Review

Understanding the therapeutic potential of modulating miRNAs in the course of thyroid and breast cancer

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Abstract

Thyroid cancer's frequency has skyrocketed in recent decades, making it one of the most prevalent endocrine cancers overall. There were 586,000 instances of thyroid cancer in 2020, according to estimates. About 3% of all people with cancer had this diagnosis. According to the World Health Organization, by 2020, 685,000 women will be undergoing treatment for breast cancer. There is still a lack of knowledge regarding the biology of carcinoma, despite the fact that it is one of the world's leading causes of mortality. MicroRNAs (miRNAs; miRs) are non-coding RNAs that may inhibit gene expression by cleaving the 3′ untranslated regions of mRNA. Due to these characteristics, they may be able to impede the process of protein synthesis. MiRNA regulates a wide variety of cellular pathways thought to have a role in cancer development. The examination of global miRNA expression in cancer indicated regulatory activity via up regulation and down-regulation in numerous malignancies, including thyroid cancer and breast cancer. Thyroid cancer miRNAs modulate MAPK, PI3K, and the RAS pathway, three cancer-related signaling pathways. Cell proliferation and cell cycle progression in breast cancer were regulated by miRNA via the cyclin protein family, protein kinases and their inhibitors, and other growth promoters or suppressors. The purpose of this article is to review the therapeutic modulation of important miRNA expressions in the treatment of thyroid and breast cancer.

Keywords: Thyroid cancer, breast cancer, and miRNA-based treatments

1. Introduction

The study of molecular pathways in cancer beginning and development has become central to the field, offering a firm foundation for the investigation of new treatments for the disease. Gene expression variations associated with cancer development have been related to the dysfunction of many regulators, microRNAs in particular, in recent decades (Condrat et al., 2020). Single-stranded non-coding RNA molecules called microRNAs (miRNAs) regulate gene expression by either inhibiting translation of mRNA or by cleaving mRNA. They are generally generated from nascent primary miRNA (pri-miRNA) transcripts by two separate cleavage processes that take place sequentially (O'Brien et al., 2018; Ling et al., 2013; Bartel, 2004), and they vary in length from 19 to 23 nucleotides. In the nucleus, DROSHA (the DROSHA gene, formerly known as RNASEN, encodes this class 2 ribonuclease III enzyme in humans) processes the pri-miRNA, resulting in the release of a hairpin precursor. When DICER cleaves pre-miRNA, exportin 5 (XPO5) transfers it out of the nucleus (an RNase III enzyme) (O'Brien et al., 2018). In order to selectively eliminate additional pieces of immature miRNA, only one strand of mature miRNA is preferred to be retained when the small RNA duplex is created and loaded onto the Argonaute (AGO) protein (Medley et al., 2021). An effector complex, GW182 (also known as TNRC6A) is required for the formation of the RISC (RNA-induced silencing complex), which is made up of miRNA-loaded Argonaute (Ago) family proteins and other cofactors (Catalanotto et al., 2016). By interacting with complementary nucleotides in the 3′-untranslated region (3′-UTR) of target gene mRNA, the miRISC (miRNA-induced

silencing complex) may possibly damage mRNA and delay translation (Akgül et al., 2018; O'Brien et al., 2018). Because of this, miRNAs may be involved in a broad variety of cellular and organismal functions, including physiological and developmental processes. Causes of cancer have been connected to environmental factors such as starvation, hypoxia, oxidative stress, and DNA damage as a result of miRNA-mediated gene expression (Ali Syeda et al., 2020). The aberrant regulation of the expression of several miRNAs, many of which may function as either tumor-inducing or tumor-inhibiting genes (oncomiRs), is strongly associated with the onset, progression, and dissemination of cancer. Changes in these miRNAs are thought to have a critical role in the initiation and development of malignancies in a wide variety of human tissues. Oncogenes are genes that regulate cell proliferation, differentiation, and apoptosis. Tumor suppressor genes may be silenced by over-expression of particular miRNAs, whereas oncogene expression can be increased by down-regulation of miRNAs (Otmani and Lewalle, 2021).

It is generally accepted that thyroid cancer progresses when tumors of the gland collect mutations that cause carcinogenesis via a process known as dedifferentiation. Analysis of the genomic sequences of these tumors has allowed for a reworking of the sequential cycle of thyroid cancer growth (Ramrez-Moya et al., 2019). Therefore, it is essential to determine the genetic pathways underlying the development of thyroid cancer, particularly for the treatment of histological subtypes that do not respond well to the conventional curative treatments. Growing diagnostic data suggests that thyroid cancer (TC) may now be regarded an epidemic, and several factors may contribute to its development (Cao et al., 2021; Ghafouri-Fard et al., 2020). The ability to discriminate between two genetic kinds is a crucial component of future study of genomic studies in thyroid cancer, particularly in regards to how BRAF and RAS signaling promote tumorigenesis and proliferation. malignancies that are activated by BRAF have high levels of MEK-ERK activity, whereas malignancies that are activated by RAS have high levels of PI3K activity. Gene expression, microRNA profiles, and epigenetic alterations in BRAF-driven cancers are widely diverse (Hussen et al., 2021; Ramrez-Moya et al., 2019).

The mammary glands and their ducts are the sites of aberrant growth that lead to breast cancer. Adenocarcinomas, a subtype of carcinoma, account for the great majority of malignant breast lesions (Feng et al., 2018). Breast cancer is a very diverse illness, with a large variety of tumor forms and a wide range of intertumoral and intratumoral non-uniformity (Dai et al., 2017; Polyak, 2011). Cancer is a complex disease involving several pathways, such as carcinogenesis, tumor growth, angiogenesis, invasion, and metastasis. Furthermore, there is a high possibility of complete remission from cancer following therapy. When the mammary gland's cellular and molecular communication channels are disrupted, it may lead to the development of malignant changes (Karagiannis et al., 2016; Castañeda-Gill and Vishwanatha, 2016; Ahmad, 2013). Also, Ohzawa et al. (2017) and Kurozumi et al. (2017) found that miRNA expression changes may significantly affect breast cancer pathology, morphology, and treatment results. Additionally, studies have shown that malignant breast tissue has atypical miRNA expression patterns compared to normal breast tissue (Fridrichova & Zmetakova, 2019). For patients with breast cancer, miRNA molecules show great promise as potential novel biological therapeutic agents, targets, or biomarkers (Teo et al., 2021).

Individual differences in miRNA expression patterns may play a role in pathogenesis, contributing to a lack of differentiation and cancer spread, as shown by a few studies. This paper offers a condensed description of the probable role that several transcripts have in the genesis of thyroid cancer and breast cancer, and how these transcripts may be used as biomarkers in the treatment of these cancers.

