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Review:

Deregulation of microRNA expression in thyroid tumors*

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Abstract: MicroRNAs (miRNAs or miRs) are endogenous non-coding RNAs that negatively regulate gene expression by binding to the 3' non-coding regions of target mRNAs, resulting in their cleavage or blocking their translation. miRNAs may have an impact on cell differentiation, proliferation, and survival, and their deregulation can be inclined to diseases and cancers, including thyroid tumors. The purpose of this review is to summarize the existing findings of deregulated miRNAs in different types of thyroid tumors and to exhibit their potential target genes, especially to demonstrate those involved in tumor invasion and metastasis. In addition, new findings of circulating miRNA expression profiles, single nucleotide polymorphism (SNP) in thyroid tumors, and the correlation of somatic mutations with deregulated miRNA expression in thyroid tumors were all included in this review.

Key words: MicroRNA, Target gene, Thyroid tumor, Single nucleotide polymorphism (SNP), Somatic mutation
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1 Introduction

There are two distinct hormone-producing cell types composing the thyroid gland: follicular cells and parafollicular C cells (Pallante *et al*., 2010). More than 95% of thyroid tumors are derived from the follicular cells, while only 3% are C-cell-derived carcinomas (Kondo *et al*., 2006). Thyroid nodules are common and their prevalence differs from 3% to 76%, depending on the detection methods and the population evaluated (Ferraz *et al*., 2011). Most thyroid nodules are benign and just 5% are malignant (Gharib, 2004; Dean and Gharib, 2008). Benign nodules are principally represented as follicular thyroid adenomas (FTAs). The malignant nodules are carcinomas mostly and the thyroid carcinomas are one of the most common malignancies of the endocrine system (Mazeh, 2012). Depending on various histological and clinical features, the follicular cell-derived carcinomas are divided into well-differentiated thyroid carcinomas (WDTCs), poorly differentiated thyroid carcinomas (PDTCs), and undifferentiated thyroid carcinomas (Kondo *et al*., 2006). WDTCs include papillary thyroid carcinomas (PTCs) and follicular thyroid carcinomas (FTCs). Anaplastic thyroid cancers (ATCs) are highly undifferentiated and extremely aggressive (Yau *et al*., 2008; Braun and Hüttelmaier, 2011). PDTCs are medium carcinomas between WDTCs and ATCs. Medullary thyroid cancers (MTCs), the neuroendocrine tumor of the thyroid gland, are derived from parafollicular C cells (Pallante *et al*., 2010) and present as the hereditary form (HMTC; 25%) and the sporadic form (SMTC; 75%) (Abraham *et al*., 2011).

MicroRNAs (miRNAs or miRs) are small endogenous non-coding RNAs of 19–23 nucleotides that negatively regulate gene expressions by degrading mRNAs or blocking their translations (Ambros, 2004; Bartel, 2004). Productions and functions of miRNAs include multiple steps and require a large number of proteins (Nikiforova *et al*., 2009). They are transcribed from endogenous DNA by RNA polymerase II, and

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then processed from primary transcript (pri-miRNAs) to hairpin precursor (pre-miRNAs), which comprise two strands (Vriens *et al*., 2012). After that, they are exported by exportin-5 to the cytoplasm (Nikiforova *et al*., 2009; Marini *et al*., 2011). In the cytoplasm, pre-miRNAs undergo further processing by endonuclease Dicer and become mature miRNAs (Nikiforova *et al*., 2009; Frezzetti *et al*., 2011a; Marini *et al*., 2011). Mature miRNAs can bind to the 3' untranslated region (UTR) of mRNAs, resulting in blockage of translation or mRNA degradation depending on the degree of complementarity between miRNA and mRNA (Ambros, 2004; Bartel, 2004).

Agretti *et al*. (2012) reported that the number of known unique mature human miRNAs is 1921. The interaction between miRNA and mRNA is complex, partly because a single miRNA can target hundreds of different mRNA molecules (Ku and McManus, 2008). The miRNAs can influence cell differentiation, metabolism, and apoptosis, etc. (Cowland *et al*., 2007; Huang *et al*., 2010). It has been reported that the deregulation of miRNAs is involved in numerous cancers, including thyroid tumors (Mattie *et al*., 2006; Murakami *et al*., 2006; Chin *et al*., 2011). For example, five miRNAs (miR-146, -221, -222, -155, and -181a) were up-regulated in human PTCs as compared with normal human tissues (Menon and Khan, 2009); four miRNAs (miR-192, -197, -328, and -346) were overexpressed in the FTC as compared with the follicular adenoma (FA) (Weber *et al*., 2006); and significant decreases of miR-30d, -125b, -26a, and -30a-5p were detected in ATCs in comparison to normal thyroid tissues (Visone *et al*., 2007). Thus, different tumor types have different miRNA expressions. Schwertheim *et al*. (2009) reported that the miRNA expression pattern in thyroid cancers depends on the cellular origin and tumor differentiation.

