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MicroRNA role in thyroid cancer pathogenesis

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1. ABSTRACT

MicroRNAs (miRNAs) are a class of endogenous, non-coding RNAs approximately 22 nucleotides in length that negatively regulate translation of the protein-coding genes. As such, miRNAs are fundamental mediators of cellular differentiation, proliferation, and survival. Each miRNA may functionally interact with a multitude of target genes to exert various effects on normal physiology to support human health or pathological processes leading to disease conditions, such as cancer. Genome-wide analyses have generated specific miRNA profiles of thyroid cancers (TCs) and identified the up- and down-regulated miRNAs related to various carcinogenesis stages and prognoses. Here, we summarize the recent knowledge on aberrant miRNA expression in the various TCs, including papillary, follicular, and other rare types. In addition, we discuss the significance of miRNA profiles and individual miRNAs in the diagnosis, treatment, and prognosis of these tumors.

2. INTRODUCTION

It is estimated that up to 25% of annual deaths in the United States are attributable to cancer. Among the endocrine system cancers, TC has emerged as the most commonly diagnosed, with 37,340 new cases reported in 2008 (1). This trend in increasing TC incidence extends to other countries across the globe as well, as rates have steadily increased since the early 1980s (2). However, increasing TC incidence in clinical and subclinical stages does not necessarily reflect the epidemiologic situation of this disease and may merely indicate the enhanced public awareness of TC, improved clinical practices for identifying suspect thyroid nodules, and advanced diagnostic technologies capable of detecting small papillary cancers (3). Regardless, the fact that TC tumors are associated with increased risk of morbidity and mortality and burden on the healthcare system has made it urgently necessary to elucidate the underlying pathogenic mechanisms in order to develop more effective treatment

and prevention strategies. Several genetic alterations, such as somatic mutations and chromosomal rearrangements, have been associated with some of the TC subtypes, and in recent years researchers have focused their attention on the miRNAs as potential contributors to the TC pathogenic process. Aberrant miRNA expression is a well-recognized feature of many different forms of human cancers, and is believed to reflect disease-related changes in the fundamental cellular processes of tumors that either initiate or result from cancer. Moreover, the aberrant miRNA profiles may represent useful diagnostic and prognostic markers as well as aid in the identification of potential therapeutic targets. In this review, we summarize the recent findings for miRNA signatures of TC and its subtypes and explore the most promising miRNAs that possesses therapeutic potential (4).

3. OVERVIEW OF THYROID CANCER

During development of the thyroid gland, embryonic stem cells (ESCs) give rise to the functionally distinct populations of thyroid follicular cells, thyroid somatic stem cells, and cancer stem cells (CSCs) (5). These cells are crucial for normal function of the thyroid gland throughout life but maintain sensitivity to stimulation by carcinogenic factors, which may trigger over-differentiation and aberrant proliferation. In TC patients, the presence of highly differentiated TC cells implies a good prognosis. In contrast, non-differentiated TC cells are indicative of short survival time, due to their feature of chemoresistance. Unlike the differentiated TC cells, which are derived from normal thyrocytes in thyroid tissue, follicular cells and medullary cells, the non-differentiated TC cells are believed to originate from the CSC component. TC of follicular origin is the most commonly diagnosed and has been sub-classified as follicular (FTC), papillary (PTC), partially differentiated (PDTC) or anaplastic (ATC) thyroid cancer. The FTC and PTC forms are characterized as differentiated cancers, and the PTCs alone account for approximately 80% of all thyroid tissue malignancies (6, 7). Other rare TC subtypes exist and include medullary thyroid carcinoma. TC subtypes share features of increased and uncontrolled cellular proliferation, angiogenesis, and reduced cell death, and several of the activated oncogenes and down-regulated tumor suppressor genes underlying these processes have been defined (6, 7). However, the various differentiation grades between the subtypes determines the degree of difficulty in treating them. For example, the well-differentiated FTCs and PTCs respond readily to the available therapies, but the less-differentiated ATCs are chemoresistant, highly invasive, and form distant metastases (4).