Rates of both breast and thyroid cancer have been demonstrated to have risen steadily over the previous several decades. Breast cancer is high on the list of the most frequently diagnosed cancers. A recent statistical study found that lung cancer, followed by breast cancer, is the leading cause of cancer-related deaths in the United States in 2018. In 2020, it is expected that 2,76,480 new cases of invasive breast cancer and 48,530 new instances of ductal carcinoma will be diagnosed in the United States, with a subsequent death toll of 42,170. Although most invasive breast cancers affect women over the age of 40, 4–5% of cases are diagnosed in younger women (Hendrick et al., 2021). Along with the incidence rate of breast cancer, the relative risk of thyroid cancer is also rapidly expanding. Thyroid cancer has a higher incidence rate than any other endocrine malignancy. Thyroid cancer rates have surged by roughly 93% in less than 10 years. The majority of patients diagnosed with this endocrine carcinoma in Thiruvananthapuram, India were over the

age of 40 (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 the recent decade, the incidence of thyroid cancer in Indian women increased from 2.4 to 3.9, whereas the incidence in Indian males increased from 0.9 to 1.3. The overall relative increase was over 62% and the respective growth was around 48%. The present review focuses on how numerous transcripts may be implicated in the etiology of thyroid cancer and breast cancer, and how they may be exploited as potential biomarkers for both types of cancer therapy, which is especially important in light of the alarmingly high incidence of these cancers in India and around the world.

2. Cancer biomarkers using microRNAs

The word "biomarker" refers to numerous sorts of quantifiable health indicators or illness. As human technology has advanced, these signs have gotten more precise and reliable. After some initial debate (Kamm and Smith, 1972a, 1972b), the idea that blood samples couldn't be used to detect RNA molecules as biomarkers was abandoned after it was discovered that microRNAs (miRNAs) were stable in samples taken from fixed tissues. Potential substantial uses of miRNAs as biomarkers for numerous illnesses have been explored in the scientific literature since 2008, when Lawrie et al. (2008) employed miRNAs to assess the serum of patients with diffuse large B-cell lymphoma as cancer biomarkers. Possibilities for using these novel compounds as biomarkers in a variety of disorders are high due to their broad range of advantages. A good biomarker, ideally, would be easy to get. This need is met by miRNAs, which can be easily extracted from bodily fluids including blood, urine, and others using the process known as "liquid biopsy." 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). MiRNAs also have the potential to be used as multimarker frameworks for the purposes of making a final diagnosis, guiding treatment, and gauging a patient's response to therapy. Multimarker panels made up of several miRNAs might provide a non-invasive method of diagnosis and prognosis. In contrast, it may be time-consuming and expensive to evaluate several protein markers (Condrat et al., 2020). In cancer, an exceedingly diverse illness, this may be of crucial importance. A multimarker approach is therefore highly suggested. Unfortunately, research into miRNAs as prospective biomarkers remain in its formative stages, and as a consequence, the results are not typically replicable at this time period.

3. Thyroid cancer: new insights

The American Cancer Society predicts that there were 62,000 new occurrences of TC diagnosed in men and women in 2014. Thyroid cancer is the sixth most prevalent disease in American women (American Cancer Society, 2014). As a consequence of advancements in diagnostic imaging and monitoring, the worldwide prevalence of TC is rising. Thyroid cancer cases are increasing but fatality rates are going down. TC may present with a wide variety of clinical characteristics, from slow-growing tumors with a low death rate to extremely aggressive malignancies. The death rate associated with TC has remained relatively stable over the last five decades, despite the disease's steadily rising frequency. Different histological types and subtypes of TC have different cellular causes, characteristics, and outcomes (Lloyd et al., 2004). There are two kinds of endocrine thyroid cells that may become a thyroid tumor: follicular thyroid cells and parafollicular (C) cells. The most common forms of thyroid cancer are follicular thyroid cell-derived carcinomas such as papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), poorly differentiated thyroid cancer (PDTC), and anaplastic thyroid cancer (ATC). Differentiated thyroid carcinoma (DTC) is a term used to describe both follicular and papillary thyroid malignancies. Parafollicular C cell-derived medullary thyroid carcinoma accounts for a negligible fraction of all thyroid cancers (Sites, 2014). The primary molecular mechanism behind MTC tumor formation is the aberrant activation of RET signaling (caused by RET mutations; Hofstra et al., 1994). Tumors that develop from follicular thyroid cells lack this molecular pathway (Xing, 2013).

More than 95% of TC cases originate in the thyroid follicular epithelial cells. Thyroid cancers with clear subtypes include papillary, follicular, and Hurthle. PTC is the most common kind of thyroid cancer and is largely responsible for the current rise in TC prevalence across the world. According to two separate studies (Papaioannou et al., 2021; Hitu et al., 2020), PTC accounts for at least 80% of all thyroid cancers in the general population. Survival rates are best

for patients under the age of 45, and over 95% for those under the age of 40 (Zembska et al., 2019) in PTC. PTC may be caused by both radiation and long-term exposure to other substances that harm DNA.

The typical age at diagnosis for PTC sufferers is 50, and women are three times more likely to be diagnosed than men. Thyroid cancer, more specifically the follicular subtype, is the second most frequent form of the illness. Ten percent of all TC cases include this, with a peak incidence in middle-aged women. FTC is known to metastasize to distant organs and spread hematogenously (via the blood) in advanced cases. Distant metastases are seen in only approximately 10–15% of individuals, and the most frequent locations are the bone and the lungs. Facial skeleton metastases from FTC are very unusual and notoriously difficult to treat. FTC facial bone metastases may spread to the gnathic bones, paranasal sinuses, and orbit (Varadarajan et al., 2017).

Parafollicular C cells of the thyroid (5-10% of all TCs) are the origin of MTC, a rare malignant tumor. Inducing higher amounts of calcitonin is a hallmark of MTC (Chen et al., 2020). Prognosis and mutational status are related to genetic alterations, which may produce fundamental changes in both sporadic and familial MTC. In occasional instances, the diagnosis is often made by fine-needle aspiration (FNA) cytology, and serum calcitonin levels are often examined in individuals at high risk of inborn or hereditary disease (Oliveira et al., 2021). In MTC, roughly 25% of cases are hereditary, whereas the remainder are sporadic (Matrone et al., 2022). More and more patients over the age of 45 are being diagnosed with MTC. Survival rates are lower for persons who are older and have more tumors. However, the prognosis for individuals who have several initial surgical resections is more optimistic (Gogna et al., 2020).

