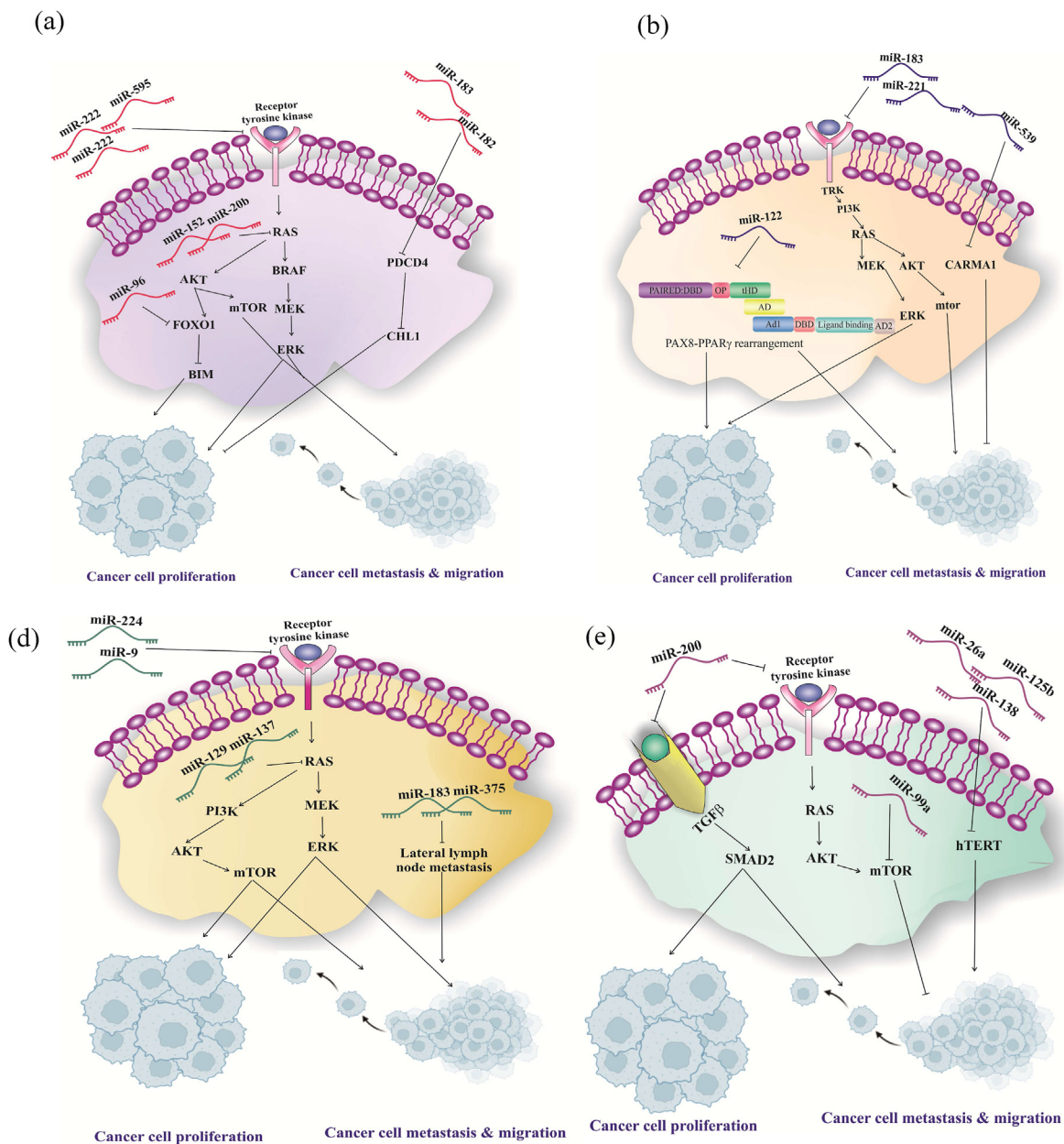


Fig. 2. Schematic presentation of several important miRNA expressions along with their regulatory activity in different kinds of thyroid cancer. miRNA expression and their modulatory role in cancer proliferation, cell metastasis and cancer migration in **(2a)**: Papillary thyroid cancer (PTC) **(2b)**: Follicular thyroid cancer (FTC) **(2c)**: Medullary thyroid cancer (MTC) and **(2d)**: Anaplastic thyroid cancer (ATC).

miRNAs from FFPE (formalin-fixed paraffin-embedded) tissues, followed by RT-qPCR and PCR arrays, revealed crucial data about miRNA idioms in MI-FTC (minimally invasive follicular thyroid cancer). The expression of miRNAs from the miRNA-92a, miRNA-10b, and miRNA-221/222 cluster was considerably enhanced in metastatic MI-FTC and WI-FTC (widely invasive FTC), both of which were typified by outlying metastases and reduced forecast. This finding suggests that the patterns of expression of miRNAs in both types of metastatic FTC (MI-FTC and WI-FTC) are strikingly comparable to one another. During the first stage of treatment, the miRNA-10b expression level was a significant contributor as a predictive marker for assessing the tumor progression of MI-FTC (Jikuzono et al., 2013).

4.3. MTC

A mutation (function gain) of the RET proto-oncogene is the key

molecular change linked to MTC genesis (almost 40% of sporadic and nearly every case of inherited MTC). MTC is caused by a RET mutation in the germ line, which can be autosomal dominant and manifest as one of three phenotypes: type IIA and IIB multiple endocrine neoplasia, and MTC in the family (familial MTC) (Matrone et al., 2021). The most common molecular modification in sporadic outbreaks is a RET mutation in somatic cells. In sporadic MTCs, other key molecular events, such as RAS mutations, have been found (approximately 35%). In multiple studies, miRNAs have been found to affect the RET gene and the MAPK signalling pathway in thyroid cancer, making them useful diagnostic and prognostic tools in cancer treatment (Galuppini et al., 2021). Differentially expressed miRNAs were detected employing a miRNA microarray expression profile in a main dataset of 12 sMTC (Sporadic Medullary Thyroid Cancer) and 7 hMTC (Hereditary Medullary Thyroid Carcinoma) cases (Mian et al., 2012). miRNA-183 and miRNA-375 over-expression in all MTCs were linked to peripheral lymph node metastases and persistent

locregional illness. Up-regulation of miRNA-224 has been identified as a predictive biomarker linked to a better prognosis in MTC patients. From the various prior studies it was reported that, miRNA-200b and miRNA-200c are considerably down-regulated in MTC metastases, whereas miRNA-375 and miRNA-10a are over-expressed and miRNA-455 is under-expressed (Galuppini et al., 2021; Hudson et al., 2013; Santarpia et al., 2013). miRNAs in MTC pathogenesis are the subject of relatively few investigations. As per the study of Nikiforova et al. (2008) miRNA-323, miRNA-370, miRNA-129, miRNA-137, miRNA-124a, miRNA-224, miRNA-127, and miRNA-9 are all up-regulated in MTCs as notable comparison against the ordinary thyroid tissues, with a fold change of 142.2 to 32.3 (Yuan et al., 2014). According to a previously reported investigation of miRNA expression associated with RET mutation in MTC, miRNA-21, miRNA-127, miRNA-154, miRNA-224, miRNA-323, miRNA-370, miRNA-9, miRNA-183, and miRNA-375 were significantly over-expressed (Fig. 2c). Patients with MTC who had their somatic RET mutations had lower levels of miRNA-127 than those who had sMTC with wild-type RET, and elevation of miRNA-224 was found to be an important predictive indicator for those patients. Both of these studies show that individuals with MTC who have miRNA-224 up-regulated have a better prognosis (Mian et al., 2012). In the study by Hudson et al. (2013) it was revealed that miRNA-375 and miRNA-10a were over-expressed, while miRNA455 was down-regulated in MTC. It did not appear that the presence or absence of RET mutations affected the expression of miRNA. In this study, it also reported that, YAP1 (growth inhibitor) was down-regulated by miRNA-375 in SCLC (small cell lung carcinoma), was likewise down-regulated in MTC. Thus, miRNA-375 associated YAP1 down-regulation may be critical for MTC tumor growth. miRNA-9, miRNA-10a, miRNA-124a, miRNA-127a, miRNA-129, miRNA-137, miRNA-154, miRNA-323 and miRNA-3370 are the ten other specific miRNAs that have been found to be up-regulated in the case of MTC by another group of researchers (Nikiforova et al., 2008). Three genes involved in miRNA synthesis, DICER, DCGR8, and XPO5, were over-expressed in the tissue of MTC harbouring RET mutations. MTC with RET codon 634 alterations had a more substantial increase in DICER1 and DGCR8 than RET wild-type tumors, but MTC with RAS mutations had no significant differences from non-mutated tumors. More research is required to determine whether or not an imbalance in the expression of enzymes that are involved in the production of miRNA can lead to the initiation of cancer (Manso et al., 2021).