4. miRNAs INVOLVED IN THYROID CANCER

4.1. Gene mutations and thyroid cancer

Recent genome-based studies of TC have identified a multitude of associated somatic mutations and chromosomal rearrangements, as well as signaling pathways (Figure 1). Specifically, point mutations in the BRAF and RAS genes, chromosomal rearrangements affecting the RET/PTC and PPARγ chromosomal rearrangements, and activation of the MAPK and PI3K-AKT signaling pathways are altered in TC (8). Epidemiologic study indicated that ~44% of PTC patients carry the BRAF V600E mutation, which changes the valine residue at position 600 to a glutamic acid; this single point mutation has subsequently provided significant insight into the pathogenesis of PTC as well as become a useful diagnostic marker and prognostic indicator (5, 9, 10). However, a study by Sheu et al. found no significant differences in the miRNA profiles of PTC patients with BRAF mutation and those with wild-type BRAF (14); this fining implies that the TC-related somatic mutations are uncorrelated with the effects of miRNA-related pathogeneses of cancer. As with all sporadic cancers, PTEN is one of the most frequently inactivated tumor suppressor genes observed in TC tumors (11). Another mutation that is frequently detected in tumors of sporadic MTC patients (~50%) is in the proto-oncogene RET; this mutation leads to aberrant activation of RET and stimulation of the downstream signal transduction pathways that support tumorigenic processes (12). Although some of the PTC-associated biomarkers have reached the clinical trial stage, their usefulness in TC diagnosis and treatment remains limited due to the fact that not all patients carry the markers and we have yet to understand the precise coincidence of protein-coding gene mutations in various PTC subtypes and stages (13).

4.2. miRNAs and thyroid cancer

miRNAs can function as oncogenes or tumor suppressors by inhibiting the translation of tumor suppressor genes or blocking the translation of oncogenes, respectively. Such activities have been demonstrated under normal human physiological conditions and implicated as contributors to the pathological process of carcinogenesis (15, 16). In particular, the miRNA-146b-5p has been characterized as a putative oncogene based on its ability to bind the 3'-untranslated region (UTR) of the Smad4 gene and modulate the downstream TGF-β signal transduction (17).

miRNAs can also cause changes to the epigenome. Histone modifications, such as methylation and acetylation, are fundamental regulatory mechanisms of gene transcription. Inhibition of the histone methyltransferases (HMTs) or the histone deacetylases (HDACs) can cause aberrant expression of oncogenes and tumor suppressor genes (18). Moreover, when a breast adenoma cell line, SKBr3, was treated with a potent HDAC inhibitor, the expressions of four miRNAs were up-regulated and 22 miRNAs were down-regulated (19).

The collective studies of miRNA expression patterns in cancer have revealed that while the miRNA profiles may share some features they also differ between cancer types, affected tissues, and tumor cell populations. Such is the case for TC; differential miRNA profiles are likely to exist that distinguish the subtypes of thyroid cancer as well as their related prognoses (Figure 1). However, there is a general trend that has been seen in the mRNA profiles of almost all cancers that have been researched to date; the overall miRNA expression level is