ATC is a rare thyroid condition that often ends in a terminal diagnosis. This illness has a rapid onset and is linked to both regional and global metastases (Jannin et al., 2022). The median survival time for patients diagnosed with atypical amorphous thyroid carcinoma (ATC) is only six months. Twenty percent of those with ATC will still be alive a year following their diagnosis (Alobuia et al., 2020). Due of its dismal outlook, it is responsible for 40–50% of all TC-related fatalities in the United States. The aggressiveness of PDTC is comparable to that of ATC. However, it also has several elements in common with FTC and PTC, namely follicular components and the generation of thyroglobulin (Saini et al., 2018). The incidence of ATC is less than 6 cases per 100,000 people per year, making it a rare disease according to the European Union's rare cancer monitoring programme (RARECARE). Statistics from the Netherlands (de Ridder et al., 2020), Denmark (Hvilsom et al., 2018), and the Wales official health register show that ATC occurred at a rate of about 0.12 per 100,000 person-years in the United States in 2014, and between 0.1 and 0.3 per 100,000 person-years in Europe. Deeken-Draisey et al. (2018) discovered that 0.5 percent (11/2106) of TC was ATC, as seen in Fig. 1.

4. Thyroid cancer: miRNA as a key modulator

Different types of thyroid cancer were shown to have miRNA expression that was dysregulated in comparison to normal tissues (Santiago et al., 2020). Although all TCs derive from a common ancestor, the miRNA expression patterns of the various forms show substantial variation (Table 1).

4.1. PTC

MicroRNAs in PTC (miRNAs) serve an important purpose in the development of PTC. The expression of miRNA-21-5p increased in PTC cell lines during angiogenesis and hypoxia, and it suppressed the expression of COL4A1 and TGFB1 (Wu et al., 2019). By downregulating PDCD4 and CHL1 expression, miRNA-183 and miRNA-182 promoted PTC cell proliferation. A research demonstrated that miRNA-5189-3p and miRNA-92a-3p were over-expressed in PTC for nodal metastasis and also worked as biomarkers for this malignancy (Papaioannou et al., 2021). The survival and development of PTC were discovered to be affected by miRNA-96. As a consequence of this miRNA's inhibition of FOXO1 gene expression, the Bim/Akt/FOXO1 axis was downregulated, and malignant cell growth ensued (Song et al., 2015). Targeting endogenous ROCK1 (Rho associated protein kinase 1), miRNA-150 is downregulated in PTC samples at the TNM stage, which is linked with lymph node and tumor node metastases. Through the ERK/MAPK signaling pathway, miRNA-152 and miRNA-20b have been related to more aggressive PTC (Papaioannou et al., 2021). Ghafouri-Fard et al. (2020) found that decreased miRNA-448 expression in PTC cells and tissue was associated with TNM stage and lymph node metastasis. Multiple miRNAs may play a role in PTC development by modulating the expression of

various genes. To name a few examples, we have miRNA-128 (via SphK1), miRNA-206 (via MAP4K3), miRNA-219-5p (via ERa), miRNA-29a-3p (via OTUB2), miRNA-361-5p (via ROCK1), miRNA-613 (via SphK2), miRNA-744 (via NOB1), miRNA-654-3p, miRNA-195 (via FGF2 and CCND1), Among the miRNAs studied, miRNA-342-3p, miRNA-150-5p, and miRNA-146a-5p were all found to be down-regulated in papillary thyroid cancer compared to benign thyroid tumor pathologies, while miRNA-10a-5p, let-7b-5p, miRNA-191-5p, and miRNA-93-5p were all found to be up-regulated (Graham et al., 2015). A number of miRNAs were down-regulated to help in the early identification of PTC. These were miRNA-138, miRNA-363, miRNA-9-1, miRNA-195, miRNA-152, miRNA-363, and miRNA-20b. Several microRNAs (miRNAs) have been identified as appropriate diagnostic tools for highly sensitive PTC, including MET and CCNDI, as well as miRNA-34a, miRNA-221, and miRNA-222 (Cong et al., 2015). Thyroid dysfunction has been related to varying degrees of circulating miRNAs. Serum levels of the miRNA precursors let-7e, miRNA-222, and miRNA-151-5p were significantly greater in PTC patients compared to healthy controls (Yu et al., 2012). Studies have shown that pre-operative PTC patients had significantly greater blood levels of miRNA-21 compared to healthy controls. Reduced levels of miRNA-151-5p, miRNA-222, and miRNA-221 were seen in patients with PTC (Yoruker et al., 2016). Patients with PTC have elevated levels of miRNA-31 in their exosomes, which significantly decreases after the tumor has been surgically removed. Patients with PTC had elevated levels of miRNA-151 in their blood. Expressions of miRNA-222, miRNA-146b, and miRNA-221 were all shown to be higher in PTC patients than in controls. One effective biomarker for PTC has been identified as the down-regulation of the thyroglobulin-encoded functional miRNA (miRNA-TG), which functions via MAP kinase signaling (Zembska et al., 2019). Prognostic miRNAs, such as let-7f and miRNA-146-5p, were shown to be particularly useful in cases with quickly progressing PTC, as reported by Geraldo et al. (2012). The RET/PTC rearrangement is the most prevalent genetic moderator observed in PTC. The BRAFT1799A mutation aided in evaluating miRNA expression as critical molecular indicators of PTC therapy. PTC is the most common endocrine gland cancer. Persistent activation of the ERK-PTC-BRAF-RAS-MAPK/RET signaling pathway promoted cell de-differentiation and proliferation (Perdas et al., 2016). It was discovered that miRNA-221 inhibited TIMP3 production by binding to its 3′ untranslated region (3′UTR), which also promoted PTC cell proliferation and invasion (Fig. 2a). It was found that this miRNA belonged to the family of onco miRNAs (Diao et al., 2017).

