The role of microRNAs in the pathogenesis of thyroid cancer

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ARTICLE INFO

Keywords:
Thyroid cancer
miRNA
Biomarker

ABSTRACT

Thyroid cancer is the most frequent type of cancers originating from the endocrine system. Early diagnosis leads to good clinical outcome in differentiated types of thyroid cancer. Yet, there are few treatment options for patients with medullary or anaplastic thyroid cancer. Thus, identification of molecular markers that explain the pathologic process during evolution of this cancer has practical significance. MicroRNAs (miRNAs) have been shown to influence the activity of thyroid cancer-related signaling pathways such as MAPK pathway and \textit{RET} gene. These small transcripts not only can differentiate malignant tissues from non-malignant tissues, but also have differential expression in different stages of thyroid cancer. Assessment of serum levels of miRNAs is a practical noninvasive method for follow-up of patients after thyroidectomy. Moreover, the therapeutic effects of a number of miRNAs have been verified in xenograft models of thyroid cancer. In the current review, we summarize the data regarding the role of miRNAs in thyroid cancer.

1. Introduction

Thyroid cancer comprises the majority of tumors that originate from the endocrine system [1]. Based on the histological characteristics, thyroid cancers can be classified to differentiated thyroid cancer (DTC) originating from epithelial cells of the thyroid follicles, medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC). Papillary thyroid cancers (PTCs) include most of DTCs. Other histological types of DTCs are follicular thyroid cancer (FTC) and Hürthle cells cancers [1]. Early detection of DTC and the appropriate surgical treatment and administration of radioactive iodine have improved prognosis of DTC. Yet, resistance to radioactive iodine is a major obstacle in the management of a proportion of patients with DTC. Besides, there are few treatment options for patients with MTC or ATC [1]. Thus, identification of molecular mechanisms for evolution of thyroid cancer is a necessity particularly for the management of histological subclasses that are less sensitive to the routine therapeutic options[2]. MicroRNAs (miRNAs) have recently attracted much attention for putative applications as tumor biomarkers and regulators of the carcinogenic process. Several studies have evaluated expression profiles of these ~20 nucleotide transcripts in thyroid cancer cell lines and clinical specimens. Based on their expression pattern in these tissues compared with non-malignant tissues and their effects on cell proliferation and apoptosis, miRNAs have been classified to oncogenic (oncomiRs) and tumor suppressor miRNAs. In the current review, we summarize the role of these transcripts in the pathogenesis of thyroid cancer and their possible application as biomarkers for thyroid malignancy.

2. OncomiRs in thyroid cancer

\textit{In vitro} and in vivo experiments have revealed the role of several miRNAs in the pathogenesis of thyroid cancer (Fig. 1). These oncomiRs have been shown to decrease expression of a number of tumor suppressors, thus enhancing cell proliferation and cell cycle progression. The role of these miRNA is exerted through modulation of cancer-related signaling pathways such as PI3K/Akt/mTOR, the adipocytokine signaling pathway, Hippo, Wnt and Jak-STAT signaling pathways.

Among the oncomiRs whose role in thyroid cancer have been assessed is miR-19a. This member of the miR-17-92 cluster is over-expressed in ATC tissues, promoting the de-differentiation and aggressiveness of the corresponding cells. Forced over-expression of this miRNA in the well-differentiated FTC cell line has enhanced cell proliferation and modified the signature of genes associated with thyroid cell differentiation and aggressiveness such as thyroid stimulating hormone receptor and thyroglobulin [3]. The oncogenic effects of the miR-223 in thyroid cancer cells are probably mediated through down-regulation of APQ-1 protein. Notably, siRNA-mediated silencing of this miRNA has inhibited cell proliferation and induced apoptosis in these...
cells [4]. Besides, miR-221 has been shown to directly bind with the 3’ untranslated region (3’UTR) of TIMP3, thus inhibiting its expression and promoting proliferation and invasion of PTC cells. The oncogenic effects of this miRNA has been also verified in xenograft model of PTC [5]. miR-222 has been identified as another oncomir in PTC based on its over-expression on PTC patients compared with goiter group. Besides, its expression levels were higher in patients with larger tumor sizes and invasive properties. Expression of miR-222 was also correlated with the risk levels provided by the American Thyroid Association, but not with the TNM staging [6]. Expression of miR-181a has also been increased in thyroid cancer tissues compared with the paired non-cancerous tissues. Functional studies showed that miR-181a silencing decreases cell growth, while its up-regulation inhibits apoptosis and enhances cell cycle progression. This miRNA inhibits expression of RB1 [7]. Another study has demonstrated up-regulation of miR-146b, miR-222, miR-21, miR-221 and miR-181b in PTC tissue samples compared with normal thyroid tissues. Over-expression of these miRNAs were also detected in recurrent PTC tumors compared with non-recurrent samples and in lymph node metastases (LNM)-positive samples compared LNM-negative ones. Yet, distribution expression levels of these miRNAs were not different between PTC patients that have high and low risk of recurrence [8]. Expression of miR-146b-5p, miR-146b-3p, miR-221-3p, miR-222-5p, miR-222-3p has been increased in PTC tissues compared with normal thyroid samples. These were significant associations between up-regulation of miR-146b-5p and miR-222-3p and higher risk of recurrence. Over-expression of miR-146b-5p and miR-146b-3p distinguishes classical type and tall-cell variant but not follicular variant of PTC. Besides, miR-21-5p was remarkably increased only in tall-cell variant. Therefore, expression profile of miRNAs might be used in the molecular classification of PTC [9]. Table 1 summarizes the function and molecular interactions of oncomirs in thyroid cancer.