Recently, a lot of researches concerning miRNA alterations occurring in thyroid tumors have been performed. This improved knowledge has promoted the understanding about thyroid cancer etiology and has offered novel diagnostic and prognostic markers for thyroid tumors (Nikiforov and Nikiforova, 2011). To our knowledge, this was the first review focused on summarizing different molecular alterations in every type of thyroid tumor, besides that, the deregulated miRNAs on thyroid tumor invasion, the circulating miRNA expression profiles, and single nucleotide polymorphism (SNP) in thyroid tumors and the correlation of somatic mutations with deregulated miRNA expression in thyroid tumors were all included in this review. We hope to offer some improved and personalized diagnostic markers for thyroid tumors.

2 miRNA expression profiles in papillary thyroid carcinomas (PTCs)

Most studies analyzed miRNA expression profiles of PTCs using miRNA microarrays, and they revealed the up-regulation of seven miRNAs in PTCs compared with the normal thyroid, including miR-221, -222, -146, -21, -155, -181a, and -181b (Tetzlaff *et al*., 2007; Nikiforova *et al*., 2008). The up-regulation of miR-221, -222, and -181b showed the values of fold-change in some cases higher than 10 (Pallante *et al*., 2010). Sheu *et al*. (2010) showed a significant difference of the expression of miR-146b between PTCs and other benign thyroid lesions, such as multinodular goitre (MNG) and FA with fold-changes up to 90. Moreover, four different studies (He *et al*., 2005; Ricarte-Filho *et al*., 2009; Leone *et al*., 2011; Xiong *et al*., 2011) identified down-regulation of miRNAs in PTC in comparison to normal thyroid tissue. The different miRNA expression profiles in PTCs are shown in Table 1.

To understand how miRNAs play parts in neoplasia, many studies have been done to find the targets of miRNAs (Fig. 1). A computational search revealed that miR-146b-5p potentially binds to the 3' UTR of *SMAD4*, an important member of the transforming growth factor-β (TGF-β) signaling pathway, which is a negative regulator of thyroid follicular cell growth (Geraldo *et al*., 2012). It has also been reported that miR-146a and -146b can significantly down-regulate interleukin-1 (IL-1) receptor-associated kinase (*IRAK1*) and tumor necrosis factor (TNF) receptor-associated factor 6 (*TRAF6*), two key adaptor/scaffold proteins in the IL-1 and Toll-like receptor (TLR) signaling pathway, known to positively regulate nuclear factor-κB (NF-κB) activity (Bhaumik *et al*., 2008). Other targets of miR-146a and -146b are chemokine receptor 4 (*CXCR4*) (Labbaye *et al*., 2008) and epidermal growth factor receptor (*EGFR*) (Hurst *et al*., 2009), etc.

Table 1 miRNAs aberrantly expressed in papillary thyroid carcinomas (PTCs)

miRNA	Specimen type	Detecting technique	Experimental group	Control group	Expression profile	Reference
miR-146, -221, -222, -21, -220, -181a, -155	Snap-frozen tissue	miRNA microarrays	Tumor tissue	Normal thyroid tissue	Up	He *et al*., 2005
miR-187, -221, -222, -146b, -155, -122a, -31, -205, -224	Snap-frozen tissue	RT-PCR	Tumor tissue	Normal thyroid tissue	Up	Nikiforov *et al*., 2008
miR-221, -222, -21, -31, -172, -34a, -213, -181b, -223, -224, -181a	FFPE tissue	miRNA microarrays	Tumor tissue	Benign proliferative multinodular goiter	Up	Tetzlaff *et al*., 2007
miR-146b, -221, -222	FFPE tissue	qRT-PCR	Tumor tissue	Follicular adenoma	Up	Chen *et al*., 2008
miR-218, -300, -292, -345, -30c, -30a-5p, -19b-1,2, -145sh, -130b	FFPE tissue	miRNA microarrays	Tumor tissue	Benign proliferative multinodular goiter	Down	Tetzlaff *et al*., 2007
miR-886-3p, miR-20a	Snap-frozen tissue	miRNA microarrays	Tumor tissue	Normal thyroid tissue	Down	Xiong *et al*., 2011
miR-1	Fresh thyroid tissue sample	qRT-PCR	Thyroid adenomas and carcinomas	Normal thyroid tissue	Down	Leone *et al*., 2011
miR-26a-1, -345, -138, -219	Snap-frozen tissue	miRNA microarrays	Tumor tissue	Normal thyroid tissue	Down	He *et al*., 2005