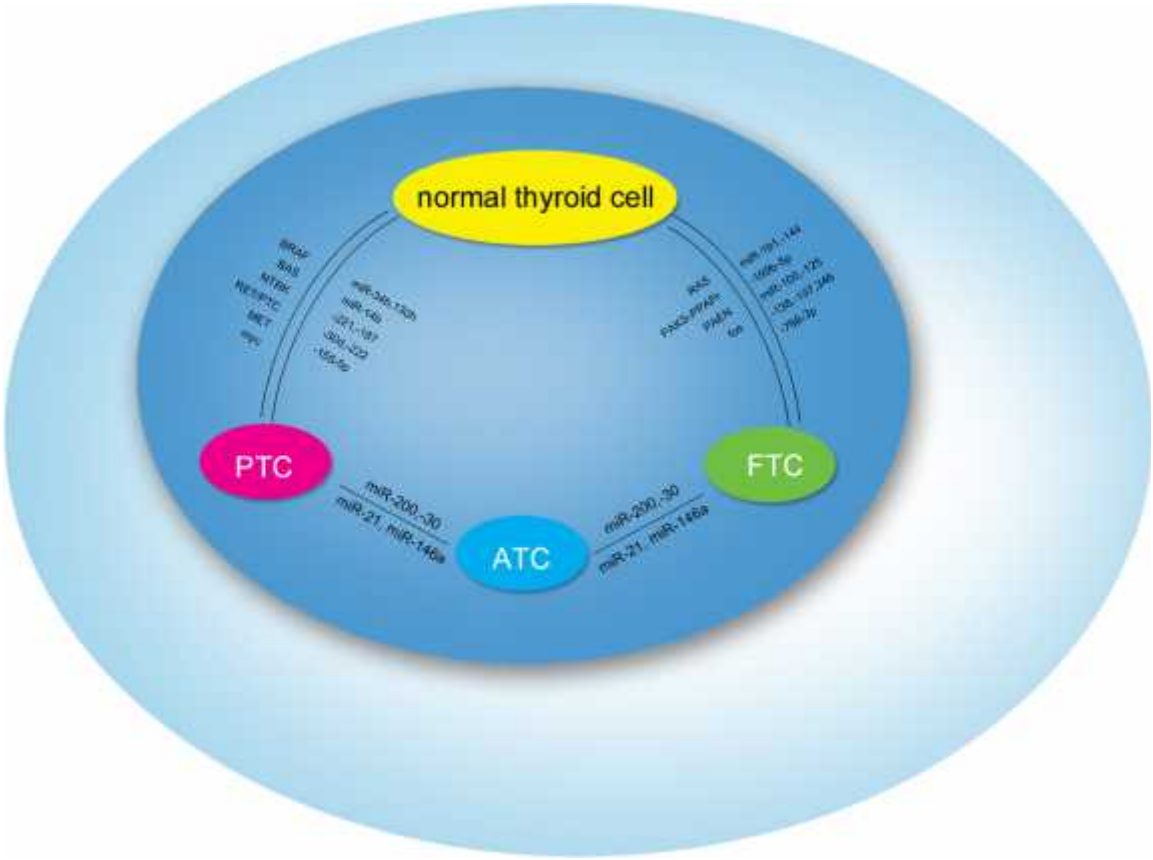

Figure 1. Gene mutations and miRNAs involved in the pathogenesis of PTC, FTC and ATC.

lower than that in the corresponding normal tissue (2, 20-23).

4.2.1. miRNAs in papillary thyroid cancer

Numerous miRNAs have been characterized as associated with the most common form of TC, PTC (24). However, the collective studies have revealed that the most differentially expressed miRNAs in PTC (miRNA-146b, -221, -187, and -30d) are up-regulated. This panel of miRNAs has been suggested as a marker set capable of distinguishing malignant from benign lesions, and to be especially helpful in diagnosing cases of "atypia of undetermined significance" (25). Another study showed that miRNA-155-5p and -222 are significantly increased in PTC thyroid tissues but decreased after tumor excision (26). Overexpressed miRNA-221 has been shown to promote carcinogenesis by directly or indirectly targeting numerous genes, including the cancer-related HOXB5 transcription factor-encoding gene (27, 28). Mazeh et al. comparatively analyzed 27 FNAB samples from 20 papillary thyroid cancer patients and seven patients with benign thyroid disorders and found that the sensitivity of miRNA-221 to detect PTC reached 95% (29).

Other putative markers for distinguishing PTC have been identified by miRNA microarray analysis and quantitative RT-PCR. For example, miRNA-146b expression was detected at significantly different levels in PTC samples and their corresponding non-malignant controls (30). The miRNA-1 was also found to be significantly differentially expressed in thyroid adenomas and carcinomas, but its precise role has yet to be evidenced; considering its known target genes (CCND2, CXCR4, and SDF-1a), it has been theorized that miRNA-1 may play a role in cell proliferation and migration (31). In contrast, while the effects of miRNA-146b, -221 and -222 on the development of papillary thyroid tumors are known, the target genes of these three microRNAs are unknown (32). The answers to these questions may be obtained in the near future by using the newly developed Gaussia luciferase reporter system (for example, CMV/Gluc-3xPT_MicroRNA221) described by Kim et al. This system allows monitoring of endogenous miRNA (for example, miRNA-221) in single cells (for *in vitro* analysis of target genes) or living organisms (for *in vivo* analysis of systemic responses) (33). Eight of the miRNAs characterized as overexpressed in PTC are known to directly inhibit the expression of a single tumor suppressor gene, THRB (13), and it is possible that some if not all of the other PTC-related miRNAs also target this gene either directly or indirectly. Still other putative PTC-related miRNAs may be identified by assessing the previous studies in different cancers; for example, Ricarte-Filho et al. stably transfected the lung cancer-related let-7f miRNA in TPC-1 cells, which harbor similar genetic changes to PTC cells, and showed decreased MAPK activity and cell growth (34). This

observation indicates that let-7 may similarly affect the growth and differentiation of PTC cells.

Use of the miRNAs as diagnostic markers is a major focus of recent research. The miRNA-126 and -7 have been shown to exhibit high diagnostic accuracy in distinguishing benign and malignant lesions by FNAB (35). Thus, these two miRNAs are considered especially promising for use with cases that prove difficult to diagnose by histology alone. However, there is still a long way to go to establishing a definitive panel for all TCs and even for the individual subtypes. Although a panel of five selected miRNAs (miRNA-146b, -181b, -21, -221, and -222) has proven capable of distinguishing common variants of PTC from FA/MNG, it lacks accuracy for individuals and doubtful patients (36). It is also important to note that different miRNAs can vary in FNAB samples from TCs and in serum samples, and that only one study to date has shown statistically significant correlations between miRNAs (specifically, let-7e, miRNA-151-5p, and miRNA-222) and certain clinicopathological variables (including tumor size, nodal phase, multifocal lesion status, and Tumor-Node-Metastasis stage) (26).