3. Tumor suppressor miRNAs in thyroid cancer

Several miRNAs have been shown to negatively regulate expression of oncogenes, thus inhibiting cell proliferation and migration. MAPK, PI3K, NF-κB, GSK-3β/β-catenin, AKT and PI3K pathways are among cancer-related pathways which are modulated by these miRNAs. An extensive number of these miRNAs have been shown to be down-regulated in thyroid cancer cell lines or clinical samples, thus facilitating malignant behavior of these cells. For instance, miRNome sequencing has shown constant down-regulation of hsa-miR-139-5p in patients with recurrent or metastatic thyroid cancer compared to disease-free patients. Functional studies have shown the role of this miRNA in attenuation of cell migration and proliferation in ATC cells. RICTOR, SMAD2/3 and HNRNPF have been identified as possible targets for this miRNA. Moreover, expression of hsa-miR-139-5p has been inversely correlated with the expression of HNRNPF transcript, which codes for an alternative splicing factor participating in cryptic exon inclusion/skipping [34]. Besides, miR-128 has been shown to target sphingosine kinase-1 (SPHK1) through direct interaction with its 3’UTR. Over-expression of this miRNA has led to attenuation of tumor growth rate and tumor weight in tumor-bearing animals [35]. Up-regulation of miR-let-7e has been shown to suppress cell migration and invasion of thyroid cancer cells. This miRNA inhibits HMGB1 expression through binding with its 3’ UTR. miR-let-7e has been regarded as a tumor suppressor miRNA in PTC and a putative therapeutic candidate for this kind of cancer [36]. miR-129 is another tumor suppressor miRNA in PTC which exerts its function through inhibition of expression. Over-expression of miR-129 inhibits growth and invasion of PTC cells. Thus, miR-129-5p/MAL2 axis is regarded as a therapeutic target in PTC [37]. Expression of miR-26b-5p has been decreased in thyroid cancer tissues compared with adjacent normal tissues in association with lymph node metastasis. In vitro studies showed the role of this miRNA in suppression of cell proliferation, invasion and migration of thyroid cancer cells. The tumor suppressor role of this miRNA might be exerted through the Gsk-3β/β-catenin pathway [38]. miR-203 has been down-regulated in PTC tissues and cell lines compared with control tissues and cells. Down-regulation of this miRNA was associated with up-regulation of survivin, through which miR-203 modulates Bcl-2 expression [39]. Table 2 summarizes the functions and molecular interaction of the tumor suppressor miRNAs in thyroid cancer.

4. Diagnostic/prognostic role of miRNAs in thyroid cancer

Several studies have assessed diagnostic accuracy of miRNAs in thyroid cancer. Among them is the study conducted by Rosignolo et al. which identified serum profile of 754 miRNAs in PTC patients prior to and after thyroidectomy [25]. Notably, expression of eight miRNAs was significantly higher in patients before treatment compared with their levels both in healthy subjects and after-treatment samples. The most promising results were reported for miR-146a-5p and miR-221-3p. Thus, expression of these miRNAs can be used as biomarkers for follow-up of patients. Prognostic significance of miRNAs in thyroid cancer has been verified through application of Kaplan-Meier analysis and cox regression methods. For instance, Wen et al. have reported consistent down-regulation of miR-486-5p in a number of PTC samples from TCGA, GEO and ArrayExpress datasets. They also reported associations between expression levels of this miRNA and clinical parameter such as cancer stage, lymph node involvement, distant metastasis and most notably overall survival [51]. Mazel et al. have assessed miRNA profiles in thyroid samples using next generation sequencing and multiplexing technologies. They recognized significant differences in miRNA signature between normal and malignant tissues. Notably, expression of 19 miRNAs were significantly different between benign and malignant tissues. In the validation step, these miRNAs could classify 35 other nodules with indeterminate cytology. This panel has sensitivity, specificity and diagnostic power of 91%, 100% and 94%, respectively, which are superior to the existing molecular assays [65]. Table 3 summarizes the results of studies which appraised diagnostic/prognostic significance of miRNAs in thyroid cancer.
### Table 1

OncomiRs which are up-regulated in thyroid cancer.