4.2. FTC

Oncogene activation is more prevalent in follicular carcinomas. Tuttle (2018) and Nikiforova et al. (2003) found that almost 80% of follicular carcinomas included either a paired box gene 8/peroxisome proliferator-activated receptor gamma (PAX8-PPAR) gene rearrangement or a RAt Sarcoma (RAS) gene change. There is evidence that MAPK, RTK, and PI3K/Akt signaling pathways, which are all controlled by growth factors and oncogenes such as RAS, also play a role in FTC malignancies. Genetic abnormalities like as aneuploidy, RAS mutations, and PAX8-PPAR rearrangements are often seen in FTC. Thirty percent of follicular thyroid cancers are caused by fusion oncogenes resulting from the chromosomal translocation of PAX8- peroxisome proliferated or activated receptor (PPAR) (Eberhardt et al., 2010). Expression of miRNA-222, miRNA-146b, and miRNA-221 is increased in FTC, as is expression of miRNA-197 and miRNA-346. Cell proliferation was increased by over-expression of miRNA-197 and miRNA-346 in in vitro studies using the FTC133 and K5 cell lines, whereas growth was inhibited by down-regulation of both miRNAs. There was no response to this miRNA in the NPA87 cell line. Tumor suppressor protein EFEMP2 (fbulin 4) activity is suppressed by miRNA-346 (Santarpia et al., 2013, Fuziwara and Kimura, 2014), confirming that dysregulation of miRNA-197 and miRNA-346 is characteristic of the FTC phenotype. A study of MI-FTCs found increased levels of miRNA-92a, miRNA-221-3p, miRNA-222-5p, miRNA-10b, and miRNA-222-3p compared to a non-metastatic group (Jikuzono et al., 2013). CARMA1 is a scaffold protein required for NF-B activation downstream of T and B cell antigen receptors. To limit the spread of thyroid cancer, miRNA-539 was developed to target the 3′-UTR of CARMA1. FTC cells treated with a plasmid to knock down CRAMA1 showed anti-metastatic efficacy. miRNA-539 was shown to have a negative effect on CRAMA1 activity (Gao et al., 2015). Over-expression of miRNA-182/-183/-221/-222/-125a-3p and down-regulation of miRNA-542-5p/-574-3p/-455/-199a were seen in conventional and oncocytic variants of two histological types of FTC compared to normal thyroid tissue. However, miRNA-885-5p was elevated in the oncocytic form. Direct repression occurs between PAX8 and NIS, the gene it regulates. Researchers conducted a meta-analysis and found that four

miRNAs have the potential to serve as biomarkers for de novo follicular thyroid cancer. Differentiating normal from malignant thyroid tissue has been shown for a number of microRNAs, including miRNA-7-5p, miRNA-206, miRNA-181c-3p, and miRNA-637. With a specificity of 87% and a sensitivity of 89%, respectively (Stokowy et al., 2016), two miRNA classifiers were discovered by Stokowy and colleagues to distinguish mutation-negative FTC from follicular thyroid adenomas. Stokowy et al. (2015) found that miRNA-7-5p and miRNA-7-2-3p may be used to differentiate between PTCs, FTCs, and benign TC. Two miRNA classifiers have a sensitivity of 82% and a specificity of 49%, respectively. MiRNA-199b was found to be down-regulated whereas miRNA-146b, miRNA-183, and miRNA-221 were all up-regulated in FTC compared to normal thyroid cells (Wojtas et al., 2014) (Fig. 2b). Important information regarding miRNA idiom in MI-FTC (minimally invasive follicular thyroid carcinoma) was uncovered by using laser micro-dissection to extract miRNAs from FFPE (formalin-fixed paraffin-embedded) tissues, followed by RT-qPCR and PCR arrays. Metastatic micrometastases (MI-FTC) and WI-FTC (widely invasive FTC) were characterized by increased expression of miRNAs from the miRNA-92a, miRNA-10b, and miRNA-221/222 cluster, and poor prognosis. This study reveals that miRNA expression patterns in MI-FTC and WI-FTC, two forms of metastatic FTC, are very similar to one another. The expression level of miRNA-10b was a major contribution as a prognostic marker for evaluating the tumor development of MI-FTC during the first phase of therapy (Jikuzono et al., 2013).

4.3. MTC

Virtually 40% of sporadic cases and virtually all hereditary cases of MTC are connected to a mutation (function gain) of the RET proto-oncogene. Type IIA and IIB multiple endocrine neoplasia, as well as familial MTC, are all produced by RET mutations in the germ line and are autosomal dominant (Matrone et al., 2021). Somatic RET mutations are the most often seen molecular change in sporadic outbreaks. Other important molecular events, such as RAS mutations, have been discovered in around 35% of sporadic MTCs. Multiple studies have shown that miRNAs are beneficial as diagnostic and prognostic tools in cancer therapy because of their effects on the RET gene and the MAPK signaling pathway in thyroid cancer (Galuppini et al., 2021). Using a miRNA microarray expression profile, the authors of a 2012 study were able to identify miRNAs that were differentially expressed in a primary dataset consisting of 12 instances of sMTC (Sporadic Medullary Thyroid Cancer) and 7 cases of hMTC (Hereditary Medullary Thyroid Carcinoma). Overexpression of miRNA-183 and miRNA-375 in all MTCs was associated with lymph node metastases and recurrent regional disease. In individuals with MTC, an improved prognosis has been associated to an increase in miRNA-224 expression. Multiple studies have shown that miRNA-375 and miRNA-10a are over-expressed in MTC metastases, whereas miRNA-455 is down-regulated (Galuppini et al., 2021; Hudson et al., 2013; Santarpia et al., 2013). There hasn't been a ton of research on the role of miRNAs in MTC pathogenesis. According to a fold change of 142.2 to 32.3 between MTCs and regular thyroid tissues, miRNA-323, miRNA-370, miRNA-129, miRNA-137, miRNA-124a, miRNA-224, miRNA-127, and miRNA-9 are all up-regulated in MTCs. miRNA-21, miRNA-127, miRNA-154, miRNA-224, miRNA-323, miRNA-370, miRNA-9, miRNA-183, and miRNA-375 were considerably over-expressed in MTC with RET mutation, as described in a prior study (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 increase of miRNA-224 was revealed to be a crucial predictive factor for those patients. Two separate studies (Mian et al., 2012) suggest that patients with MTC who have up-regulated miRNA-224 had a better prognosis. Hudson et al. (2013) found that miRNA-375 and miRNA-10a were both highly expressed in MTC, but miRNA455 was significantly down-regulated. The expression of miRNA did not seem to be influenced by the presence or absence of RET mutations. MiRNA-375 was shown to suppress tumor development in both small cell lung cancer (SCLC) and Merkel cell carcinoma (MTC) in this research. Therefore, the down-regulation of YAP1 by miRNA-375 may be essential for the development of MTC tumors. Nikiforova et al. (2008) identified ten more particular miRNAs that are up-regulated in the case of MTC: miRNA-9, miRNA-10a, miRNA-124a, miRNA-127a, miRNA-129, miRNA-137, miRNA-154, miRNA-323, and miRNA-3370. Tissue from MTC with RET mutations showed an upregulation of the miRNA production genes DICER, DCGR8, and XPO5. MTC with RAS mutations did not vary significantly from non-mutated MTC, but MTC with RET codon 634 changes showed a more pronounced rise in DICER1 and DGCR8. More study is needed to discover if an imbalance in the expression of enzymes involved in miRNA synthesis might initiate cancer (Manso et al., 2021).