4.4. ATC

There have only been a handful of studies that have investigated miRNA expression profiles in ATCs (Das et al., 2020). According to a previous study, microarray analysis in ATC patients revealed down-regulation of many miRNAs, such as miRNA-125b, miRNA-30a-5p, miRNA-30d, and miRNA-26a. Induced over-expression of miRNA-26a and miRNA-125b suppressed cell development in two human ATC cell lines, showing that these miRNAs are associated with cell cycle down-regulation and that their decreased expression contributes to thyroid carcinogenesis (Visone et al., 2007; Wójcicka et al., 2016; Wang et al., 2020). Using the same cell lines, over-expression of miRNA-30d and miRNA-30a had no effect on cell proliferation. The epigenetic gene suppressor miRNA-26a interferes with cell cycle progression by reducing the appearance of the EZH2 oncogene. In another study, miRNA expression was compared among the cell lines derived from ATC and PTC and tissue samples from both ATC and PTC. miRNA-21, miRNA146b, miRNA-221 and miRNA-222 were identified as over-expressed in ATC cell lines and tissues, while miRNA-26a, miRNA-138, miRNA-219 and miRNA-345 were down-regulated (Braun et al., 2010; Wu et al., 2013). The researchers looked into miRNA-138's role in ATC carcinogenesis because it had a distinctive expression pattern in ATCs as well as other follicular cell-derived thyroid malignancies. miRNA-138 directly targets the hTERT (human telomerase reverse transcriptase) gene. hTERT is

over-expressed in primary ATCs compared to PTCs and is associated with dedifferentiation and higher metastatic potential. Following the down-regulation of miRNA-138, the over-expression of hTERT may be responsible for the malignant development of well-differentiated PTCs to ATCs (Salh et al., 2022; Wu et al., 2013). In a study that investigated the function of the miRNA-17-92 cluster, miRNA-17-3p and miRNA-17-5p, were found to have higher levels of expression in ATCs as compared with the non-tissues that were located nearby in a study that investigated the function of the miRNA-17-92 cluster (Takakura et al., 2008). ATC cells were treated with antisense oligonucleotides that included caged nucleic acids, which seem to be antagonists of miRNA-17-3p and miRNA-17-5p, in order to ascertain the effects that these miRNAs play (Fig. 2d). Full growth arrest was induced in ATC cells, which was then followed by apoptosis when the expression of miRNA-17-3p was inhibited. On the other hand, the miRNA-17-5p inhibitor caused a significant slowdown in cellular development and ultimately led to senescence in ATC cells (Takakura et al., 2008; Das et al., 2020). Suppression of miRNA-18a, which is also a member of the cluster, resulted in a moderate reduction in cell proliferation, which indicates that the components of the cluster in ATC cells each served a distinct functional purpose. Caspase activity boosted apoptosis when miRNA-17-3p expression was inhibited. Transfection with additional miRNA-17-3p cluster inhibitors did not activate any type of caspase mechanism (Takakura et al., 2008; Das et al., 2020). Down-regulation of miRNA-34b was observed in metastatic ATC (BHT-101), but this expression was not found in cell derived from ATC (8505C). Moreover, the exogenous over-expression of miRNA-34b in ATC cells resulted in reduced cell explosion, lower wound curative phenomenon, slowed development through the cell cycle, and an elevated level of apoptosis. Additionally, the liposome-mediated transport of miRNA-34 in ATC cells led mostly to the down-regulation of vascular endothelial growth factor-A (VEGF-A). When compared with the control group, *in vivo* studies demonstrated that dosage of liposome-loaded miRNA-34b was able to reduce tumor size (Das et al., 2020). Gene silencing with the use of siRNA has been incorporated into the ATC model of cell proliferation, invasion, migration, metastasis, and death. As an illustration, the inhibition of proliferation and spread of ATC cells (8505C, C643, and HTH7) by siRNA-based inhibition of MADD (MAPK-activating death domain activating protein) production is effective (Zhou et al., 2016; Colombo et al., 2015; Saini et al., 2019). By inhibiting TNF-mediated cell death, MADD has the potential to play a role that encourages survival. MADD is also responsible for activating MAPKs through the recruitment of Grb2 and Sos1/2, which, in turn, leads to the ignition of ERK signaling devoid of impacting the functioning of p38, Jun, or NF- κ B (Kurada et al., 2009). According to the findings of the *in vitro* investigation, pretreatment by MADD siRNA was successful in inhibiting the growth of 8505C, C643 and HTH7 cell lines. In addition to this an *in vivo* study suggested, the reduction of the development of ATC-derived orthotopic tumor replica (8505C) as compared with the treatment free control group and the treated group with siRNA (Saini et al., 2019).

5. miRNA-mediated therapeutic approaches against thyroid cancer

Although miRNA's role in the pathogenesis of cancer is increasing nowadays, there were some studies that mentioned significant miRNA dysregulation in cancer appears as a capable therapeutic goal (Table 2). The pathogenic influence of miRNA is able to be eliminated by using some synthetic component like anti-miRNA, which will be the chief binding obstacle to its target site. In the synthetic RNA technology, lowered levels of a miRNA can be up-regulated with the help of the delivery of synthetic mature miRNA mimics, the release of primary miRNAs or miRNA precursors expressed from plasmids (Lam et al., 2015). miRNA is considered a potential targeted therapy in *in vivo* studies, which can be further gone through in clinical trials. The first breakthrough in the therapeutic field of miRNA gained success when miRNA-122 inhibitors

Table 2
Some important miRNA mediated therapeutic approaches against thyroid cancer.