| microRNA   | Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signaling Pathways | Function                                                                 | Ref |
|------------|-----------------------------|--------------------|--------------------|--------------------|--------------------------------------------------------------------------|-----|
| miR-19a    | Focally invasive follicular thyroid cancer (FTC) samples and ANTs | FTC-133, 8505c     | PTEN, TSHr, Tg, TTF1 and Pax8, CDH1, an E-cadherin | –                  | miR-19a overexpression stimulates cell proliferation and alters the expression signature of genes associated with thyroid cell differentiation and aggressiveness. | [3] |
| miR-222    | 10 patients with medullary thyroid carcinoma (MTC) and ANTs | –                  | –                  | –                  | miR-222 expression was correlated with ATA risk levels.                 | [6] |
| miR-223    | Serum from 39 PTC patients and 30 HCs | –                  | –                  | –                  | miR-223 inhibitor suppresses proliferation and activates apoptosis of thyroid cancer cells by down-regulating AQP-1. | [4] |
| miR-34a    | FFPE MTC samples along with ANTs | –                  | AXL                | PDK/Akt/mTOR       | miR-34a suppresses the expression and functions of AXL and impairs migration, invasion, and formation of distant metastasis. | [10] |
| miR-144    | FFPE MTC samples along with ANTs | –                  | mTOR               | PDK/Akt/mTOR       | Its repression decreases cell proliferation, differentiation, migration, invasion, and tumor formation in an animal model. | [10] |
| miR-181a   | 15 paired thyroid cancer tissues and ANTs | –                  | RB1                | –                  | miR-181a overexpression decreased apoptosis and promoted cell cycle progression | [7] |
| miR-222    | The PTC biopsy specimens (n = 65) | –                  | –                  | –                  | miR-222 could aggravate cell proliferation and invasion by targeting TIMP3. | [5] |
| miR-375    | Thyroid tissues from 130 patients affected by MTC (104 sporadic and 26 familial) | –                  | YAP1               | AKT                | miR-375 plays an essential role in MTC progression.                    | [11] |
| miR-146a and miR-146b | FFPE MTC samples and ANTs | –                  | IRAK1              | TLRs/IL-1          | Expression levels of miR-146a and miR-146b influence the cell proliferation and migration. | [12] |
| miR-375    | Plasma from 37 MTC patients with persistent or recurrent metastatic disease, 9 non-metastatic MTC patients in remission and 36 HCs | –                  | YAP1, SRC21A       | PDK/Akt             | Deregulation of miR-375 participates in MTC tumorigenesis. Circulating miR-375 is as an independent prognostic marker for metastatic MTC. | [13] |
| miR-9-3p   | Frozen biopsy specimens from 12 patients with MTC and eight non-tumor donors | –                  | BLCA               | Bcl-XL/Bcl-2        | Upregulated miR-9-3p has a positive role in human MTC progression by modulating the growth and apoptosis of cancer cells. | [14] |
| miR-205    | FFPE MTC samples and ANTs | –                  | VEGF-A, ZEB1       | –                  | Up-regulation of miR-205 significantly suppressed angiogenesis.       | [15] |
| miR-340-5p | FFPE MTC samples and ANTs | –                  | BMP4               | –                  | miR-340-5p promotes thyroid cancer proliferation.                     | [16] |
| let-7      | Plasma from 49 PTC, 21HC | –                  | –                  | –                  | Abnormal expression of let-7 has been associated with cancer initiation and progression. | [17] |
| miR-222    | Five PTC tumor samples and ANTs | –                  | –                  | the adipocytokine signaling pathway and Jak-STAT signaling pathway | miR-222 may play critical roles in tumorigenesis of PTC. | [18] |
| hsa-miR-181a-2-3p | Serum from 32 pairs of PTC and ANTs | –                  | –                  | –                  | This miRNA signature could predict survival of patients with PTC. | [19] |
| miR-221    | 32 pairs of PTC and ANTs | –                  | –                  | –                  | miR-221 promoted the proliferation, migration and invasion activities of PTC K1 cells. | [20] |
| miR-222    | Blood from 38 PTC patients and 30 HCs | –                  | –                  | –                  | Causing more aggressive behavior of the tumor | [21] |
| miR-155    | Blood from 38 PTC patients and 30 HCs | –                  | –                  | –                  | Causing more aggressive behavior of the tumor | [21] |
| miR-146b-5p | FFPE MTC samples and ANTs | –                  | –                  | –                  | miR-146b increases proliferation, migration, and invasion. | [21] |
| miR-222-3p, miR-17-5p, and miR-451a | Serum from 295 participants including 100 patients with PTC, 91 patients with benign nodules, 15 patients with MTC, and 89 HCs | –                  | –                  | –                  | miR-222-3p, miR-17-5p and miR-451a might discriminate PTC and benign thyroid nodules from controls. miR-222-3p and miR-17-5p serum levels may be biomarkers for differential diagnosis of MTC from benign thyroid nodules. | [22] |
| microRNA Numbers of clinical samples | Assessed cell line | Targets/Regulators | Signaling Pathways | Function |
|------------------------------------|-------------------|-------------------|-------------------|----------|
| hsa-miR-6843, hsa-miR-6730 | 491 PTC tissues and 59 ANTs | Hippo signaling pathway, Wnt signaling pathway, protein guidance | – | These miRNAs were identified as potential prognostic predictors of the 5-year survival and OS in patients with PTC. |
| miR-146b, miR-222, miR-21, miR-221, miR-181b | – | – | – | The levels of miRNA-146b, -222, -21, -221 and -181b expression in PTC were strongly associated with PTCC. |
| miR-146b, miR-221-3p, miR-222-5p, miR-222-3p, miR-22-1p | 76 normal and neoplastic thyroid tissues from 29 PTC patients | – | – | These miRNAs were potential clinical applications for diagnosis, prognosis, and targeted therapy in thyroid disease. |
| miR-146b-5p, miR-146b-3p, miR-221-3p, miR-222-5p, miR-222-3p | 56 normal and neoplastic thyroid tissues from 57 PTC patients | – | – | These miRNAs were potential clinical applications for diagnosis, prognosis, and targeted therapy in thyroid disease. |
| miR-146a-5p and miR-221-3p | Serum from 44 patients with sporadic PTCs and 39 controls | TRAF1 and PML cancer, apoptosis, and calcium signaling pathways | – | Serum levels of miR-146a-5p and miR-221-3p are biomarkers for the early noninvasive detection of PTC. |
| miR-221, miR-222, miR-146b, miR-34a, miR-144 | 499 PTC samples and 59 normal thyroid tissues | – | – | These miRNAs may be potential diagnostic/prognostic biomarkers and therapeutic targets. |
| miR-146b-5p, miR-146b-3p, miR-221-3p, miR-222-5p, miR-222-3p | 25 PTC samples and ANTs | – | – | The identified miRNAs may be potential diagnostic/prognostic biomarkers and therapeutic targets. |
| miR-146b | 48 samples from paired PTC tumors and matched normal thyroid tissues | – | – | These miRNAs were potential clinical applications for diagnosis, prognosis, and targeted therapy in thyroid disease. |
| miR-375 | Tissues from 62 MTC patients | Nthy-ori 3-1, TT cells, 8505C, B-CPAP | SEC23A ERK, AKT pathways | Expression of miR-375 in Nthy-ori 3-1 cells decreased cell proliferation after with an increase in the percentage of cells in the G1 phase. |
| miR-182 | 30 pairs of ATC and ANTs | SW1736, 8305C, and Nthy-ori 3-1 | TRIM8 – | miR-182 enhances cellular growth by repressing TRIM8 expression. |
| miR-23a | Twenty paired tissue specimens of human PTC and ANTs | K1 cells | PTEN | miR-23a enhances cell proliferation and invasion and suppresses apoptosis in PTC cells. |
| miR-146b | 71 paired tissue specimens of human PTC and ANTs | BCPAP | – | miR-146b is a novel prognostic biomarker of PTC. |