FFPE tissue: formalin-fixed paraffin-embedded tissue; RT-PCR: reverse transcription-polymerase chain reaction; qRT-PCR: quantitative real-time polymerase chain reaction

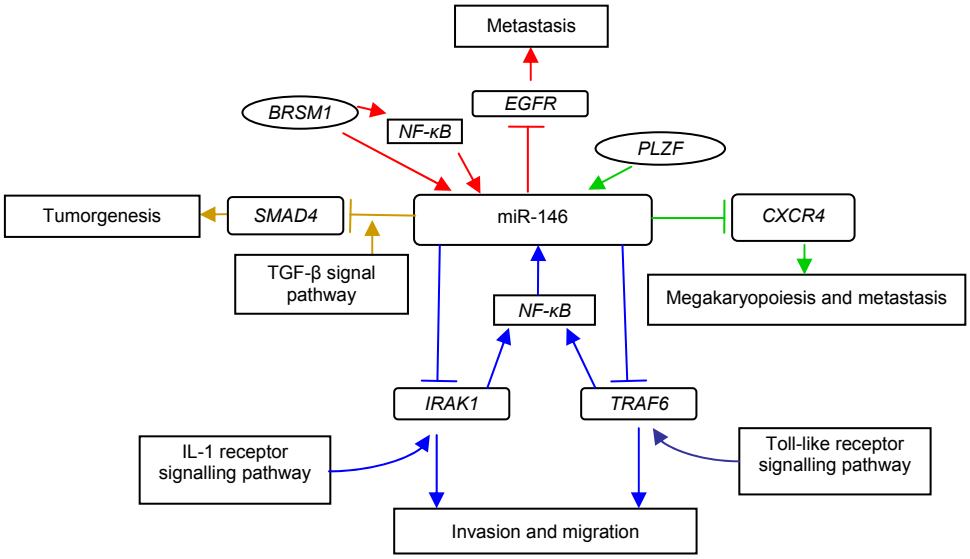

Fig. 1 Potential target genes and their working models of miR-146 in papillary thyroid carcinomas (PTCs)
BRSM1: breast cancer metastasis suppressor-1; *CXCR4*: chemokine receptor 4; *EGFR*: epidermal growth factor receptor; *PLZF*: promyelocytic leukaemia zinc-finger; *NF-κB*: nuclear factor-κB; *TRAF6*: tumor necrosis factor receptor-associated factor 6; *IRAK1*: interleukin-1 receptor-associated kinase

miR-221 and -222 are very similar in sequence, clustered on chromosome X, and are likely transcribed as polycistron (Ciafrè *et al*., 2005). Several targets for the miR-221/222 cluster have been identified (Table 2). One of them is *c-KIT*, also called *CD117*, a cytokine receptor for stem cell factors expressed on the surface of hematopoietic stem cells and other cell types (Felli *et al*., 2005). More recently, the

CDKN1B ($p27^{Kip1}$) gene was identified as a target of miR-221 and -222 (Galardi *et al*., 2007; Visone *et al*., 2007). $p27^{Kip1}$ is a member of the *Cip/Kip* family, which is related to cell differentiation, proliferation, migration, and apoptosis (Liu *et al*., 2012). Because $p27^{Kip1}$ has a key role in cell cycle, particularly in the G1/S transition, the enforced expression of miR-221 and -222 can stimulate thyroid carcinoma cells to break the G1/S block (Pallante *et al*., 2010). Other studies have also shown that miR-221 can target *CDKN1C/p57* that has a critical role in the cell cycle control (Garofalo *et al*., 2008).

3 miRNA expression in follicular thyroid carcinomas (FTCs)

Follicular adenoma and follicular carcinoma of the thyroid gland with microfollicular architecture are lined by cuboidal epithelial cells (McHenry and Phitayakorn, 2011). Because of the significant similarities at morphology and molecule among FTCs and FTAs (Braun and Hüttelmaier, 2011), miRNAs may become valuable markers to distinguish these tumors. As shown in Table 3, the most highly up-regulated miRNAs in conventional FTCs were miR-187, -224, -155, -222, and -221, and those in oncocytic variants were miR-187, -221, -339, -183, -222, and -197, whereas the most highly up-regulated miRNAs in conventional FTAs were miR-339, -224, -205, -210, -190, -328, and -342, and those in oncocytic variants were miR-31, -339, -183, -221, -224, and -203 (Nikiforova *et al*., 2008). Weber *et al*. (2006) revealed four miRNAs (miR-346, -328, -192, and -197) moderately up-regulated by 1.34–1.82-fold in FTCs when compared to FTAs.