4.4. ATC

MiRNA expression patterns in ATCs have only been studied in a few number of studies (Das et al., 2020). Many miRNAs, including miRNA-125b, miRNA-30a-5p, miRNA-30d, and miRNA-26a, were shown to be down-regulated in ATC patients using microarray analysis, as was previously reported. Overexpression of miRNA-26a and miRNA-125b inhibited cell growth in two human ATC cell lines (Visone et al., 2007; Wójcicka et al., 2016; Wang et al., 2020), demonstrating that these miRNAs are linked to cell cycle down-regulation and that their reduced expression contributes to thyroid carcinogenesis. Over-expression of miRNA-30d or miRNA-30a in the same cell lines showed no impact on cell growth. The oncogene EZH2 is suppressed by the epigenetic gene suppressor miRNA-26a, which in turn impedes cell cycle progression. In another study, researchers evaluated miRNA expression in ATC and PTC cell lines and tissue samples. Over-expressed microRNAs in ATC cell lines and tissues include miRNA-21, miRNA-146b, miRNA-221, and miRNA-222, whereas down-regulated microRNAs include miRNA-26a, miRNA-138, miRNA-219, and miRNA-345 (Braun et al., 2010; Wu et al., 2013). Due to its unique expression pattern in ATCs and other follicular cell-derived thyroid malignancies, miRNA-138 was investigated for its involvement in ATC carcinogenesis. miRNA-138 directly targets the hTERT (human telomerase reverse transcriptase) gene. Primary ATCs have more hTERT expression than PTCs, and this is correlated with dedifferentiation and increased metastatic potential. Over-expression of hTERT after miRNA-138 downregulation has been linked to the transformation of well-differentiated PTCs into ATCs (Salh et al., 2022; Wu et al., 2013). According to research into the role of the miRNA-17-92 cluster (Takakura et al., 2008), two of these microRNAs, miRNA-17-3p and miRNA-17-5p, were found to be expressed at higher levels in ATCs than in nearby non-tissues. Antisense oligonucleotides containing caged nucleic acids, which seem to be antagonists of miRNA-17-3p and miRNA-17-5p, were used to study the roles of these miRNAs in ATC cells (Fig. 2d). Inhibiting miRNA-17-3p expression caused complete growth arrest in ATC cells, which was eventually followed by apoptosis. As opposed to this, ATC cells were significantly slowed in their growth and eventually entered senescence when treated with the miRNA-17-5p inhibitor (Takakura et al., 2008; Das et al., 2020). Suppression of miRNA-18a, which is also a member of the cluster, led in a modest decrease in cell proliferation, which shows that the components of the cluster in ATC cells each had a separate functional role. Inhibiting miRNA-17-3p expression increased caspase activity, which in turn increased apoptosis. Extra miRNA-17-3p cluster inhibitors did not induce caspase activation after transfection (Takakura et al., 2008; Das et al., 2020). In metastatic ATC (BHT-101), miRNA-34b was shown to be down-regulated, however in ATC-derived cells (8505C), it was not. Exogenous over-expression of miRNA-34b in ATC cells also led to decreased cell proliferation, impaired wound healing, slower cell cycle progression, and increased apoptosis. Down-regulation of vascular endothelial growth factor-A (VEGF-A) was also a major result of miRNA-34 delivery to ATC cells via liposomes. Liposome-loaded miRNA-34b was shown to diminish tumor growth in in vivo experiments when compared to a control group (Das et al., 2020). The use of siRNA to silence genes has been included into the ATC model of cell division, migration, invasion, metastasis, and death. For instance, siRNA-based suppression of MADD (MAPK-activating death domain activating protein) synthesis is efficient in reducing the proliferation and metastasis of ATC cells (8505C, C643, and HTH7) (Zhou et al., 2016; Colombo et al., 2015; Saini et al., 2019). MADD may promote cell survival by blocking TNF's ability to cause cell death. By recruiting Grb2 and Sos1/2, MADD activates MAPKs, which in turn initiates ERK signaling without affecting p38, Jun, or NF-B activity (Kurada et al., 2009). The in vitro study showed that pretreatment with MADD siRNA was effective in suppressing the expansion of 8505C, C643, and HTH7 cell lines. The growth of an orthotopic tumor replica formed from ATCs (8505C) was also suppressed in an in vivo research compared to a treatment-free control group and a group treated with siRNA (Saini et al., 2019).

5. Therapeutic strategies based on miRNA targeting in the treatment of thyroid cancer

Despite growing evidence for miRNA's involvement in carcinogenesis, some research suggests targeting miRNA dysregulation in cancer might be an effective therapeutic target (Table 2). The pathogenic impact of miRNA is possible to be removed by employing some synthetic component like anti-miRNA, which will be the major binding impediment to its target site. Using synthetic RNA technology, miRNA levels may be increased by releasing primary miRNAs, miRNA precursors generated from plasmids, or the delivery of synthetic mature miRNA mimics (Lam et al., 2015). In vivo investigations have shown that miRNA may be useful as a targeted therapeutic, and this might be pursued in