(HC: healthy control, PTC: papillary thyroid carcinoma, ANT: adjacent normal tissue, MTC: medullary thyroid cancer, ATC: anaplastic thyroid cancer, FTC: follicular thyroid cancer, HC: healthy control).
| microRNA | Numbers of clinical samples | Assessed cell line | Function |
|----------|----------------------------|-------------------|----------|
| hsa-miR-139-5p | a fresh frozen thyroid tissue series including 3 normal tissues, 4 adenomas and 42 carcinomas | CAL-62, BRL, TPC-1, CAL-62, PRK1, ARO and K1, Nthy-ori3-1 | Overexpression of miR-139-5p in thyroid cancer cells. |
| miR-128 | | | |
| miR-129 | 30 pairs of PTC tissues and ANTs | BCPAP, K1, Nthy-ori3-1 | Overexpression of miR-129 suppresses PTC cell proliferation, migration and invasion. |
| miR-34a | 48 pairs of PTC tissues and ANTs | BCPAP, KTC-1, TPC-1 and K1, Nthy-ori3-1 | miR-34a inhibits growth and invasion of PTC cells by targeting MAL2. |
| miR-214 | 42 paired thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-214 reduces cell proliferation, migration and invasion. |
| miR-212 | 67 paired human thyroid cancer tissue samples and 67 ANTs | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and K1, Nthy-ori3-1 | miR-212 overexpression significantly inhibited cell proliferation, migration and invasion. |
| miR-335-5p | 53 paired thyroid cancer and non-tumor tissue samples | TPC-1, FTC133, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-335-5p negatively regulates the proliferation and invasion of PTC cells. |
| miR-125b | 30 paired thyroid cancer and non-tumor tissue samples | SW1736, 8305C, Nthy-ori3-1 | miR-125b represses migration and invasion. |
| miR-132 | 30 paired thyroid cancer and non-tumor tissue samples | SW1736, 8305C, Nthy-ori3-1 | miR-132 represses migration and invasion. |
| miR-133 | 36 paired thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and K1, Nthy-ori3-1 | miR-133 suppresses migration and invasion. |
| miR-127-1 | 30 paired thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and K1, Nthy-ori3-1 | miR-127-1 inhibits PTC cell proliferation, migration and invasion. |
| miR-199b-5p | 40 cases of PTC tissues and 8 cases of ANTs | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-199b-5p inhibits PTC cell proliferation, migration and invasion. |
| miR-718 | 60 paired fresh frozen PTC tissue samples | TPC-1 and BCPAP | miR-718 negatively regulates PTC cell proliferation, migration and invasion. |
| miR-429 | 59 thyroid cancer and ANTs | Nthy-ori3-1, TCP-1 and NPA | miR-429 suppresses migration and invasion. |
| miR-26b-5p | 67 TC tissues and 67 ANTs | TPC-1, FTC133, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-26b-5p overexpression significantly inhibited cell proliferation, migration and invasion. |
| miR-381-3p | 53 paired thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-381-3p inhibits PTC cell proliferation, migration and invasion. |
| miR-524 | 30 matched paired thyroid cancer and non-tumor tissue samples | TPC-1, FTC133, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-524 inhibits migration and invasion. |
| miR-9 | 60 paired thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-9 inhibits migration and invasion. |
| miR-205 | 35 PTC tissues and matched ANTs | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-205 inhibits migration and invasion. |
| miR-577 | 50 pairs of thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-577 inhibits migration and invasion. |
| miR-486-5p | 30 paired human thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-486-5p inhibits migration and invasion. |
| miR-431 | 60 paired thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-431 inhibits migration and invasion. |
| miR-486-5p | 30 paired human thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-486-5p inhibits migration and invasion. |
| miR-577 | 50 pairs of thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-577 inhibits migration and invasion. |
| miR-431 | 60 paired thyroid cancer and non-tumor tissue samples | FTC133, BCPAP, TEC, TPC-1, SV726, TPC-1 and TPC-1 cell line | miR-431 inhibits migration and invasion. |
| microRNA     | Numbers of clinical samples                                                                 | Assessed cell line                                      | Targets/Regulators                          | Signaling Pathways | Function                                                                                           | Ref |
|-------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------|--------------------|----------------------------------------------------------------------------------------------------|-----|
| miR-217     | 58 paired thyroid cancer tissues and ANTs                                                    | 8505C, TPC-1, and SW1736, Nthy-ori3-1                   | AKT3                                       | –                  | miR-217 overexpression inhibited proliferation, migration, and invasion.                           | [56]|
| miR-199a-3p | 188 tissue samples (136 PTCs, 52 normal thyroid tissue)                                      | –                                                       | –                                          | –                  | miR-199a-3p activation in PTC cells suppresses migration and proliferation.                        | [57]|
| miR-199a-5p | 24 pairs of primary PTC tissue specimens and ANTs                                           | TPC-1/33, TPC-1 and K1, STC, SW579, Nthy-ori3-1         | SNAI1                                      | –                  | miR-199a-5p overexpression suppressed tumor growth.                                               | [58]|
| miR-150     | Ten pairs of thyroid tissues, consisting of human thyroid cancer tissue and ANTs             | K1 and TPC-1                                            | RAB11A                                     | WNT/b-catenin      | Overexpression of miR-150 suppressed cell proliferation via inducing the cell cycle arrest and promoting cell apoptosis. | [59]|