The potential target genes of miR-197 and -346 are reported as extracellular matrix (ECM) components epidermal growth factor-containing fibulin-like extracellular matrix protein 2 (*EFEMP2*), tetraspanin 3 (*TSPAN3*), and activin A receptor type 1 (*ACVR1*). *EFEMP2* seems to have tumor suppressor functions (Gallagher *et al*., 2001; Argraves *et al*., 2003) and was reported to be overexpressed in colon carcinomas but down-expressed in prostate cancer (Wlazlinski *et al*., 2007). *TSPAN3* belongs to the tetraspan superfamily, whose members are inversely correlated with the metastatic potential in melanoma (Boucheix *et al*., 2001), and *ACVR1* is involved in the control of cell growth (Schulte *et al*., 2001). Colamaio *et al*. (2011) found that the miR-191 is down-regulated in FA, FTC, and follicular variant of PTC and identified *CDK6*, a serine-threonine kinase involved in the control of cell cycle, as a novel target of miR-191.

Table 2 Potential target genes of miR-221/222 in papillary thyroid carcinomas (PTCs)

miRNA	Potential target gene	Potential function	Reference
miR-221/222	*c-KIT* (*CD117*)	Stem cell factor	Felli *et al*., 2005
miR-221/222	*CDKN1B* ($p27^{Kip1}$)	Cell cycle	Pallante *et al*., 2010
miR-221	*CDKN1C*/*p57*	Cell cycle control	Garofalo *et al*., 2008

Table 3 miRNAs aberrantly expressed in follicular thyroid carcinomas (FTCs)

Tumor histotype	miRNA	Specimen type	Detecting technique	Experimental group	Control group	Expression rofile	Reference
Follicular thyroid adenoma (FTA)							
Conventional type	miR-339, -224, -205, -210, -190, -328, -342	Snap-frozen tissue	RT-PCR	Tumor tissue	Normal thyroid tissue	Up	Nikiforova *et al*., 2008
Oncocytic type	miR-31, -339, -183, -221, -224a, -203						
Follicular thyroid carcinoma (FTC)							
Conventional type	miR-187, -224, -155, -222, -221, -146b	Snap-frozen tissue	RT-PCR	Tumor tissue	Normal thyroid tissue	Up	Nikiforova *et al*., 2008
Oncocytic type	miR-187, -221, -339, -183, -222, -197						

4 miRNA expression in poorly differentiated thyroid carcinomas (PDTCs)

PDTC is a follicular cell derived from malignant neoplasm, it is intermediate between differentiated thyroid carcinomas and ATCs through morphologically and biologically (Schwertheim *et al*., 2009). Aiming to distinguish the miRNA expression in PDTCs, Schwertheim *et al*. (2009) investigated the expression levels of two distinct sets of miRNAs in 15 PDTCs. The results showed that the 'set 1' (miR-146b, -181b, -21, -221, and -222) expressions were slightly increased in PDTCs, while they were significantly up-regulated in PTCs and ATCs when compared to normal thyroid tissue. As to 'set 2' miRNAs (miR-30d, -125b, -26a, -30a-5p, and -let-7c), which are expressed at low levels in PDTCs and ATCs but are significantly up-regulated in PTCs. The integrated results were useful to discriminate PDTCs from PTCs and ATCs. Nikiforova *et al*. (2008) investigated that there were ten miRNAs overexpressed in PDTCs relative to normal thyroid tissues, and further seven miRNAs (miR-187, -221, -129, -222, -146b, -339, and -183) significantly overexpressed in PDTCs as compared with hyperplastic nodules. According to Chiappetta *et al*. (2008), high-mobility group AT-hook 2 (*HMGA2*), which correlates with malignancy in human thyroid neoplasias, was a possible target of miRNA-125b and -26.

5 miRNA expression in anaplastic thyroid cancers (ATCs)

As far as ATCs are concerned, the most striking difference between ATCs and other thyroid carcinomas derived from follicular cells is that they displayed a significantly decreased expression of various miRNAs (Visone *et al*., 2007; Schwertheim *et al*., 2009; Braun *et al*., 2010). The most significantly decreased miRNAs in expression were miR-30d, -125b, and -26a (Visone *et al*., 2007; Schwertheim *et al*., 2009). Contrary to the expression in PTCs, miR-138 was found to be severely decreased in ATC samples as well as in ATC-derived cell lines (Mitomo *et al*., 2008; Takakura *et al*., 2008; Braun *et al*., 2010). Braun *et al*. (2010) identified two significantly reduced miRNA families that can certainly distinguish ATCs from PTCs and FTCs: miR-200 and miR-30. While recent studies have also revealed up-regulation of several miRNAs in ATCs. Nikiforova *et al*. (2008) revealed that miR-302c, -205, and -137 were overexpressed in ATCs when compared to hyperplastic nodules. Visone *et al*. (2007) observed four miRNAs (miR-222, -198, -let-7f-1, and -let-7a-2) elevated in ATCs by comparing them with non-transformed thyroid tissues. Takakura *et al*. (2008) reported that the miR-17-92 cluster of seven miRNAs (miR-17-5p, -17-3p, -18a, -19a, -20a, -19b, and -92-1) as well as miR-106a and -106b were overexpressed in ATC cell lines. miR-17-3p and -17-5p displayed overexpression also in human ATC samples when compared to normal tissues. Other studies also found that miR-21, -146b, -221, and -222 were overexpressed in ATCs (Mitomo *et al*., 2008; Nikiforova *et al*., 2008; Frezzetti *et al*., 2011b). These findings are summarized in Table 4.