Sl.No.	miRNAs	Used model	Therapeutics	Type of cancer	Reference
1	miRNA-101 and miRNA-145	<i>In vitro</i> (TPC-1 cells and HTH83, 293T cells)	Tumor suppression	Thyroid Cancer	Paskaš et al. (2015); Wang et al. (2014)
2	miRNA-219-5p	<i>In vitro</i> (PTC cell line K1)	Tumor suppression	Thyroid Cancer	Huang et al. (2015)
3	miRNA-182	PTC-derived thyroid cell lines, TPC-1 and BCPAP and Four-week-old male BALB/c nu/nu mice	Tumor suppression	Thyroid Cancer	Zhu et al. (2014)
4	miRNA-122	WRO cells and <i>in vivo</i> xenograft model (4-week-old athymic nude mice)	Tumor suppression	Thyroid Cancer	Reddi et al. (2011)
5	Combination of cabozantinib and miRNA153-3p	Human MTC TT cell lines and mouse xenograft model (female athymic (nu/nu) mice (5–6 weeks old)	Tumor suppression	Thyroid Cancer	JooLJ et al., 2019
6	miRNA-564	TPC-1, BCPAP, and HTH83 and a normal human thyroid cell line (HT-ori3) & <i>in vivo</i> tumor xenograft model (BALB/c nude mice)	Tumor suppression	Thyroid Cancer	Song et al. (2019)
7	miRNA-204-5p	TCP-1 and BCPAP and HEK293T cell line and xeno-graft model (Male BALB/c nude mice (4–6 weeks of age)	Tumor suppression	Thyroid Cancer	Liu et al. (2015)
8	Cubosomes (lipid nanoparticles) loaded with miRNA-7-5p	Human glioblastoma-derived A172 (TMZ-sensitive) and T98G (TMZ-resistant) cell lines	Tumor suppression	Thyroid Cancer	Gajda et al. (2020)

were preclinically tested against chronic hepatitis C in chimpanzees. The hepatitis C virus term that is defined was reduced greatly by the miRNA inhibitor when it was administered intravenously, or the investigated molecule was demonstrated toward being to be safe (Lanford et al., 2010). In an unresectable liver cancer patient, the MRX34 molecule, which mimics miRNA-34, was reported. Among 24 oncogenes, miRNA-34 is one of the potent regulators of liver cancer, which was targeted for the first time in a clinical trial (Austin, 2013). Researchers focus on PTC as it is the most prevalent cancer type among any other types of thyroid cancer. PTC miRNA-101 and miRNA-145 over-expression inhibit the growth, development and metastasis of PTC (Paskaš et al., 2015; Wang et al., 2014). PTC cell proliferation was inhibited by miRNA-291-5p, which was directly targeted to the oestrogen receptor (ER), and apoptosis was observed in PTC as a result (Huang et al., 2015). It may fail due to the lower expression of the Na⁺/I-symporter (NIS). Research revealed that inhibition of miRNA-339, miRNA-875-5p, and miRNA-146b increased the iodine uptake in thyroid cells (Tang et al., 2020; Riesco-Eizaguirre et al., 2015). Several studies have looked into the possibility of using miRNA inhibitors to control cellular miRNA levels. In the TPC-1 cell line, miRNA-182 was inhibited and injected into nude mice, which resulted in an inhibition of tumor growth. This study indicates that miRNA-182 can be a therapeutic target for PTC (Zhu et al., 2014). In the thyroid, miRNA-142-3 appears to decrease tumor growth in FTC. Its decreased expression in tumors' was linked to significant abnormal activity of Trithorax group proteins, which are regulators of the expression of the homeobox gene (Colamaio et al., 2015). miRNA-122 was increased in FTC, which is directly correlated with the elevated level of PAX8/PPAR γ fusion protein. This protein plays a key role in the invasion and metastasis of FTC. Over-expression of miRNA-122 in a mouse xenograft model resulted in a significant reduction in tumor development (Reddi et al., 2011). SMAD2 and TGFBR1 genes were up-regulated by the influence of miRNA-200 and miRNA-30 in ATC. These two genes are accountable for Epithelial-mesenchymal transition (EMT) in ATC (Wójcicka et al., 2016). miRNA-122 and miRNA-375 diminished angiogenesis and inactivated the AKT pathway by up-regulating PAX8/PPAR γ fusion. So, ATC is inhibited by re-differentiation and activation of tumour suppressor miRNA-122 and miRNA-375 by the PAX8/PPAR fusion protein, which is a potential therapeutic strategy for ATC (Reddi et al., 2013). The tumor suppressive action of RET controlled miRNA-1533p in MTC was mediated by suppression of mTOR signaling. MTC tumor growth was efficiently inhibited by a combination of cabozantinib and miRNA1533p (JooLJ et al., 2019). Ramírez-Moya et al. (2019) identified that oncogenic miRNA-146b-5p slows down the biosynthesis process of miRNA through interacting with DICER1 and lowering its expression. All of the destructive phenotypes that miRNA-146b caused in thyroid cells were stopped by DICER1

up-regulation. When the small molecule enoxacin was used to increase the activity of the DICER1 complex, the aggressiveness of the tumor was lowered in both *in vitro* and *in vivo* models. Their results show that DICER1 is a tumor suppressor and that oncogenic miRNA-146b helps to inhibit its expression. In a recent *in vivo* and *in vitro* analysis, it was reported the anticancer role of miRNA-143 against the PTC, which has a very important role in PTC development. They also proposed a novel signalling pathway for HMGA2 up-regulation in PTC via miRNA-143 down-regulation (Ding et al., 2022). Moreover, a published report by Zhang et al. (2021) demonstrated miRNA-144-5p/ITGA3 potentially suppressed the development of thyroid cancer by down-regulating the expression of the ITGA3 gene.

6. Breast cancer: special reference towards its molecular intrinsic subtypes

According to the most recent study reported by the IARC (International Agency for Research on Cancer), the entire number of fatalities caused by alarming carcinomas around the world has increased by 66% since 1960. Following lung cancer, breast cancer is currently the kind of carcinoma that is diagnosed in the second most people around the world (Sung et al., 2021). As a consequence of this, it is anticipated that around one in eight women in the United States may acquire invasive breast cancer at some point throughout their lifespan. When compared to the number of research articles that have been published on the subject of diagnosing and treating cancer of the breast, research into its early detection is still substantially behind (Zubair et al., 2021; Akram et al., 2017). Depending on gradual appearance assessments of multiple genetic materials in a particular trial, gene expression microarray investigations have demonstrated unique molecular (intrinsic) breast cancer types (Perou et al., 2000). Breast carcinoma that has high levels of gene expression associated with luminal cells (ER-responsive gene expression, luminal cytokeratins, and other luminal-related markers) is referred to as luminal tumors. Basal-like, ErbB2-positive, and normal-like subgroups of the ER negative population were also recognized (Russnes et al., 2017; Charafe-Jauffret et al., 2006). Luminal-A is the most prevalent type of breast cancer, accounting for between 50% and 60% of all cases (Guo et al., 2018). These tumors are characterized by lower histological grade, a limited form of nuclear pleomorphism, reduced mitotic activity, and special histopathologic kinds (such as tubular, invasive cribriform, mucous, and lobular), all of which indicate a favorable prognosis for the patient (Erber and Hartmann, 2020; Makki, 2015). Genes linked with ER's role like, erbB3, FOXA1 (hepatocyte nuclear factor 3 alpha), X-box binding protein 1 (XBP1), BCL2, LIV1 (Zinc transporter ZIP6 or SLC39A6; solute carrier family 39 zinc transporter, member 6), erbB4 and GATA binding protein 3 are all expressed in luminal epithelium (Carey, 2010;

Shah, 2017; Abdulhadi, 2019). Luminal-B carcinomas account for 15–20% of breast cancers and have a phenotype that is much more aggressive, a higher proliferative index, and a poorer prognosis than other types of breast cancer. Compared to the luminal-A subtype, this subtype has a higher rate of relapse and a lower rate of survival after relapse (Allouch et al., 2020; Serrano-Gomez et al., 2016). Up-regulation of proliferation-related genes such as CCNE1 (cyclin E1), GGH (gamma glutamyl hydrolase), NSEP1 (nuclease sensitive element binding protein 1), LAPTM4 (lysosome-associated transmembrane protein 4-beta), and v-MYB (avian myeloblastosis viral oncogene homolog) in luminal-B breast cancers is the main difference between the two luminal groups (Shrihastini et al., 2021; Carey, 2010). The HER2 gene, which may be found on chromosome 17q21, is responsible for encoding the human

epidermal growth factor receptor-2, which is a member of the tyrosine kinase family. HER2-positive (Human epidermal growth factor receptor-2) breast cancer accounts for 15–25% of all breast cancer subtypes and is characterized by aggressive behavior both biologically and clinically (Kumar and Aggarwal, 2016; Shao et al., 2012). Basal-like breast cancer accounts for 8–37% of all breast cancer cases, relying here on the proportion of individuals with weakly divided G3 cells included in the research. Triple-negative tumors are those that do not express the estrogen receptor (ER), the progesterone receptor (PR), or HER2. Tumors that belong to the basal-like subcategory express elevated amounts of basal myoepithelial markers, such as CK5, CK 14, CK 17, and laminin (Dai et al., 2017; Hachim et al., 2020; Iqbal and Buch, 2016). It is essential to make it clear that the terms “triple-negative” and “basal-like”