| miR-144     | 59 paired PTC tissues and ANTs                                                              | BCPAP and TPC-1                                         | E2F8                                       | –                  | miR-144/E2F8/CCD1 regulatory axis controls PTC development.                                       | [60]|
| miR-211-5p  | Forty pairs of the thyroid cancer and ANTs                                                  | K1/BCPAP/TPC-1, Nthy-ori3-1                            | SOX11                                      | –                  | mir-211-5p affected the viability, proliferation and invasion of TC.                              | [61]|
| miR-135a-5p | Fifty-three pairs of human thyroid carcinoma and ANTs                                        | FTC1/33, TPC-1 and K1, STC, SW579, Nthy-ori3-1          | VCAN                                       | –                  | mir-135a-5p could affect the proliferation, invasion and migration of thyroid carcinoma cells.    | [62]|
| miR-7-2     | Five PTC tumor samples and ANTs                                                             | –                                                       | CLDN1                                      | tight junction pathway | miR-7-2 and CLDN1 may be used as biomarkers of stage and prognosis in PTC. miR-153-3p acts as a tumor suppressor in MTC tumorigenesis. | [18]|
| miR-153-3p  | 32 pairs of PTC and ANTs                                                                   | The human MTC T4 cell line                              | RPS6KB1                                    | mTOR               | this miRNA signature could independently predict the survival of patients with PTC.             | [62]|
| hsa-miR-138-1-3p | Paired PTC and ANTs obtained from 47 patients                                              | –                                                       | –                                          | –                  | miR-564 upregulation suppressed cell proliferation, migration, and invasion and induced cell apoptosis. | [63]|
| miRNA-564   | 58 cases of PTC and their ANTs                                                             | TPC-1, BCPAP, and HTH83, HTh-ori3                        | AEG-1                                      | PTEN/Akt           | miR-384 is a tumor suppressor that targets the 3′-UTR of PTKACB gene.                            | [64]|
| miRNA-384   | 30 cases of PTC and ANTs                                                                   | BCPAP, K1                                              | PRKACB                                     | PKA signal transduction pathway | mir-203 inhibits cell proliferation and migration, and enhances apoptosis.                     | [39]|
| miR-7-2     | Serum from 295 participants including 100 patients with PTC, 91 patients with benign nodules, 15 patients with FTC, 89 HCs | –                                                       | –                                          | Survivin           | mir-146-5p, mir-132-3p, and mir-183-3p might be biomarkers for discrimination of PTC and benign thyroid nodules from controls. | [22]|
| hsa-miR-196a-2, and hsa-miR-206 | 491 PTC tissues and 59 ANTs                                                                  | –                                                       | –                                          | Hippo signaling pathway, proteoglycan in cancer, axon guidance, Wnt signaling | These miRNAs are potential prognostic predictor of the 5-year survival and OS in patients with PTC. | [23]|
| hsa-miR-146b, hsa-miR-146a, hsa-miR-222, hsa-miR-221, hsa-miR-134, hsa-miR-34a, hsa-miR-101, hsa-miR-143, hsa-miR-144, hsa-miR-615, hsa-miR-575, hsa-miR-181b, hsa-miR-194, hsa-miR-130a, hsa-miR-199a-3p, hsa-miR-30a, hsa-miR-424, hsa-miR-148a, hsa-miR-24 | 102 TC tumors and contralateral normal thyroid tissue patients | –                                          | –                                          | These 19 miRNAs may be used to discriminate benign from malignant thyroid nodules.                 | [65]|
| miR-1179, miR-486-5, miR-204-5, miR-7-2-3p, miR-144-5, miR-140-3p | 76 normal and neoplastic thyroid tissues from 29 PTC patients | –                                          | –                                          | –                                          | Dysregulated expressions of these miRNAs distinguish these cancers from normal thyroid tissue. miR-138 expression was not only associated with onset of PTC, but also the aggressiveness of PTC. Combination of miR-138 and miR-21 could increase the diagnostic accuracy for PTC. Let-7b overexpression inhibited cell proliferation, migration, and invasion. Let-7b suppressed in vivo tumor growth. The identified microRNAs may be potential diagnostic/prognostic biomarkers and therapeutic targets. | [9] |
| miR-138-5p, miR-21-2 | 20 pairs of PTC tissues, and ANTs, and 10 cases of adjacent thyroid benign lesions | BCPAP, BH4, TPC-1, and GTHH-3, HGMA2 | –                                          | –                                          | Let-7b overexpression inhibited cell proliferation, migration, and invasion. Let-7b suppressed in vivo tumor growth. The identified microRNAs may be potential diagnostic/prognostic biomarkers and therapeutic targets. | [27]|
| miR-181-5p, miR-138-5p | Twenty-five PTC samples and ANTs                                                        | –                                                      | –                                          | –                                          | (continued on next page)                                                                       |     |
5. Role of miRNAs in chemoresistance in thyroid cancer