The research concerning the targets of the miRNAs of ATCs (Table 5) reveal that the potential target gene of miR-30a may be *Beclin 1*, which is a key autophagy-promoting gene that plays a critical role in regulation of cell death and survival of several cell types (Zhu *et al*., 2009). Kota *et al*. (2009) demonstrated that *cyclins D2* and *E2* are potential target genes of miR-26a in liver cancer cells. A potential target of miR-138 is the human telomerase reverse transcriptase (*hTERT*), whose overexpression has been associated with dedifferentiation, tumor stage, and increased metastatic and invasive phenotypes (Mitomo *et al*., 2008). The miR-17 family has been demonstrated to modulate the fibroblast growth factor 10 (*FGF10*) and fibroblast growth factor receptor 2b (*FGFR2b*), which can modulate epithelial bud morphogenesis in response to FGF10 signaling (Carraro *et al*., 2009). More recently, Esposito *et al*. (2012) reported that miR-25 and -30d putatively targeted the polycomb protein enhancer of zeste 2 (*EZH2*), which has oncogenic activity and was drastically up-regulated in ATCs but not in the differentiated ones.

Table 4 miRNAs aberrantly expressed in anaplastic thyroid cancers (ATCs)

miRNA	Specimen type	Detecting technique	Experimental group	Control group	Expression profile	Reference
miR-30d, -125b, -26a, -30a-5p	Thyroid sample	miRNA microarrays	ATC	Normal thyroid tissue	Down	Visone *et al*., 2007
miR-138	Snap-frozen tissue	RT-PCR	ATC	Papillary thyroid carcinoma	Down	Mitomo *et al*., 2008
miR-302c, -205, -137, -187, -214, -155, -224, -222, -221	Snap-frozen tissue	RT-PCR	Tumor tissue	Normal thyroid tissue	Up	Nikiforova *et al*., 2008
miR-222, -198, -let-7f-1, -let-7a-2	Thyroid sample	miRNA microarrays	ATC	Normal thyroid tissue	Up	Visone *et al*., 2007
miR-192, -196a, -194, -429, -200b, -7, -10a, -16	Cell line	miRNA microarrays	ATC cell lines ARO	PT	Up	Takakura *et al*., 2008

PT: cells isolated from thyroid tissues of patients with Graves' disease

Table 5 Potential target genes of unregulated miRNAs of anaplastic thyroid cancers (ATCs)

miRNA	Potential target gene	Potential function	Reference
miR-30a	*Beclin 1*	Regulate cell death and survival of various cell types	Zhu *et al*., 2009
miR-26a	*Cyclins D2* and *E2*	Cell cycle arrest	Kota *et al*., 2009
miR-138	*hTERT*	Dedifferentiation, tumor stage, and increased metastatic and invasive phenotypes	Mitomo *et al*., 2008
miR-17 family	*STAT3* and *MAPK14*	Modulate epithelial bud morphogenesis	Carraro *et al*., 2009
miR-25, -30d	*EZH2*	Oncogenic activity	Esposito *et al*., 2012

6 miRNA expression in medullary thyroid cancers (MTCs)

Few studies have been conducted to investigate the function of miRNAs in MTC pathogenesis. Nikiforova *et al*. (2008) revealed up-regulation of miR-323, -370, -129, -137, -10a, -124a, -224, -127, -9, and -154, which showed a value of fold-change from 142.2 to 32.3 in MTCs compared to normal thyroid tissues (Table 6). A study conducted by Abraham *et al*. (2011) in a series of 19 patients including 12 SMTC and 7 HMTC and their results, which were further validated by quantitative polymerase chain reaction (qPCR), indicated that miR-183 and miR-375 were overexpressed, whereas miR-9* was down-expressed in SMTC compared with HMTC. Mian *et al*. (2012) verified the overexpression of nine miRNAs (miR-21, -127, -154, -224, -323, -370, -9*, -183, and -375) by quantitative real-time PCR (qRT-PCR) in MTC patients. To further study the potential target genes of miR-21, they analyzed the immunohistochemical expression of programmed cell death 4 (*PDCD4*) and found that the *PDCD4* expression was significantly down-regulated in MTC samples in line with the up-regulation of miR-21.