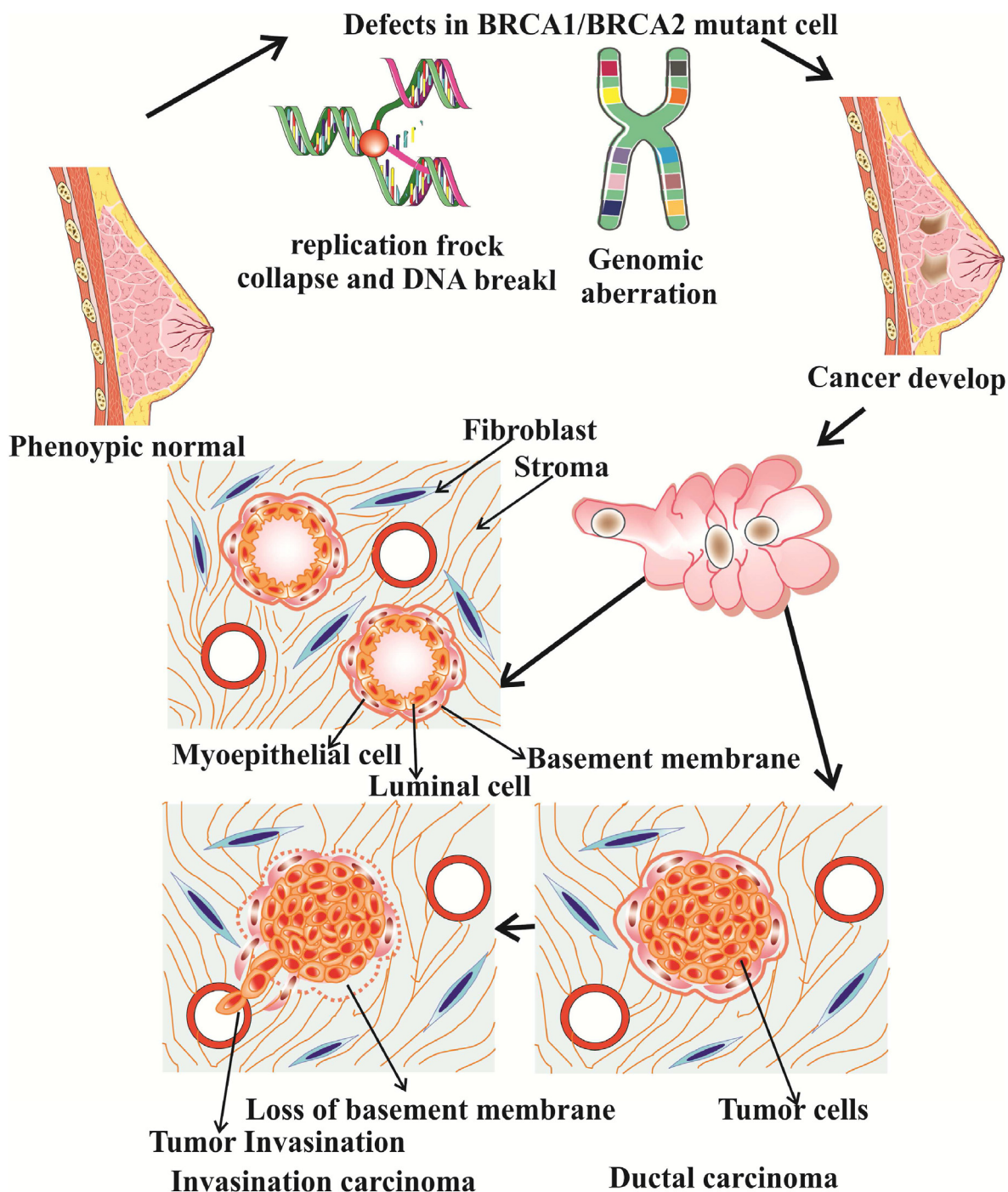


Fig. 3. Diagrams of various breast cancer subtypes, depending on their specific location.

are not totally synonymous, and that there is around 20–30% dissonance between them (Feng et al., 2018). Additionally, another subtype known as normal breast-like tumors is responsible for around 5–10% of the total number of breast carcinomas. They have a limited amount of characterization and have been lumped into the same intrinsic subtype classification as fibroadenomas and normal breast samples despite this (Yersal and Barutca, 2014).

Breast cancer can affect the ducts, lobules, or tissue in between. Cells impacted by breast cancer define its kind. Breast cancers are classified as carcinomas or sarcomas based on cell origin. Carcinomas arise from the milk-producing lobules and terminal ducts of the breast's epithelial layer. Sarcomas (1% of primary breast cancer) arise from myofibroblasts and blood vessel cells in the breast stroma. Common breast cancers can be categorized into three broad classes based on pathological traits and invasiveness: non-invasive (or *in situ*), invasive, and metastatic breast cancers. Non-invasive (or *in situ*) breast cancer subtypes include Ductal carcinoma *in situ* (DCIS), Invasive or infiltrating breast cancer, Invasive Ductal Carcinoma (IDC), and Invasive Lobular Carcinoma (ILC), whereas other types of breast cancer include inflammatory breast cancers (IBC), Papillary carcinoma, Phyllodes tumour, Angiosarcoma of the breast etc. (Feng et al., 2018) (Fig. 3 & Fig. 4).

7. Breast cancer associated important miRNA expression

Well over half of the human miRNA genes are located in cancer associated genomic regions or in fragile sites (Melo and Esteller, 2011). Since the function of miRNA deregulation in breast cancer was initially

reported in 2005, multiple studies have shown that breast cancer is associated with modulating the expression of miRNAs (Iorio et al., 2005; Cookson et al., 2012). Similar to the TC oncomiRNAs in breast cancer are also up-regulated which blocks specific tumor suppressor genes from being expressed and results in breast carcinoma (Table 3). Moreover, tsmiRNAs can be able to prevent the expression of oncogenes that also lead to breast cancer (Otmani and Lewalle, 2021).