The significance of miRNAs in determination of response to anti-cancer agents has been addressed in thyroid cancer patients. For instance, the tumor suppressor miRNA, miR-199b-5p has been shown to enhance sensitivity of thyroid cancer cells to the chemotherapeutic agent paclitaxel [43]. Moreover, miR-125b has significantly sensitized thyroid cancer cells to the effects of cisplatin by activating autophagy through an Atg7 dependent route [70]. Notably, miR-375 expression levels has been associated with reduced cell proliferation and improved sensitivity to vandetanib, a multi-kinase inhibitor which is used as a therapeutic option for metastatic MTC [30]. Table 4 summarizes the results of studies which reported association between expression levels of miRNAs and response to anti-cancer drugs.

6. Discussion

Recent studies have revealed aberrant expression of miRNAs in tissues or peripheral blood of patients with thyroid cancer. These miRNAs have been involved in the regulation of signaling pathways such as MAPK, PI3K, AKT, GSK-3β/β-catenin, Wnt, mTOR and NF-κB. Recent studies have revealed association between DTC and mutations in the RAS/RAF/MAPK pathway or RET/PTC rearrangements [1]. Moreover, MTC tumors have been linked with activating mutations in the RET gene [1]. The observed dysregulation of MAPK-associated miRNAs in thyroid cancer further shows the complex interactive network between miRNAs and signaling pathways in the context of thyroid cancer. Few studies have shown association between RET and miRNAs in this kind of cancer. For instance, miR-153-3p has been shown to have a synergic effects with the tyrosine kinase inhibitor cabozantinib as well [62]. Thus, miRNA-targeted therapies might also reverse resistance to other anti-cancer therapies.