7 Association between miRNA expression and thyroid tumor invasion

The migration and metastasis of cancer cells take place in three steps: adherence, degradation, and movement (Gao *et al*., 2010). In order to invade the circulatory and lymphatic systems to get metastasis, the tumor cells must initiate and completely come through all of these steps (Ponta *et al*., 2001). Gao *et al*. (2010) have done experiments between highly metastatic PTC cell lines and common human PTC cell lines to illustrate the relationship between deregulated miRNAs and metastasis of PTCs. The results showed that 11 miRNAs were differentially expressed in the metastatic and control cell lines. Among the 11 miRNAs, 9 (let-7b, miR-222, -106, -193, -34, -29, -26a, -15a, and -200) were reported to have an important role in tumor metastasis (Nikiforova *et al*., 2008) or epithelial-mesenchymal transition (EMT)

Table 6 miRNAs aberrantly expressed in medullary thyroid cancers (MTCs)

miRNA	Specimen type	Detecting technique	Experimental group	Control group	Expression profile	Reference
miR-323, -370, -129, -137, -10a, -124a, -224, -127, -9, -154	Snap-frozen tissue	RT-PCR	Tumor tissue	Normal thyroid tissue	Up	Nikiforova *et al*., 2008
miR-183, -375	Snap-frozen tissue	qPCR	SMTC	HMTC	Up	Abraham *et al*., 2011
miR-9*	Snap-frozen tissue	qPCR	SMTC	HMTC	Down	Abraham *et al*., 2011
miR-21, -127, -154, -224, -323, -370, -9*, -183, -375	Snap-frozen tissue	qRT-PCR	MTC	Normal thyroid tissue	Up	Mian *et al*., 2012

HMTC: hereditary medullary thyroid cancer; SMTC: sporadic medullary thyroid cancer

(Gregory *et al*., 2008; Korpal and Kang, 2008; Gebeshuber *et al*., 2009), while another two miRNAs (miR-199b and -16) were respectively involved in the tumor stem cell fate determination and apoptosis (Garzia *et al*., 2009; Guo *et al*., 2009). In another study, Yip *et al*. (2011) observed that miR-146b, -221, -222, and -155 were enhanced by up-regulation, while miR-1, -34b, -130b, and -138 were significantly down-regulated in aggressive tumors compared with non-aggressive PTCs. miR-183 and miR-375, which can predict lateral lymph node metastases in MTC, are associated with residual disease, metastases, and mortality (Abraham *et al*., 2011). While high miR-224 levels have been associated with lower stages of diagnosis, and none lymph node metastases or a biochemically free status was at the terminal of the follow-up in MTCs (Mian *et al*., 2012).

Because miRNAs play their functions by influencing their target genes, the metastasis-related genes have become the focus of the ongoing research. One study about miR-146b was conducted *in vitro* in a highly metastatic human breast cancer cell line (Hurst *et al*., 2009). The breast cancer metastasis suppressor 1 (*BRSM1*) up-regulates miR-146a and -146b, which can suppress breast cancer metastasis since they are likely to reduce the signaling through the NF-κB pathway (Fig. 1). *TSPAN3*, the potential target of miR-197, which belongs to the tetraspan superfamily, was inversely correlated with the metastatic potential in melanoma (Argraves *et al*., 2003; Colamaio *et al*., 2011). One potential target gene of miR-1 is *CXCR4*, which is often overexpressed in PTCs and plays a major role in lymph node metastasis from a primary tumor (Castellone *et al*., 2004).

8 Circulating miRNA expression profiles in thyroid tumor

There have previously been lots of diagnostic and/or prognostic markers for thyroid tumor tissues or cells from fine-needle aspiration (FNA). Yu *et al*. (2012) stuided the relationship between genome-wide serum miRNA expression profiles and thyroid tumors using Solexa sequencing followed by extensive qRT-PCR validation in 245 subjects (106 PTCs, 95 benign nodules, and 44 healthy controls). The results suggested that the expressions of serum let-7e, miR-151-5p, and miR-222 were significantly increased in the PTC cases compared to the benign cases and healthy controls. Receiver operating characteristic curve analyses indicated that these three miRNAs had a high diagnostic sensitivity and specificity for PTCs and their expression levels were well-correlated with certain clinicopathological features, such as nodal status, tumor size, multifocal lesion status, and the tumor-node-metastasis stage. Besides, one important thing of the serum miRNAs profiles may be their convenient and minimally invasive characters as novel diagnostic markers for PTC, though large-scale and multi-center studies are needed.