Eleven miRNAs were identified as putative markers of invasion and metastasis of PTC, common behaviors underlying malignancy, by transwell invasion experiments *in vitro*. The miRNA microarray technique was used to validate the differential expression of these 11 miRNAs between invasive cell lines and their respective non-invasive controls (37). The miRNA microarray approach was also used to identify putative markers of aggressive and non-aggressive PTC, and aggressive PTC was found to have significant up-regulation of miRNA-146b and -222 and significant down-regulation of miRNA-34b and -130b. The MET gene was reported to be the most likely target of miRNA-34b, as well as of miRNA-1, based on its positive correlation with these two miRNAs (38).

4.2.2. miRNAs in follicular thyroid cancer

Another common type of TC is FTC. Compared with normal thyroid tissue, miRNA-191 is down-regulated and CDK6 is up-regulated in follicular adenoma, PTC, and a follicular variant of PTC. Under normal physiologic conditions, miRNA-191 targets CDK6, a serine-threonine kinase regulator of the cell cycle; however, in conditions of miRNA-191 underexpression, CDK6 becomes overexpressed, promoting formation of neoplasias (39). Rossing and colleagues quantified the aberrant expression levels of miRNAs in follicular adenoma (FA) and follicular carcinoma (FC), and found that miRNA-199b-5p and -144 were uniquely absent in the FC samples but expressed at appreciable levels in both normal thyroid tissue and FA. This finding was confirmed when pre-miRNA-199b was added to a cultured follicular thyroid carcinoma cell line and led to reduced cellular proliferation. Another study of actively deteriorating thyroid cells showed that decreased expression of miRNAs, including miRNA-199b-5p and -144, directly correlated with increased expression of known target genes that encode tumorigenic factors (40). In addition to the two miRNAs that are down-regulated in FC, another four miRNAs (miRNA-100, -125b, -138, and -768-3p) were found to be up-regulated in malignant tumors of follicular origin. Of those, however, only miRNA-125b was also significantly up-regulated in follicular carcinoma samples. A study of the potential for miRNA-138 as a marker of malignancy for FNA samples indicated an accuracy of 75% (41). Finally, the miRNA-197 and -346 markers that are overexpressed in PTC might have potential for distinguishing FTC from FA (42).

4.2.3. miRNAs in rare subtypes of thyroid cancer

Differential expression of miRNAs has also been studied in the less common TCs. Frezzetti et al. reported that miRNA-21 was overexpressed both *in vivo* and *in vitro* in ATC, the most aggressive TC subtype. The miRNA-21 has been characterized as an oncogene, according to its regulation of genes involved in the cell cycle checkpoints (43). Another study found significant up-regulation of miRNA-146a, the expression of which is known to be positively regulated by nuclear factor (NF)-kappaB, itself a key player in carcinogenesis and inflammation (44). Down-regulated expressions of miRNA-200 and -30 were observed in ATC and proposed as markers to distinguish ATC from PTC and FTC (45). Finally, miRNA profiling by microarray analysis using the highly tumorigenic anaplastic cell line, ARO, and primary thyrocytes indicated that the miRNA-17-92 cluster comprising seven miRNAs was robustly overexpressed in ATC (46).

5. SUMMARY AND PERSPECTIVES

The histologic criteria currently used to classify different subtypes of thyroid tumors are limited by their subjective nature and inter-observer variability. In some circumstances, FNAB have difficulty in distinguishing benign and malignant lesions. Detection of somatic mutations via genotyping and of gene expression signatures by microarray analysis have recently demonstrated significant potential as improved diagnostic strategies for TC and its subtypes. However, the relative stability and condition-specificity of miRNA expression suggests that miRNA profiling may be more beneficial for diagnostic applications in clinical settings (47, 48). Basic and preclinical researchers have already begun to exploit the tumor-specific miRNA profiles to develop novel therapeutic strategies using miRNA inhibitors to specifically target tumor cells and avoid damage to the non-cancerous healthy tissues; such promising results as decreased cell growth, proliferation and migration of tumor cells, and induced tumor cell death have been reported (46). The most recent research efforts are continuing to evaluate the diagnostic accuracy of miRNAs for TC and its subtypes and are investigating the potential of these miRNAs as targets for new, highly specific TC therapies (49, 50). Although many of the dysregulated miRNAs are shared among the different subtypes of TC, continued research efforts are identifying additional putative markers and determining the quantifiable differential expression which may be useful in differentiating the subtypes. Ultimately, miRNA profiling may prove to be the most accurate and sensitive method of TC diagnosis, but systematic and large-scale investigations still need to be conducted and their findings validated before we reach the point when miRNA profiling enters into routine clinical practice.

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Abbreviations: FNAB, fine-needle aspiration biopsy; TC: thyroid cancer; ESCs: embryonic stem cells; FTCs: follicular thyroid cancer; PTCs: papillary thyroid cancer, PDTCs: partially differentiated thyroid cancer; ATCs: anaplastic thyroid cancer; C cells: parafollicular cells; UTR: untranslated region; FA: follicular adenoma; FC: follicular carcinoma

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