clinical trials. Preclinical testing of miRNA-122 inhibitors against chronic hepatitis C in chimpanzees was the first successful breakthrough in the therapeutic area of miRNA. When given intravenously, the miRNA inhibitor significantly decreased the viral load of the hepatitis C virus, or the studied molecule was proved to be safe (Lanford et al., 2010). The chemical MRX34, which mimics miRNA-34, was reported in a patient with liver cancer that was not resectable. Among 24 oncogenes, miRNA-34 is one of the powerful regulators of liver cancer, which was addressed for the first time in a clinical experiment (Austin, 2013). Given its prevalence, PTC has been the primary research focus of thyroid cancer studies. Inhibition of PTC proliferation, development, and metastasis is achieved by upregulation of miRNA-101 and miRNA-145, respectively (Paska et al., 2015; Wang et al., 2014). Specifically targeting the oestrogen receptor (ER), miRNA-291-5p reduced PTC cell growth and induced death (Huang et al., 2015). Reduced Na+/I-symporter (NIS) expression might spell doom for the process. Iodine absorption in thyroid cells was shown to improve when their expression of three microRNAs was suppressed, according to studies (Tang et al., 2020; Riesco-Eizaguirre et al., 2015). Inhibitors of microRNA (miRNA) have been investigated for their potential to regulate miRNA levels in cells. Tumor development was stifled when the miRNA-182 inhibitor was administered into nude mice derived from the TPC-1 cell line. This work reveals that miRNA-182 may be a therapeutic target for PTC (Zhu et al., 2014). miRNA-142-3 inhibits FTC tumor development in the thyroid. The Trithorax group proteins, which regulate the expression of the homeobox gene, have been related to its reduced expression in malignancies (Colamaio et al., 2015). The increasing amount of PAX8/PPAR fusion protein in FTC is closely associated with the increased level of miRNA-122. This protein is essential for the invasion and spread of FTC. In a mouse xenograft model, over-expression of miRNA-122 significantly suppressed tumor growth (Reddi et al., 2011). Increased expression of SMAD2 and TGFBR1 genes in ATC was caused by miRNA-200 and miRNA-30. Epithelial-mesenchymal transition (EMT) in ATC is regulated by these two genes (Wójcicka et al., 2016). Increased PAX8/PPAR fusion was shown to be responsible for the downregulation of angiogenesis and the activation of the AKT pathway by miRNA-122 and miRNA-375. Thus, the PAX8/PPAR fusion protein might be used as a treatment method for ATC by inducing re-differentiation and activating tumour suppressor miRNA-122 and miRNA-375 (Reddi et al., 2013). In MTC, miRNA-1533p, which is regulated by RET, inhibited tumor growth by blocking mTOR signaling. Inhibiting tumor development in MTCs with a combination of cabozantinib and miRNA1533p was very effective (JooLJ et al., 2019). Ramírez-Moya et al. (2019) discovered that oncogenic miRNA-146b-5p slows down the manufacturing process of miRNA by interacting with DICER1 and reducing its expression. To counteract the negative effects of miRNA-146b on thyroid cells, researchers up-regulated DICER1. Tumor aggressiveness was reduced in in vitro and in vivo models when the DICER1 complex was activated with the small chemical enoxacin. Conclusion: DICER1 is a tumor suppressor and its expression is downregulated by oncogenic miRNA-146b. Recent in vivo and in vitro research has shown miRNA-143's anticancer function against PTC, which plays a crucial role in PTC progression. Ding et al. (2022) have hypothesized a new signaling mechanism for up-regulating HMGA2 in PTC by down-regulating miRNA-143. In addition, a study published by Zhang et al. (2021) showed that miRNA-144-5p/ITGA3 might prevent thyroid cancer by reducing ITGA3 expression.

6. Insights into the molecular intrinsic subtypes of breast cancer

Recent research from the International Agency for Research on Cancer (IARC) indicates a shocking 66 percent rise in global deaths attributable to worrisome carcinomas since 1960. Breast cancer is the second most common form of carcinoma diagnosed worldwide after lung cancer at the present time (Sung et al., 2021). Since this is the case, about one in eight American women will get invasive breast cancer over their lifetimes. Research on early detection of breast cancer lags far behind its diagnosis and treatment (Zubair et al., 2021; Akram et al., 2017) despite the increasing number of literature on these topics. Gene expression microarray studies have shown distinct molecular (intrinsic) breast cancer kinds based on progressive emergence evaluations of numerous genetic materials in a single trial (Perou et al., 2000). Breast cancer that exhibits 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 discovered (Russnes et al., 2017; Charafe-Jauffret et al., 2006). Between half and two-thirds of breast cancer diagnoses are of the Luminal-A kind (Guo et al., 2018). These tumors have unique histopathologic types (such as tubular, invasive cribriform, mucous, and lobular) and have a lower histological grade, limited nuclear pleomorphism, reduced mitotic activity, and a favorable prognosis (Erber and

Hartmann, 2020; Makki, 2015). Luminal epithelium expresses a large number of ER-related genes, including 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. About 15% to 20% of breast cancers are Luminal-B carcinomas, which have a more aggressive phenotype, higher proliferative index, and worse prognosis than other kinds of breast cancer. This subtype has a greater recurrence rate and a worse relapse-free survival rate than the luminal-A subtype (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), LAPTMB4 (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). A member of the tyrosine kinase family, the human epidermal growth factor receptor-2 is encoded by the HER2 gene, which maps to chromosome 17q21. The aggressive biology and clinical behavior of HER2-positive (Human epidermal growth factor receptor-2) breast cancer is well-documented (Kumar and Aggarwal, 2016; Shao et al., 2012). HER2-positive breast cancer accounts for 15-25% of all breast cancer subtypes. Depending on how many people with poorly dividing G3 cells were included in the study, basal-like breast cancer might account for anywhere from 8 percent to 37 percent of all breast cancers. Tumors that lack expression of the ER, PR, and HER2 proteins are known as "triple-negative." CK5, CK14, CK17, and laminin are all basal myoepithelial markers that are overexpressed in basal-like tumors (Dai et al., 2017; Hachim et al., 2020; Iqbal and Buch, 2016). It's important to note that there's a discrepancy of around 20-30% between the words "triple-negative" and "basal-like" (Feng et al., 2018). In addition, anywhere between 5 and 10% of all breast carcinomas are caused by a different subtype called normal breast-like tumors. They have a limited degree of characterisation and have been put into the same intrinsic subtype categorization as fibroadenomas and normal breast samples despite this (Yersal and Barutca, 2014).

Breast cancer may develop in either the ducts or the lobules, or in the connecting tissue. Breast cancer is classified by the kind of cells it affects. Breast cancers are categorized as carcinomas or sarcomas depending on cell origin. Breast cancers develop in the epithelial lobules and terminal ducts that produce milk. Breast stromal myofibroblasts and blood vessel cells give rise to sarcomas (1% of initial breast cancer). On the basis of their clinical characteristics and degree of invasiveness, the most common types of breast cancer may be roughly divided into three categories: non-invasive (or in situ), invasive, and metastatic. 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). Non-invasive (or in situ) breast cancer subtypes include Ductal carcinoma in situ (DCIS), invasive or infiltrating breast cancer, invasive ductal carcinoma, and invasive lobular carcinoma.