7.1. miRNA expression profiles in luminal A and luminal B breast cancer

miRNAs are a subset of short non-coding RNAs that control gene expression by transcriptional activation or mRNA breakdown, and they've been around for a long time (O'Brien et al., 2018). By looking at how different miRNAs are expressed, it is possible to find biomarkers that can identify and differentiate between both healthy people and those with early breast cancer (Cookson et al., 2012). Several studies investigated the ways in which patients with luminal-A and healthy controls differed from one another in terms of the expression of miRNAs (Fig. 5a). Early breast cancer patients had greater levels of circulating miRNA-195, miRNA-21, miRNA-155, and miRNA-16 than healthy controls; these raised levels of miRNA were also seen in the serum of patients with luminal-A. As a result, an elevated level of circulating miRNA, specifically the combination of miRNA-195, miRNA-21, miRNA-155, and miRNA-16, is the determining factor for the diagnosis of luminal-A breast cancer (Fan et al., 2018; Heneghan et al., 2010; Hamam et al., 2017). The abridged expressions of miRNA-652, miRNA-181a and un-modulated expression of miRNA-29a were identified in the blood samples of

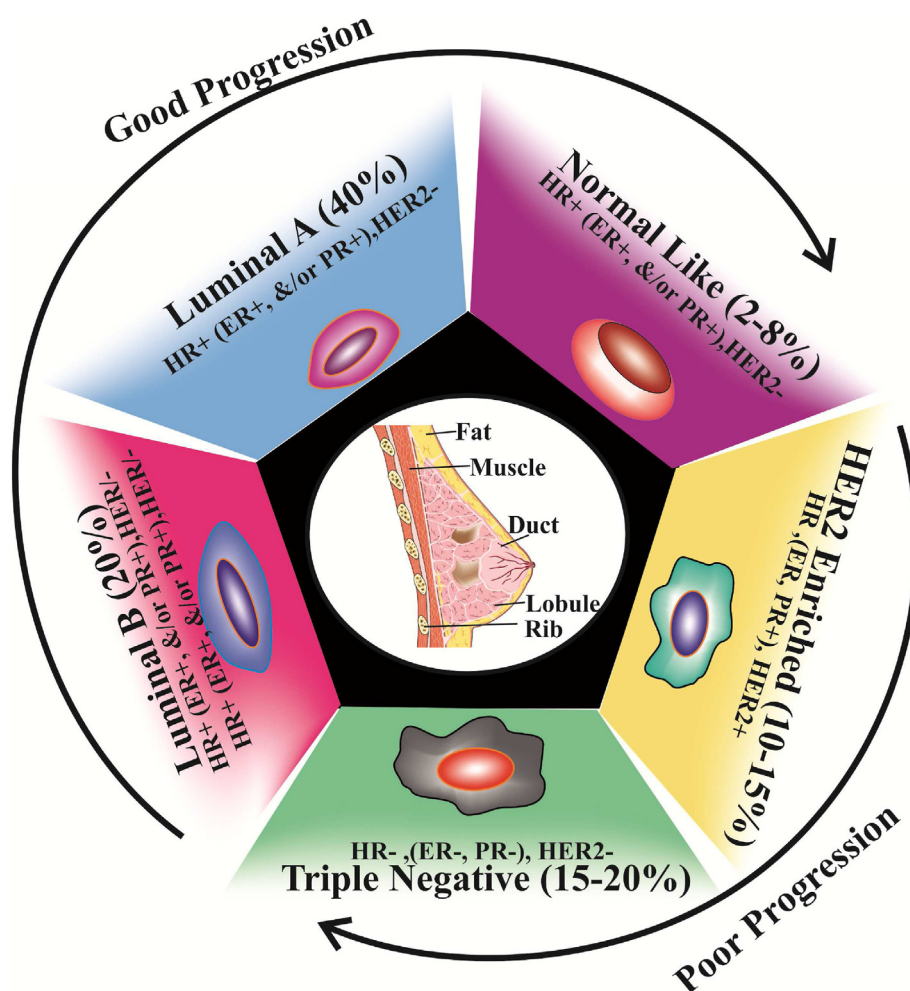


Fig. 4. Different molecular intrinsic subtypes of breast cancer.

Table 3

A tabular representation of the miRNA expressions seen in the numerous distinct subtypes of breast cancer cells.

Sl. No.	miRNAs	Sample type	Expression	Targeted gene	Oncogenic or TSG role	Reference
1	miRNA-127-3p, miRNA-148b, miRNA-376a, miRNA-376c, miRNA-409-3p, miRNA-652, and miRNA-801	Plasma	Higher expression	ITGA6	Oncogene	Hironaka-Mitsuhashi et al. (2022)
2	miRNA-1, miRNA-92a, miRNA-133a, and miRNA-133b	Serum	Over or higher expression	SERTAD3	Oncogene	Hironaka-Mitsuhashi et al. (2022)
3	miRNA-195	Tissue	Down-regulation	SEMA6D	Oncogene	Baxter et al. (2021)
4	miRNA-92	Tissue	Less expression	ERβ1	Oncogene	Smith et al. (2015).
5	miRNA –26b	Tissue	Down-regulation	TNKS1BP1, CPSF7, COL12A1	Oncogene	Verghese et al. (2013)
6	miRNA –222	Tissue	Up-regulation	LBR	Oncogene	Chatterjee et al. (2019)
7	miRNA-155	Tissue	High-expression	tumor protein 53-induced nuclear protein 1	Oncogene	Zhang et al. (2013)
8	miRNA-124-3p	Tissue	Lower expression	MGAT5	TSG	Yan et al. (2019)
9	miRNA-205	Tissue	Over-expression	TG2	TSG	Seo et al. (2019)
10	miRNA -21-3p	Tissue	Dysregulation	CYP1A1	TSG	Lo et al. (2017)
11	miRNA-628	Tissue	Over-expression	SOS1	TSG	Lin et al. (2018)
12	miRNA-382-3p and miRNA-1246	Serum	Up-regulated	CCNG2	Oncogene	Fu et al. (2016)
13	miRNA-598-3p and miRNA-184	Serum	Down-regulated	LRP6	Oncogene	Fu et al. (2016)
14	miRNA-24-3p	Plasma	Higher expression	p27Kip1	Oncogene	Jang et al. (2021)
15	miRNA-206	Tissue	Up-regulated	Neurokinin-1 Receptor	Oncogene	Zhou et al. (2019)

women with luminal-A complications (McDermott et al., 2014). Lower expression of miRNA-29a, miRNA-652, and miRNA-181a was found in luminal-A breast cancer compared to controls, regardless of nodal status or stage of disease, implying that transformed miRNA expression is an important biomarker in both early and late stage disease, as well as a potential target for miRNA-related therapeutics (McDermott et al., 2014). Furthermore, decreased expression of miRNA-152-3p and miRNA-23a-3p is also a potential biomarker for the luminal-A cancer type, particularly linked to stage I-II (Li et al., 2020). According to a recent study by Søkilde et al. (2019), the miRNA-99a/let-7c/miRNA-125b miRNA cluster, which was linked to proliferative signaling including ETS1, RAS, STAT3, AKT/mTOR, c-Myc, and JAK, was found to be over-expressed in luminal-A cancers. Surprisingly, the miRNA-152-3p, which is a tumor suppressor that regulates breast cancer cell proliferation via the PIK3CA pathway, was found to be reduced in luminal-A than another subtype of breast cancer like luminal-B (Li et al., 2020). In luminal-A breast cancer, the expression of miRNAs like miRNA-30a-3p and miRNA-29c-5p went up, and the expression of miRNAs like miRNA-185-5p, miRNA-130b-3p, miRNA-362-5p, and miRNA-378a-3p went down (Haakensen et al., 2016). From a RT-qPCR quantification study, it was reported that the combination of three miRNAs indicates the best diagnostic biomarker in case of luminal-A cancer subtype, i.e. down-regulation of miRNA-195 and up-regulation of miRNA-145, miRNA-486 (Arabkari et al., 2020). A group of researchers investigated 93 breast cancer samples, focusing on the 309 numbers of miRNA, to determine the level of miRNA expression in breast cancer. miRNA-100, miRNA-146b, miRNA-99a, miRNA-126, miRNA-130a, and miRNA-136 have been shown to be over-expressed, while miRNA-15b, miRNA-103, and miRNA-107 have been found to be dysregulated. The expression of these nine miRNAs can be used to distinguish between the luminal-A and luminal-B subtypes of breast cancer (Blenkiron et al., 2007).