Diagnostic power of miRNAs in thyroid cancer has been evaluated by several groups. miRNAs not only can differentiate malignant tissues from non-malignant tissues, but also have differential expression in different stages of thyroid cancer. Assessment of serum levels of miRNAs is a practical noninvasive method for follow-up of patients after thyroidectomy. Notably, a transcript signature consisting of 19 miRNAs could discriminate benign lesions from malignant thyroid nodules with unknown cytology at better accuracy and lower expense compared with existing molecular assays [65]. However, diagnostic power of these panels of miRNAs should be appraised in different populations to obtain the best panel for each ethnic group. It is worth mentioning that the presence of single nucleotide polymorphisms in both miRNAs and the mRNA targets might alter their bindings. Thus, the significance of each oncomiR or tumor suppressor miRNA in the pathogenesis of thyroid cancer might vary in different populations based on the frequencies of these variants in each population.

Taken together, miRNAs have critical roles in regulation of thyroid cancer-related signaling pathways. Their availability in body fluids provides the possibility of application of non-invasive sampling in diagnosis of thyroid cancer. A number of miRNAs panels have been shown to be applicable in determination of cancer course and patients prognosis in thyroid cancer. Verification of these results in larger
| Sample number | Area under curve | Sensitivity | Specificity | Kaplan-Meier analysis | Univariate cox regression | Multivariate cox regression | Ref |
|---------------|------------------|-------------|-------------|------------------------|--------------------------|-----------------------------|-----|
| 10 human normal and neoplastic thyroid tissues from 29 PTC patients | 0.91 | 84% for miR-138, 76% for miR-21 | 89% for miR-138, 93% for miR-21 | 52% for miR-138, 100% for miR-21 | – | – | [66] |
| 127 thyroid tumors (26 follicular adenomas, 21 follicular carcinomas, and 78 PTCs) and 17 normal thyroid tissues | 0.88 | – | – | – | – | – | – |
| Serum from 44 patients with sporadic PTCs and 39 controls | 0.96 for miR-146-5p, 0.95 for miR-221-3p, 0.95 for miR-222-3p, 0.95 for miR-34a, 0.95 for miR-144 | 91.4% for miR-221-3p, 91.4% for miR-222-3p, 84.5% for miR-46b, 91.4% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | – | – | – |
| 40 PTC tissues and 8 normal thyroid tissues | 0.98 for miR-192 | 93% for miR-192 | 93% for miR-192 | – | – | – | – |
| Serum from 44 patients with sporadic PTCs and 39 controls | 0.96 for miR-146-5p, 0.95 for miR-221-3p, 0.95 for miR-222-3p, 0.95 for miR-34a, 0.95 for miR-144 | 91.4% for miR-221-3p, 91.4% for miR-222-3p, 84.5% for miR-46b, 91.4% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | – | – | – |
| Serum from 44 patients with sporadic PTCs and 39 controls | 0.96 for miR-146-5p, 0.95 for miR-221-3p, 0.95 for miR-222-3p, 0.95 for miR-34a, 0.95 for miR-144 | 91.4% for miR-221-3p, 91.4% for miR-222-3p, 84.5% for miR-46b, 91.4% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | – | – | – |
| Serum from 44 patients with sporadic PTCs and 39 controls | 0.96 for miR-146-5p, 0.95 for miR-221-3p, 0.95 for miR-222-3p, 0.95 for miR-34a, 0.95 for miR-144 | 91.4% for miR-221-3p, 91.4% for miR-222-3p, 84.5% for miR-46b, 91.4% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | – | – | – |
| Serum from 44 patients with sporadic PTCs and 39 controls | 0.96 for miR-146-5p, 0.95 for miR-221-3p, 0.95 for miR-222-3p, 0.95 for miR-34a, 0.95 for miR-144 | 91.4% for miR-221-3p, 91.4% for miR-222-3p, 84.5% for miR-46b, 91.4% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | 96.6% for miR-221-3p, 94.8% for miR-222-3p, 96.6% for miR-46b, 94.8% for miR-34a, 81% for miR-144 | – | – | – | (continued on next page)
| Sample number | Area under curve | Sensitivity | Specificity | Kaplan-Meier analysis | Univariate cox regression | Multivariate cox regression | Ref |
|---------------|-----------------|-------------|-------------|------------------------|---------------------------|-----------------------------|-----|
| 188 tissue samples (136 PTCs, 52 normal thyroid tissue) | 0.87 | – | – | group was 1,015 days. The curves suggested that PTC cases with higher miR-486-5p expression levels were likely to have an improved clinical outcome. | Low miR-199a-3p expression levels were linked to TNM stage (p = 0.026), extra-thyroidal extension (p = 0.02), lymph node (LN) metastasis (p = 0.036), distant metastasis (p = 0.002) and recurrence of LN metastasis | – | [57] |
| 73 PTC tissues and ANTs | – | – | – | It was observed that the survival time of the patients with high expression of miR-146a and miR-146b was significantly shorter than that of the patients in the normal or low expression groups | – | – | [75] |
| Plasma from 37 MTC patients with persistent or recurrent metastatic disease, 9 non-metastatic MTC patients in remission and 36 HCs | 0.88 | 86.1% | 88.9% | Patients with higher levels of miR-375 had a striking and significantly worse OS. | Poor prognosis was associated only with male sex, tumor burden and high plasmatic levels of miR-375. | Only high levels of miR-375, but not male sex or tumor burden, maintained the prognostic significance of worse outcome. | [13] |
| Plasma from 49 PTC, 21 HC Forty-eight pairs of human PTC and ANTs | 0.66 | 74% | 38% | Patients with lower miR-215 expression exhibited significantly DFS than patients with higher miR-215 expression. | Downregulation of miR-215 expression was negatively associated with tumor size, differentiation, and lymph node metastasis status. | – | [17] |
| 71 paired tissue specimens of human PTC and ANTs | – | – | – | Patients with primary tumors expressing higher miR-146b levels had a lower DFS rate than those with lower miR-146b expressions. | – | miR-146b expression was a prognostic factor for DFS rate in patients with PTC. Advanced tumor stages and cervical LN metastasis were poor prognostic factors of DFS in patients with PTC at follow-up. | [33] |