7. Critical miRNA Expression in Breast Cancer

Melo and Esteller (2011) found that over 50% of human miRNA genes are situated in areas of the genome linked with cancer or in fragile locations. Multiple studies have revealed that breast cancer is linked to altering the expression of miRNAs since 2005, when the role of miRNA dysregulation in breast cancer was first identified (Iorio et al., 2005; Cookson et al., 2012). Similarly to TC oncomiRNAs, breast cancer is characterized by an increase in the expression of oncomiRNAs that silence tumor suppressor genes (Table 3). In addition, tsmiRNAs have been shown to silence oncogenes that contribute to breast cancer (Otmani and Lewalle, 2021). Short non-coding RNAs known as microRNAs (O'Brien et al., 2018) regulate gene expression via transcriptional activation or mRNA degradation. Biomarkers that may distinguish between healthy individuals and those with early breast cancer have been identified by analyzing the expression levels of several miRNAs (Cookson et al., 2012). Luminal-A patients and healthy controls were compared in a number of studies looking at miRNA expression levels (Fig. 5a). Higher amounts of miRNA-195, miRNA-21, miRNA-155, and miRNA-16 were found in the blood of patients with early-stage breast cancer compared to healthy controls. Therefore, the presence of an abnormally high amount of circulating miRNA is the gold standard for diagnosing luminal-A breast cancer (Fan et al., 2018; Heneghan et al., 2010; Hamam et al., 2017). Blood samples from women with luminal-A problems showed reduced expressions of miRNA-652 and miRNA-181a and un-modulated expression of miRNA-29a (McDermott et al., 2014). Despite nodal status or disease stage, luminal-A breast cancers were found to have lower expression of miRNA-29a, miRNA-652, and miRNA-181a compared to controls, suggesting

that transformed miRNA expression is an important biomarker in both early and late stage disease and a potential target for miRNA-related therapeutics (McDermott et al., 2014). In addition, stage I-II luminal-A cancers have been associated to lower expression of miRNA-152-3p and miRNA-23a-3p (Li et al., 2020). According to a recent research by Søkilde et al. (2019), the miRNA-99a/let-7c/miRNA-125b miRNA cluster, which was connected to proliferative signaling including ETS1, RAS, STAT3, AKT/mTOR, c-Myc, and JAK, was shown to be over-expressed in luminal-A malignancies. MiRNA-152-3p is a tumor suppressor that unexpectedly plays a less role in luminal-A breast cancer than in luminal-B (Li et al., 2020). This miRNA controls breast cancer cell proliferation via the PIK3CA pathway. Some miRNAs, such as miRNA-30a-3p and miRNA-29c-5p, were upregulated in luminal-A breast cancer, whereas others, such as miRNA-185-5p, miRNA-130b-3p, miRNA-362-5p, and miRNA-378a-3p, were downregulated (Haakensen et al., 2016). Down-regulation of miRNA-195 and up-regulation of miRNA-145, miRNA-486 were identified as the best diagnostic biomarker for the luminal-A cancer subtype in an RT-qPCR quantification investigation (Arabkari et al., 2020). Researchers looked at 309 miRNA values in 93 breast cancer samples to identify miRNA expression in the disease. In addition to miRNA-15b, miRNA-103, and miRNA-107 being dysregulated, over-expression of miRNA-100, miRNA-146b, miRNA-99a, miRNA-126, miRNA-130a, and miRNA-136 has been shown. Breast cancer subtypes luminal-A and luminal-B may be distinguished based on the expression of these nine miRNAs (Blenkiron et al., 2007).

7.2. Analyzing microRNA (miRNA) Expression in HER2 Breast Cancer

Several studies, both preclinical and clinical, have looked at microRNAs that are linked to HER2 pathway activity in breast cancer (Gorbatenko et al., 2019) (Fig. 5b). In the HER2 positive subtype of breast cancer, miRNA-155 is overexpressed (Song et al., 2012). By inhibiting SOCS1 gene expression and boosting AKT and Src, this miRNA may interact with MAPK signaling pathways (Nami and Wang, 2017; Jiang et al., 2010). One miRNA that has gotten a lot of interest in cancer is called miRNA-21. This gene is often overexpressed in the HER2-positive hormone receptor-negative subtype of breast cancer, while it is present in all breast cancer subtypes (Lee et al., 2011). miRNA-205 was detected in breast cancer patients' serum. Researchers have shown that its expression is lower in breast cancers that are less hostile and greater in those that are more aggressive, such as HER2-positive and triple-negative tumors (Xiao et al., 2019; Plantamura et al., 2020). The miRNA-125 family contains miRNA-125b as a member. The majority of the time, miRNA-125b is made by the combination of two different genes, miRNA-125b-1 and miRNA-125b-2. Increased miRNA-125b expression in breast tumors has been linked to both metastasis and the spread of the disease (F Tang et al., 2012; J Tang et al., 2012). More specifically, the existence of HER2 status is targeted by miRNAs such as miRNA-195, miRNA-107, miRNA-154, miRNA-126, miRNA-10b, let-7g, and let-7f (Mattie et al., 2006). A profile of five miRNAs, including miRNA-181c, miRNA-302c, miRNA-520d, miRNA-30e-3p, and miRNA-376b, may accurately predict HER2 status in early-stage breast tumors. There is a strong association between the expression levels of these five miRNAs and HER2-positive breast cancer, with miRNA-520d and miRNA-376b being upregulated and miRNA-181c being downregulated (Ramanto et al., 2019). Additional miRNAs, including miRNA-342, miRNA-30b, miRNA-363, miRNA-217, miRNA-377, miRNA-383, miRNA-422a, and miRNA-130a, play an important role in distinguishing HER2 positive carcinomas from HER2 negative carcinomas (Lowery et al., 2009).

The research conducted by Mojdeh Mahmoudian et al. revealed that certain microRNAs had heightened levels of expression in breast cancer tumors as compared to the surrounding tissues. In this study, it was observed that the expression levels of hsa-miR-25-3p, -29a-5p, -105-3p, and -181b1-5p were increased, but the expression levels of hsa-miR-335-5p and -339-5p were decreased. The association between the overexpression or downregulation of these putative microRNAs and TNM stages was seen, with the exception of hsa-miR-339-5p. Furthermore, save from hsa-miR-105-3p, all the potential microRNAs exhibited a correlation with HER-2 status. Moreover, the examination of receiver operating characteristic (ROC) curves revealed that the amalgamation of these six microRNAs has the potential to function as a biomarker for distinguishing between samples of breast tissue with tumors and those without tumors.