7.2. miRNA expression profiles in HER2 breast cancer

The investigation of microRNAs that are associated with HER2 pathway activity in breast cancer has been the subject of a number of investigations, both preclinical and clinical (Gorbatenko et al., 2019) (Fig. 5b). The up-regulated expression of miRNA-155 has been identified in HER2 positive subtype of breast cancer (Song et al., 2012). This miRNA can interface with the MAPK signaling pathways through the stimulation of STATs proteins via suppressing SOCS1 gene expression

and promoting AKT and Src (Nami and Wang, 2017; Jiang et al., 2010). In the field of oncology, miRNA-21 is among the miRNAs that have received the most attention. This gene has been found to be over-expressed in all breast cancer subtypes, but it is most common in the HER2-positive hormone receptor negative subtype (Lee et al., 2011). miRNA-205 was found in the blood serum of breast cancer patients. Its expression was noted to be reduced in less hostile breast cancer subtypes and higher in more aggressive breast cancer subtypes, particularly in HER2-positive and triple-negative tumors (Xiao et al., 2019; Plantamura et al., 2020). The miRNA-125 family includes miRNA-125b as a member. miRNA-125b is generally produced by the fusion of multiple gene i.e. miRNA-125b-1 and miRNA-125b-2. It was observed that breast cancers with an up-regulated miRNA-125b level enhance EMT expression, which in turn leads to the development of metastasis (F Tang et al., 2012; J Tang et al., 2012). miRNAs those are inversely correlated with over-expression of HER2 miRNA-195, miRNA-107, miRNA-154, miRNA-126, miRNA-10b, let-7g and let-7f are more narrowly focused on the presence of HER2 status (Mattie et al., 2006). HER2 status in initial stage breast cancers can be correctly predicted by a profile of five miRNAs i.e. miRNA-181c, miRNA-302c, miRNA-520d, miRNA-30e-3p and miRNA-376b. Among these five miRNAs, the elevated appearance of miRNA-520d and miRNA-376b and the lower expression of miRNA-181c have the significant correlation with the HER2-positive breast cancer (Ramanto et al., 2019). In the process of differentiating HER2 positive carcinomas from HER2 negative carcinomas, certain additional miRNAs play a significant role; these are miRNA-342, miRNA-30b, miRNA-363, miRNA-217, miRNA-377, miRNA-383, miRNA-422a and miRNA-130a (Lowery et al., 2009).

7.3. miRNA expression profiles basal like and triple-negative breast cancer

The most aggressive subtype of breast cancer, with an alarming prevalence of malignant transformation and a poor prognosis, was determined by microarray analysis to be triple-negative breast cancer (ER-, PR-, and HER2-negative) (Elidrissi Errahhali et al., 2017). Numerous miRNAs that are related to EMT/CSC and invasion were shown to have considerably increased expression levels in triple-negative breast cancer; these miRNAs include miRNA-373, miRNA-9, miRNA-21, miRNA-29, miRNA-221/222, and miRNA-10b (Fig. 5c). Moreover, some significant down-regulation of miRNAs was also observed from various molecular analysis of triple-negative breast cancer such as, miRNA-205, miRNA-199a-5p, miRNA-145, miRNA-200 family, miRNA-203 etc.

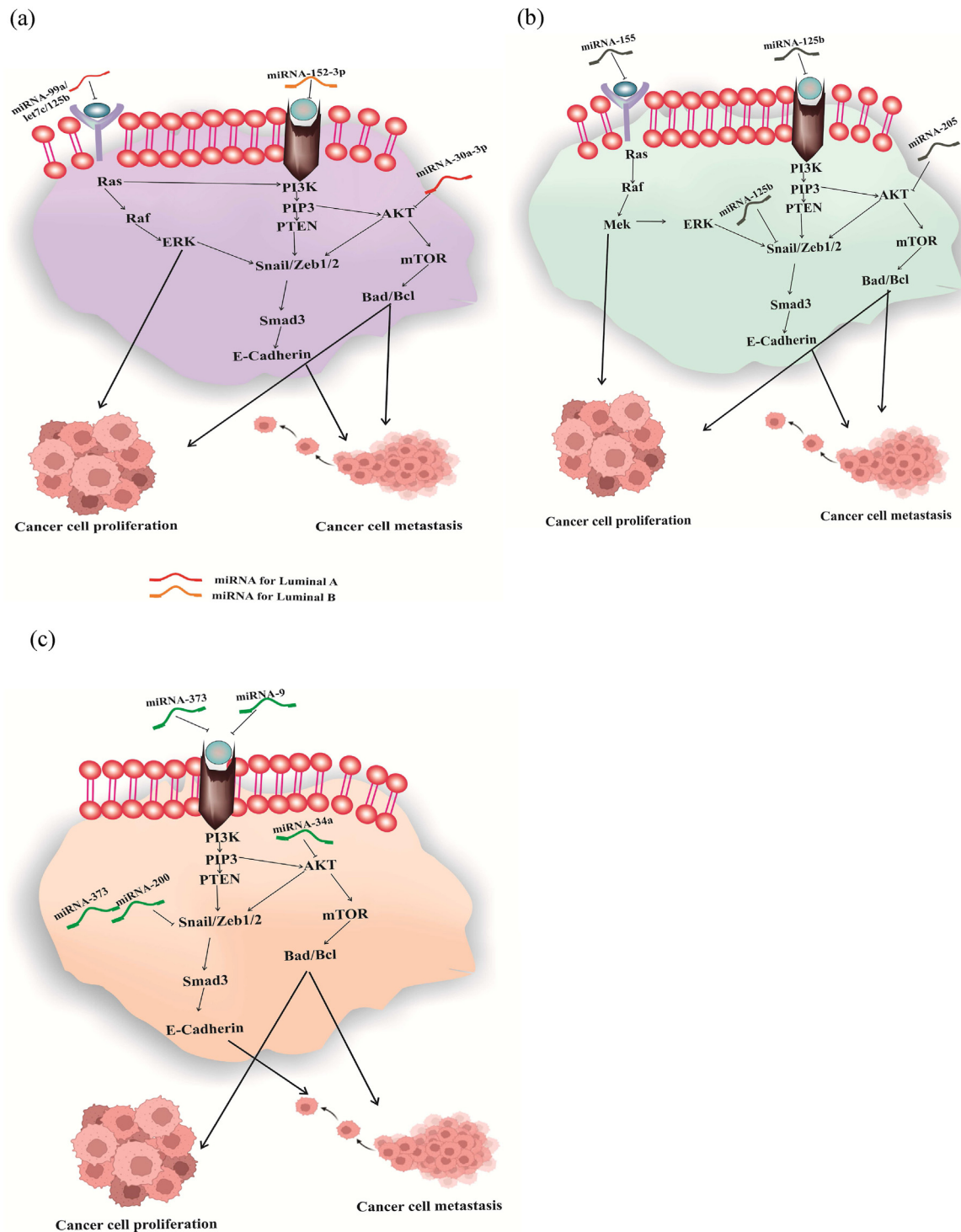


Fig. 5. Schematic presentation of some important miRNA expressions along with their regulatory activity in different kind of breast cancer. miRNA expression and their modulatory role in cancer proliferation, cell metastasis and cancer migration in (5a): Luminal A and luminal B breast cancer (5b): HER2 positive/negative breast cancer (5c): Triple negative breast cancer.