(A NT: adjacent normal tissue, OS: overall survival, RFS: relapse-free survival, DFS: disease-free survival, PTC: papillary thyroid carcinoma, HC: healthy control, DTC: differentiated thyroid cancer, MTC: medullary thyroid cancer, LN: lymph node).
samples sizes of patients from various ethnicities would pave the way for their applications in clinical settings.

Declaration of competing interest

The authors declare they have no conflict of interest.

Acknowledgment

This study was financially supported by Shahid Beheshti University of Medical Sciences.

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Table 4

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
| Resistance to paclitaxel | miR-149b-5p | [43] |
| Resistance to cisplatin | miR-182 | [31] |
| Resistance to Vandetanib | miR-125b | [70] |
| Resistance to paclitaxel | miR-375 | [30] |
| Resistance to Vandetanib | miR-125b | [70] |
| Resistance to paclitaxel | miR-375 | [30] |
| Resistance to Vandetanib | miR-146b | [33] |

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
| Resistant to paclitaxel | miR-149b-5p | [43] |
| Resistant to cisplatin | miR-182 | [31] |
| Resistant to Vandetanib | miR-125b | [70] |
| Resistant to paclitaxel | miR-375 | [30] |
| Resistant to Vandetanib | miR-146b | [33] |

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
| Resistant to paclitaxel | miR-149b-5p | [43] |
| Resistant to cisplatin | miR-182 | [31] |
| Resistant to Vandetanib | miR-125b | [70] |
| Resistant to paclitaxel | miR-375 | [30] |
| Resistant to Vandetanib | miR-146b | [33] |

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
| Resistant to paclitaxel | miR-149b-5p | [43] |
| Resistant to cisplatin | miR-182 | [31] |
| Resistant to Vandetanib | miR-125b | [70] |
| Resistant to paclitaxel | miR-375 | [30] |
| Resistant to Vandetanib | miR-146b | [33] |

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
| Resistant to paclitaxel | miR-149b-5p | [43] |
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| Resistant to Vandetanib | miR-125b | [70] |
| Resistant to paclitaxel | miR-375 | [30] |
| Resistant to Vandetanib | miR-146b | [33] |

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
| Resistant to paclitaxel | miR-149b-5p | [43] |
| Resistant to cisplatin | miR-182 | [31] |
| Resistant to Vandetanib | miR-125b | [70] |
| Resistant to paclitaxel | miR-375 | [30] |
| Resistant to Vandetanib | miR-146b | [33] |

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
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| Resistant to Vandetanib | miR-125b | [70] |
| Resistant to paclitaxel | miR-375 | [30] |
| Resistant to Vandetanib | miR-146b | [33] |

| Function | miRNA | Reference |
|----------|-------|-----------|
| Resistant to chemotherapy | miR-146b | [33] |
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| Resistant to Vandetanib | miR-125b | [70] |
| Resistant to paclitaxel | miR-375 | [30] |
| Resistant to Vandetanib | miR-146b | [33] |
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