9 Contribution of single nucleotide polymorphism (SNP) to thyroid tumors

SNPs are the most common type of genetic variation which can lead to alterations in miRNA expression resulting in diverse functional consequences (Wang *et al*., 2012), such as population

diversity, disease susceptibility, and individual response to medicine (Shastry, 2009). SNPs located in miRNA-related regions including primary and precursor miRNA sequences, seed sequence of miRNAs, miRNA processing genes, and 3' UTR of target genes, can diversify miRNA production and the affinity and specificity between miRNAs and mRNAs (Landi *et al*., 2012). Since a specific miRNA has the ability to regulate hundreds of target mRNAs, SNPs in miRNAs may produce varied functions (Wang *et al*., 2012). Here, miR-146a rs2910164 was one of the most common studied miRNA polymorphisms (Yue *et al*., 2011; Zhou *et al*., 2011).

Human miR-146 comes in two distinct forms: miR-146a encoded on chromosome 5q33 and miR-146b encoded on chromosome 10q24 (Jazdzewski *et al*., 2008). The two related miR-146s are differentially regulated, with miR-146a strongly induced by lipopolysaccharide and regulated by NF-κB (Taganov *et al*., 2006; Jazdzewski *et al*., 2008). The miR-146a rs2910164 polymorphism is located at a position +60 relative to the first nucleotide of pre-miR-146a. The G to C change in the passenger strand results in a decreased mature miR-146a (Yue *et al*., 2011). Jazdzewski *et al*. (2008) found that the miR-146a rs2910164 CC genotype in pre-miR-146a was associated with a reduced production of mature miR-146a and contributed to a genetic predisposition to PTC. Because miR-146a is known to be an NF-κB-dependent gene (Taganov *et al*., 2006; Cameron *et al*., 2008) and can inhibit the downstream target genes, *TRAF6* and *IRAK1*, two key downstream adapter molecules of the TLR and cytokine receptors, Jazdzewski *et al.* (2008) speculated that the SNP can affect the negative feedback regulation loop in TLR and cytokine signaling pathway.

10 Correlation of somatic mutations with deregulated miRNA expression in thyroid tumors

Recent studies have suggested that genetic alterations in oncogenes may be of clinical use in thyroid neoplasms. The most common genetic alterations occurring in thyroid cancers are related with signal transduction pathways, including tyrosine kinase receptors [*RET/PTC* and neurotrophic tyrosine receptor kinase (*NTRK*)], signaling proteins (*BRAF* and *RAS*), and nuclear proteins [paired box (*PAX*) *8* and peroxisome proliferator-activated receptor γ (*PPAR-γ*)] (Vriens *et al*., 2009). These genetic changes are always mutually exclusive (Shibru *et al*., 2008) and have something to show about the deregulated miRNAs.

Mutation of the *BRAF* gene is most prominent in PTCs with an appearance up to 50% (Kondo *et al*., 2006; Pallante *et al*., 2010). The *BRAF* mutation in primary PTC is a T-A substitution at nucleotide 1799 in exon 15, which results in a change from valine acid to glutamic acid at codon 600 (V600E) of the BRAF protein (Wellbrock *et al*., 2004; Wojciechowska and Lewinski, 2006; Mitsiades *et al*., 2007), resulting in activation of the mitogen-activated protein kinase (MAPK) pathway (Wan *et al*., 2004; Knauf *et al*., 2005). The presence of a *BRAF* mutation has been associated with the poorer prognosis in PTC patients, such as an advanced stage at diagnosis, extrathyroidal extension, and lymph node metastasis (Xing, 2007; Elisei *et al*., 2008a; Yip *et al*., 2009). Recently, studies aiming to show an association between *BRAF* positivity and miR-146b in aggressive PTCs (Chou *et al*., 2010; Yip *et al*., 2011) found that miR-146b was significantly overexpressed in *BRAF*-positive PTCs with aggressive tumor behaviors. Mutations of the *RAS* genes (*K-RAS*, *H-RAS*, and *N-RAS* presented in codons 12, 13, and 61, respectively) were found in all thyroid cancers. The mutation frequencies are 10%–20% in PTCs, 20%–40% in FTAs, 40%–50% in FTCs, 20%–55% in PDTCs, and 20%–60% in ATCs (Kondo *et al*., 2006; Pallante *et al*., 2010). RAS proteins are plasma membrane GTPases activated by growth factor receptors, non-receptor tyrosine kinases, and G-protein-coupled receptors (Fagin and Mitsiades, 2008). It was reported that *RAS*-positive PTCs expressed the highest amount of miR-146 (Nikiforova *et al*., 2008). *RET* rearrangement is caused by interchromosomal translocations and there have been reported a total of 15 different *RET/PTC* rearrangements. The most widely occurring are *RET/PTC1* (RET kinase fused with *H4* gene) and *RET/PTC3* (RET kinase fused with *RFG* gene) (Pallante *et al*.,