Several other miRNAs, including miRNA-221/222, miRNA-10b, miRNA-29, the miRNA-200 family, miRNA-203, and miRNA-21, were found to be dysfunctional in triple-negative breast cancer (Koleckova et al., 2021; Piasecka et al., 2018). Through the qPCR analysis, researchers were able to establish a connection between the development of triple-negative breast cancer and the responsible miRNAs like, miRNA-135b-5p, miRNA-136-5p, miRNA-182-5p, miRNA-190a, and miRNA-126-5p. Tumor angiogenesis is inhibited by miRNA-190a, which

acts as a tumor suppressor by inhibiting VEGF-mediated tumor growth (Paszek et al., 2017; Yang et al., 2015). Members of the miRNA-135b family perform an oncogenic function by controlling the cell cycle, as well as boosting the adhesion and proliferation as well as cell migration of triple-negative breast cancer cells by inducing the TGF-beta, WNT, and ERBB signaling pathways (Uva et al., 2018). A comparison analysis was performed between the basal-like and non-basal-like triple-negative breast cancers. The analysis was categorized as quintuple negative breast

cancer by immunohistochemistry basal-markers like, EGFR+ and CK5/6+. Over-expression of miRNA-135b exhibited a poor prognostic impact, which might be connected to a positive connection with a higher proliferative index; more specifically, miRNA-135b expression alteration could be a therapeutic objective in basal-like triple-negative breast cancer (Uva et al., 2018). In the prior study, it was suggested that the identification of discrete risk groups for triple-negative breast cancer and the establishment of a predictive survival factor were made possible using a unique four-biomarker profile i.e., RMDN2 mRNA, miRNA-221, miRNA-1305 and miRNA-4708 (Andrade et al., 2020). Over-expressed miRNA-433, miRNA-335, miRNA-382 and miRNA-376c in triple-negative breast cancer identified as the signature distinguishers between HER2-positive and triple-negative breast cancer (Stevic et al., 2018).

8. miRNA-mediated therapeutic strategies for breast cancer

The use of a chemically modified nucleic acid to reestablish the regular activities of miRNAs is an example of a nucleic acid-based treatment approach (Damase et al., 2021). Both miRNA replacement therapy and anti-miRNA therapy fall under the umbrella of nucleic acid-based strategies. Although miRNA substitute studies were carried out in some animal cancer models, this strategic approach is still yet to be tested in breast cancer cells. A replacement strategy shows potential approach for building techniques to substitute flashing tsmiRs and defeat breast cancer. For non-tumorigenic cells, miRNA mimic delivery is considered acceptable as intracellular miRNAs already stimulate or repress the pathways they initiate or restrict, and healthy cells can regulate the pathway even as cancer cells cannot (Teo et al., 2021). Because BRCA1 regulates the tsmiRNAs miRNA-145 and miRNA-205 in breast cancer, its absence reduces the levels of these miRNAs. miRNA-145 and miRNA-205 mimics may be capable of restoring BRCA1's functional roles even if BRCA1 is inactive. miRNA-451, Let-7, miRNA-126, miRNA-335, and miRNA-205 are all miRNAs that could be revived via the use of miRNA replacement therapy (Yu et al., 2007; Kota and Balasubramanian, 2010; Nickel and Stadler, 2015; Chang and Sharan, 2012). Some important methods for getting rid of over-expressed oncomiRs i.e. miRNA sponges, genetic knockout, and anti-sense oligonucleotides (antagomiRs) (Lima et al., 2018; Soriano et al., 2013). AntagomiRs are miRNA antagonists that interfere with miRNA-related processes by conditional and obstructing oncomiRs. Because these nucleic acid adversaries to inhibit oncomiRs, it is possible that using them as a treatment for cancer is a fruitful course of action (Garofalo and Croce, 2013; Gambari et al., 2016). Antisense oligonucleotides can be used to tear down the up-regulated oncomiRNAs miRNA-9 and miRNA-21, which are well-known oncomiRs in breast cancer (Ma et al., 2010; Teo et al., 2021; Alyami, 2021). Furthermore, miRNA-9 sponges were used against 4T1 metastatic breast cancer cell lines, and miRNA-21 sponges for MDA-MB231 and MCF-7 cell lines, with metastatic function of these cell lines reduced by approximately 50% (Tay et al., 2015). In contrary to approaches based on nucleic acids, the appearance of miRNAs could be altered by the administration of a variety of drugs. Resveratrol is able to up-regulate the expression of miRNA-141 and miRNA-200c in the MDA-MB231 breast cancer cell line; whereas over-expression of miRNA-141 and miRNA-200c potentially inhibit EMT invasiveness (Chandra, 2013; Simpson et al., 2022). It has been demonstrated that curcumin, another type of polyphenol, can activate miRNA-181b (Kronski et al., 2014). Breast cancer cells are made more susceptible to apoptosis and less likely to proliferate and metastasize as a result of this stimulation. It would appear that curcumin's apoptotic impacts are caused by the elevation of miRNA-15a and miRNA-16, which in turn leads to a down-regulation of Bcl2 (Cadieux et al., 2019). A powerful antitumor agent, miRNA-200c is a member of the miRNA-200 family of miRNAs. Up-regulation of the miRNA-200c gene was already demonstrated to decrease P-glycoprotein levels, which leads to increased susceptibility to the chemotherapy agent epirubicin in breast cancer (Jung et al., 2016). High expression of E-cadher

is linked to miRNA-200c, which is also related to increase cell susceptibility. As a result of these dual activities, miRNA-200c is a prospective target for simultaneously decreasing drug resistance and metastasis (Knezevic et al., 2015a,b; Peng et al., 2020). Intriguingly, the expression of miRNA-92 at the onset of breast epithelial carcinoma is related to a shift in the expression of ER β 1. Changes in miRNA-92 expression, on the other hand, can have a significant impact on the breast cancer epithelial cells long-term invasive capacity (Smith et al., 2015). According to the Baxter et al. (2021), found that miRNA-195 and miRNA-26b significantly increased resistance in breast carcinoma by lowering the level of the protein SEMA6D. As a result, the levels of SEMA6D in breast tumors are able to accurately forecast the patient survival following chemotherapy. SEMA6D is a prognostic marker, and activation of SEMA6D signaling offers a potential pharmacological possibility for adapting cells to chemotherapy. The reduced expression of miRNA-26b in carcinoma-associated fibroblasts of ER-positive breast tumors contributes to an increase in the rate of cell migration and invasion (Verghese et al., 2013). Controlling the progression-promoting effects of carcinoma-associated fibroblasts in breast cancer is mostly the responsibility of miRNA-222/LBR. This route may give prospects for the development of therapeutic interventions to limit carcinoma-associated fibroblasts-induced progression of cancer (Chatterjee et al., 2019). Another study revealed a potential new therapeutic target to impede P-glycoprotein-mediated drug efflux, as well as the prospect that conventional predictions of miRNA binding based purely on seed regions may be excessively conservative. Specifically the non-canonical bonding of miRNA-19b, which is guided by HuR and provides chemo-sensitivity in breast cancer through regulating P-glycoprotein, occurs under the control of HuR (Thorne et al., 2018). It is observed that miRNA-10b and miRNA-21 will have elevated levels in breast cancer (Ali et al., 2022). Several silicon nanowires were intended to identify miRNA-10b and miRNA-21, the two main prevalent oncomiRNAs revealed in breast cancer; the amount of miRNA-21 in normal tissues has been found to be four times that of miRNA-10b (Table 4). In ER-negative breast cancer cells (MDA-MB231), scientists were successful in delivering antagomiRNA-10b by using poly-L-lysine (Dorvel et al., 2012; Djafari et al., 2020).