7.3. Breast cancers with a basal-like or triple-negative expression profile of microRNAs

Microarray analysis has identified triple-negative breast cancer (ER-, PR-, and HER2-negative) as the most aggressive subtype of breast cancer, with an alarmingly high prevalence of malignant transformation and a poor prognosis

(Elidrissi Errahhali et al., 2017). MiRNA-373, miRNA-9, miRNA-21, miRNA-29, miRNA-221/222, and miRNA-10b, all of which are associated with EMT/CSC and invasion, were found to have significantly higher expression levels in triple-negative breast cancer (Fig. 5c). Multiple molecular analyses of triple-negative breast cancer have also shown down-regulation of miRNAs, including miRNA-205, miRNA-199a-5p, miRNA-145, miRNAs from the miRNA-200 family, miRNA-203, etc. Multiple microRNAs have been shown to be dysregulated in triple-negative breast cancer (Koleckova et al., 2021; Piasecka et al., 2018). These include miRNA-221/222, miRNA-10b, miRNA-29, the miRNA-200 family, miRNA-203, and miRNA-21. Researchers used qPCR to identify miRNAs—miRNA-135b-5p, miRNA-136-5p, miRNA-182-5p, miRNA-190a, and miRNA-126-5p—that contributed to the progression of triple-negative breast cancer. MiR-190a functions as a tumor suppressor by suppressing VEGF-mediated tumor growth (Paszek et al., 2017; Yang et al., 2015), thereby reducing tumor angiogenesis. By regulating the cell cycle and increasing adhesion, proliferation, and cell migration of triple-negative breast cancer cells via induction of the TGF-beta, WNT, and ERBB signaling pathways, members of the miRNA-135b family serve an oncogenic function (Uva et al., 2018). Basal-like and non-basal-like triple-negative breast cancers were compared statistically. Immunohistochemistry basal-markers, such as EGFR+ and CK5/6+, grouped the study's findings into the quintuple-negative subtype of breast cancer. Uva et al. (2018) found that miRNA-135b overexpression was associated with a poor prognosis in patients with basal-like triple-negative breast cancer, and that this association might be due to miRNA-135b's positive correlation with a higher proliferative index. Four biomarkers (RMDN2 mRNA, miRNA-221, miRNA-1305, and miRNA-4708) were found to be useful in a previous study (Andrade et al., 2020) for the classification of patients with triple-negative breast cancer into distinct risk groups and the establishment of a predictive survival factor. Signature distinguishers between HER2-positive and triple-negative breast cancer were found to be over-expressed miRNA-433, miRNA-335, miRNA-382, and miRNA-376c (Stevic et al., 2018).

8. Therapeutic approaches based on the manipulation of miRNAs in 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-tumorgenic 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 potently 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, Knezevic et al., 2015b; 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 ERβ1. 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 led by HuR and gives chemo-sensitivity in breast cancer by modulating P-glycoprotein, happens under the supervision of HuR (Thorne et al., 2018). It is reported that miRNA-10b and miRNA-21 will have higher levels in breast cancer (Ali et al., 2022). Several silicon nanowires were meant to detect miRNA-10b and miRNA-21, the two primary prevalent oncomiRNAs revealed in breast cancer; the level of miRNA-21 in normal tissues has been reported 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 employing poly-l-lysine (Dorvel et al., 2012; Djafari et al., 2020).

9. Limitations and future viewpoint

The fact that miRNAs are tied to nuclease-mediated degradation before attaining target alteration is one of the primary difficulties for miRNA distribution. Different chemical changes are explored to ameliorate this issue, although they may have unforeseen effects such reduced miRNA function and the creation of several toxic metabolites (Rupaimoole et al., 2011). It was shown that TMTME (too many targets for miRNA effect) is an intrinsic property of miRNA molecules brought on by inadequate complementation with the target sequence. This TMTME may induce miRNAs to attach to a number of suitable sequences for the interaction (like lncRNA, protein-coding genes, 25 circRNA etc). The difficulty is that since it only has a few targets, this varies from all the licensed treatments (like siRNA therapies). Another reasonable issue is that exogenous manufactured miRNAs may exacerbate the effects of saturation and competition between exogenous and all endogenous miRNAs in the intracellular system, which may have negative side effects (Zhang et al., 2021). Published research have indicated that the specific properties of RNA oligonucleotides limit the effectiveness and design of medications. 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 concerns are addressed with in many ways during therapeutic applications; although miRNA administration is now a potential revolutionary therapeutic technique (Segal and Slack, 2020). Additional exploration into the biological, functional, pharmacological, and bioengineering processes is necessary to develop miRNA therapeutics. Once possible barriers to miRNAs are overcome, miRNA therapies should continue to advance as therapeutic agents for a number of disorders (Segal and Slack, 2020). Side effects and toxicity from medications may be reduced by targeting their administration to locations where pathogenic processes are occurring (Zhang et al., 2021; Chakraborty et al., 2021). Emerging experimental platforms (in vivo and in vitro preclinical experimental models) and cutting-edge bioinformatics programs for identifying miRNA-binding sites in the target genes have facilitated the

translation of miRNAs into clinical medicine (Hanna et al., 2019). Safer methods of administering drugs systemically via the bloodstream, directing therapeutic miRNAs to particular cells for beneficial absorption, and enhancing the specificity with which target cells target genes have all been the subject of much research. While much has been learned about miRNAs, the process of fully exploiting their remarkable therapeutic efficacy has only just begun (Diener et al., 2022).

10. Conclusion

Overall, miRNAs' functions in controlling thyroid cancer-related signaling pathways are crucial. Since they may be found in bodily fluids, non-invasive sampling procedures may be used to help diagnose and treat thyroid cancer. Different miRNA panels can evaluate thyroid cancer risk and disease complications. Similar evidence from a pool of data points indicated that miRNAs play a crucial role in cancers like breast cancer. Disturbances in the activity of these miRNA molecules may have deleterious impacts on a wide variety of disease pathways due to the crucial role they play in regulating gene expression to maintain homeostasis. miRNA-based medicines thus have tremendous potential as highly specialized approaches or focussed treatments for the treatment of breast cancer. As standardized methods for assessing circulating miRNAs become available, this approach to developing individualized thyroid cancer treatment strategies will become more widely used. Both forms of carcinomas have been connected to the up-regulation and down-regulation of many miRNAs, which may be the cause of cancer. Focused on the expression profile of miRNAs, researchers are putting all of their efforts into finding therapies that are mediated by miRNA in order to confront this serious disease. miRNA-based therapies are an effective and promising application for dealing with the high mortality toll connected with thyroid and breast cancer. Authentic research on miRNA background has to be expanded if therapeutic treatments mediated by miRNAs are to grow in the future. The number of individuals who die from both forms of cancer has gone higher since not enough study has been done and the specific molecular mechanism of numerous current miRNAs is still unclear. Therefore, we anticipate that this publication will serve as a springboard for further study into the expression of miRNAs in thyroid and breast cancer.

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