2010). Nikiforova *et al*. (2008) reported that miR-187 was expressed at high levels in PTCs harboring *RET/PTC* rearrangements, while miR-221 and -222 were found at the highest level in *BRAF*- and *RAS*-positive PTCs. The frequencies of *RET* rearrangements are lower in PTCs (20%–40%) and PDTCs (~10%) (Vriens *et al*., 2009; Braun and Hüttelmaier, 2011). However, it has been documented that the frequency of *RET* rearrangement in MTC cases is in the range of 40%–50% (Elisei *et al*., 2008b). And significantly lower miR-127 levels were observed in SMTC carrying somatic *RET* mutations in comparison to SMTC carrying a wild-type *RET* (Mian *et al*., 2012).

11 Summary

MicroRNAs constitute a recently identified class of small endogenous noncoding RNAs that act as negative regulators of the protein-coding gene expression and may impact cell differentiation, proliferation, and survival, i.e., all fundamental cellular processes implicated in carcinogenesis. The miRNA expressiones are deregulated in many types of human cancers, including thyroid cancer. There are many types of thyroid carcinomas, such as PTCs, FTCs, ATCs, and MTCs. Several studies have shown the deregulation of miRNA expression in human thyroid carcinomas, such as miR-146, -221, -222, -155, and -181a up-regulated in human PTC as compared with normal human tissue; miR-192, -197, -328, and -346 overexpressed in FTC as compared with Fas; and, miR-17-92 cluster overexpressed in ATC cell lines as compared with normal tissues and follicular carcinoma cell lines. Among these deregulated miRNAs, some have relevance with the thyroid tumor invasion and metastasis. Besides, circulating miRNA (serum or peripheral blood miRNAs) expression profiles in thyroid tumor have been studied recently, as novel diagnostic and/or prognostic tools. SNPs, as the most common type of genetic variation, which exist in miRNA genes, can lead to diverse functional consequences, including thyroid carcinomas. And the somatic mutations have relevance with the deregulated miRNA expression in thyroid tumors. For example, miR-146b was significantly overexpressed in the *BRAF*-positive PTC that also had aggressive tumor behaviors and it was reported that *RAS*-positive PTCs expressed the highest amount of miR-146.

In this review, the documented miRNA profiles and their potential target genes in each type of thyroid tumor were summarized. We also recorded the latest researches on circulating miRNA expression profiles in thyroid tumors and the contribution of SNPs to thyroid tumors, in order to contribute to the search for thyroid tumor diagnosis and treatment.

Compliance with ethics guidelines

Zi-ming YUAN, Zhi-li YANG, and Qi ZHENG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要：

本文题目：甲状腺肿瘤中 microRNA 表达失调的研究进展

Deregulation of microRNA expression in thyroid tumors

研究目的：MicroRNAs（miRNAs 或 miRs）是一种内源性非编码 RNA，通过与信使 RNA（mRNA）的 3'非编码区结合，引起 mRNA 的断裂或蛋白质翻译的阻断，进而对基因表达进行负性调控。miRNAs 可影响细胞的分化、增殖和生存等过程，其表达失调有引起疾病甚至肿瘤的可能。miRNA 表达失调已在多种人类肿瘤中出现，包括甲状腺肿瘤。本文对不同类型的甲状腺肿瘤中出现的 miRNAs 表达失调及 miRNAs 可能的下游靶基因进行综述，为甲状腺肿瘤的临床诊断及治疗提供依据。

创新要点：已有大量关于滤泡细胞起源，尤其是乳头状甲状腺癌（PTC）中 miRNAs 表达失调的综述，但对 C 细胞起源的甲状腺髓样癌（MTC）中 miRNAs 表达失调的研究并未形成系统。同时，在此之前没有关于各型甲状腺肿瘤 miRNAs 表达与其靶基因的综述报道。在这篇综述中，我们还列入了对甲状腺肿瘤患者外周循环血液中 miRNAs 表达谱的最新研究以及单核苷酸多态性（SNP）对甲状腺肿瘤的影响。

重要结论：总结了 miRNAs 在各型甲状腺肿瘤中的表达谱（见表 1、3、4、6）；描述了在各型甲状腺肿瘤中不同 miRNAs 潜在的靶基因及其在肿瘤发生、发展、浸润、转移等多方面的作用（见图 1；表 2、5）。

关键词组：MicroRNA；靶基因；甲状腺肿瘤；单核苷酸多态性；体细胞突变