9. Limitations and future perspective

The fact that miRNAs are connected to nuclease-mediated degradation before achieving target modification is one of the main problems for miRNA delivery. Different chemical alterations are tried to alleviate this problem, however they may have unintended consequences like decreased miRNA activity and the formation of numerous hazardous metabolites (Rupaimoole et al., 2011). It was found that TMTME (too many targets for miRNA effect) is an inherent characteristic of miRNA molecules brought on by insufficient complementation with the target sequence. This TMTME can cause miRNAs to bind to a variety of appropriate sequences for the interaction (like lncRNA, protein-coding genes, 25 circRNA etc). The issue is that because it only has a few targets, this differs from all the approved medications (such siRNA medicines). Another valid concern is that exogenous manmade miRNAs will increase the effects of saturation and competition between exogenous and all endogenous miRNAs in the intracellular system, which may have harmful side effects (Zhang et al., 2021). Published investigations have shown that the unique characteristics of RNA oligonucleotides hamper the efficacy and design of drugs. Weak cell membrane access, endosome trapping, low binding affinity with complementary sequences, inadequate delivery to expected or desired target cells, undesirable-target and toxicities, and stimulation of innate immune responses are a few of the challenging characteristics that will be covered shortly. These issues are dealt with in various ways during therapeutic applications; however miRNA administration is currently a possible innovative therapeutic approach (Segal and Slack, 2020). Additional investigation into the biological, functional, chemical, and bioengineering pathways is

Table 4
Different types of miRNA-mediated therapeutic approaches for breast cancer.

Sl.No.	miRNAs	Used model	Therapeutics	Type of cancer	Reference
1	Nanoparticle (AuNPs) delivery of miRNA-708 mimetic	MDA-MB-231 cells and Xenograft model(CB-17 SCID mice and CB17	Tumor suppression	Breast cancer	Ramchandani et al. (2019)
2	1626 miRNA combination with trastuzumab and lapatinib	HER2 + breast cancer cell lines	Tumor suppression	Breast cancer	Normann et al. (2021)
3	miRNA-155 Antisense Oligonucleotide	MDA-MB-157 cell line and xenografting mouse model (4-week-old male BALB/c athymic nude mice)	Tumor suppression	Breast cancer	Zheng et al. (2013)
4	miRNA-26a/26b	MDA-MB-231, MCF-7 and human epithelial breast cell line MCF-10A and Female athymic nude mice (aged 4–6 weeks)	Tumor suppression	Breast cancer	Ma et al. (2016)
5	miRNA-124	MCF-7 and MDAMB-231 and 293T cell line and female athymic BALB/c nude mice (4 weeks old)	Tumor suppression	Breast cancer	Yan et al. (2019)
6	miRNA-34a silences C-SRC	Breast cancer cell lines and 5-to-6-week-old female CrTac; NCr-Foxn1 nu mice (Taconic)	Tumor suppression	Breast cancer	Adams et al. (2016)
7	miRNA-451 agomir	Drug resistance in breast cancer cell lines and in xenograft model	Tumor suppression	Breast cancer	Wang et al. (2017)
8	miRNA-3613-3p	MDA-MB-231 and MCF-7 and Female NOD/SCID mice, 6–8 weeks of age	Tumor suppression	Breast cancer	Chen et al. (2021)
9	Polymer Nanoparticles MediatedCo-Delivery (antisense-miRNA-21 and antisense-miRNA-10b loaded PLGA-b-PEG polymer NPs)of AntimiRNA-10b and AntimiRNA-21	MDA-MB-231 cell line and xenograft model (female nude mice)	Tumor suppression	Breast cancer	Devulapally et al. (2015)
10	miRNA oligonucleotide and sponge for miRNA-21 inhibition mediated by PEI-PLL in breast cancer therapy	MCF-7 cell line	Tumor suppression	Breast cancer	Gao et al. (2015)
11	Expression of miRNA-200c	<i>In vivo</i> (wild-type Balb/c recipient mice.)	Tumor suppression	Breast cancer	Knezevic et al. (2015)
12	miRNA-497	T-74D, MCF-7, MDA-MB-453, MDA-MB-468 and MDA-MB-435 cell line and male athymic BALB/c nu/nu mice (4–6 weeks old)	Tumor suppression	Breast cancer	Wu et al. (2016)
13	miRNA-603	MCF-10A, TNBC, MDA-MB-436, MDA-MB-231, MDA-MB-468, BT-549, BT-20 cell lines and xenograft tumor model (Athymic female nude mice (4–5 weeks old)	Tumor suppression	Breast cancer	Bayraktar et al. (2017)
14	miRNA-205-5p inhibition by locked nucleic acids impairs metastatic potential of breast cancer cells	BCSCs and mouse xenograft (NSG mice)	Tumor suppression	Breast cancer	De Cola et al., 2018
15	miRNA-7-5p	BT549, MDA-MB-231,MDA-MB-468, MCF7, SK-BR-3, T47D, HBL100, and MCF-10A cell line and <i>in vivo</i> (nude mice)	Tumor suppression	Breast cancer	Shi et al. (2015)
16	miRNA-10b	Luciferase-expressing 4T1-Red-Fluc breast cancer cell line, derived originally from mouse mammary gland adenocarcinoma and eight-week-old female Balb/c mice	Tumor suppression	Breast cancer	Yoo et al. (2017)
17	miRNA-4306	ZR-75-1, MCF-7, T47D, SK-BR-3, HCC1937, MDA-MB-468, MDA-MB-231 and CAL-51 cell line and four-week-old female BALB/c nude mice	Tumor suppression	Breast cancer	Zhao et al. (2019)
18	DOX + tRNA-miRNA-34a/POEG-PCre	<i>In vitro</i> and <i>in vivo</i> female BALB/c mice (4–6 weeks)	Tumor suppression	Breast cancer	Xu et al. (2019)

required to advance miRNA therapies. miRNA therapies should continue to advance as therapeutic agents for a number of disorders once potential barriers to miRNAs are overcome (Segal and Slack, 2020). miRNA medication delivery to pathogenic areas may help prevent unwanted side effects and toxicity (Zhang et al., 2021; Chakraborty et al., 2021). The translation of miRNAs into clinical medicine has been aided by the development of advanced bioinformatics programmes for identifying miRNA-binding sites in the target genes and their consistent associated biological pathways, in addition to emerging experimental platforms (*in vivo* and *in vitro* preclinical experimental models) (Hanna et al., 2019). There have been numerous studies on improved techniques for delivering therapeutic miRNAs to the body, including safe blood-borne drug delivery, targeting of miRNAs to specific cells for helpful uptake, and improved gene targeting by target cells. Although there has been extensive research, while we are only now beginning a process that will finally fully exploit the unquestionably astoundingly high therapeutic efficiency of miRNAs (Diener et al., 2022).

10. Conclusion

When considered as a whole, the roles that miRNAs play in the regulation of signaling pathways relevant to thyroid cancer are essential. The fact that they are present in body fluids opens the door to the option

of using non-invasive sample techniques in the treatment process of thyroid cancer. Thyroid cancer risk and the complications of the disease can both be assessed using various responsible miRNA panels. Similarly, collective data proof demonstrated that miRNAs act a significant part in malignancies like breast cancer. These miRNA molecules perform critical functions in gene expression regulation to maintain homeostasis, and if their activity is out of whack, it can have detrimental effects on an extensive array of disease pathways. miRNA-based therapeutics consequently hold considerable promise as highly specific methods or focused treatments for the treatment of breast cancer. Methods for measuring circulating miRNAs are becoming more standardized, which will allow for more widespread use of this strategy in determining personalized thyroid cancer treatment plans. It was noted that, up-regulation and down-regulation of numerous miRNAs have been linked to both types of carcinomas and may be responsible for cancer progression or cancer development. Focused on the expression profile of miRNAs, researchers are putting all of their efforts into developing treatments that are mediated by miRNA in order to tackle this worrying condition. miRNA-based interventions are an effective and promising application for dealing with the high death toll correlated with thyroid and breast cancer. The key challenge for the future expansion of miRNA-mediated therapeutic approaches is to broaden the authentic study on miRNA background. The number of people who die from both types of cancer has gone up because

not enough research has been done and the exact molecular mechanism of several existing miRNAs is still unknown. So, we hope that this article will be a starting point for future cancer research that looks at how miRNAs are expressed in thyroid and breast cancer.

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CRedit authorship contribution statement

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Declaration of competing interest

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