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Novel role of lncRNAs regulatory network in papillary thyroid cancer

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ABSTRACT

Papillary thyroid cancer (PTC) is the most common endocrine malignancy. The incidence of PTC has increased annually worldwide. Thus, PTC diagnosis and treatment attract more attention. Noncoding RNAs (lncRNAs) play crucial roles in PTC progression and act as prognostic biomarkers. Moreover, microRNAs (miRNAs) and epithelial-mesenchymal transition (EMT)-associated proteins have potential biomarkers for diagnosing and treating PTC. However, the correlation of lncRNAs with miRNAs and EMT-associated proteins needs further clarification. The present review highlights the recent advances of lncRNAs in PTC. We significantly summarized the two molecular regulatory mechanisms in PTC progress, including lncRNAs-miRNAs-protein signaling axes and lncRNAs-EMT pathways. This review will help our understanding of the association between lncRNAs and PTC and may assist us in evaluating the prognosis for PTC patients. Taken together, targeting the lncRNAs regulatory network has promising applications in diagnosing and treating PTC.

1. Introduction

Over the past few decades, the incidence of thyroid cancer has been steadily increasing worldwide [1–3]. Among thyroid cancer cases, papillary thyroid cancer (PTC) is the most common histological subtype, accounting for 89.1% of all cases [4]. As the most common endocrine malignancy [5], thyroid cancer diagnosis and treatment attract more attention. In addition to conventional imaging and treatment methods such as surgery and radiation therapy, molecular and biomarker analysis has become an essential supplement to traditional pathological assessments of thyroid cancer in recent years [6]. These tools represent valuable resources for improving thyroid cancer diagnosis and clinical management [7]. As indicated by research, with advancements in early tumor diagnosis and novel treatment approaches such as proteogenomics, DNA methylation, lncRNAs, and microRNAs (miRNAs), the survival rate of cancer patients is improving [8]. Several key points include: specific biomarkers participate in thyroid cancer cell processes like proliferation, migration, and apoptosis [9]; some relate to the tumor microenvironment, affecting prognosis [10]; other biomarkers help tumor cells evade the immune system [11,12], highlighting immunotherapy's potential as an effective treatment option.

As mentioned earlier, the majority of thyroid cancers are PTC. As a well-differentiated subtype of malignant tumors, PTC is generally considered to have a good prognosis [13]. However, studies have indicated that PTC can progress toward a poorly differentiated state, significantly decreasing life expectancy [14,15]. Furthermore, the diagnosis of PTC currently relies mainly on histopathological biopsy and fine-needle aspiration biopsy. These diagnostic methods are time-consuming in clinical practice, and the sampled tissues can significantly influence the test results. Therefore, it is crucial to identify tumor biomarkers that can be used for early and precise diagnosis. Here are some common PTC biomarkers:1.long noncoding RNAs (lncRNAs): lncRNAs also display altered expression levels in PTC, such as NEAT1 [16], H19 [17], HAGLROS [18], MFSD4A-AS1 [19] and MALAT1 [20]. These lncRNAs can be utilized as biomarkers to aid diagnosis and prognostic evaluation. 2. Altered expression levels of proteins: In PTC, some proteins exhibit altered expression levels, such as cell adhesion molecules (CAMs) in the epithelial-mesenchymal transition (EMT) pathway associated with N-cadherin, E-cadherin, and P-cadherin [21]. These proteins can serve as biomarkers to facilitate diagnosis and prognostic evaluation of tumors. 3.microRNAs (miRNAs): TO et al. have proposed that miRNAs can be used as a novel biomarker for tumors, and employing miRNAs in conjunction with gene treatments can effectively prevent the growth of tumors [22]. Similarly, several miRNAs in PTC

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demonstrate changed expression levels, such as miR-146b, miR-221, and miR-222 [23]. These miRNAs also have potential use as biomarkers for diagnosing, prognostic assessment, and treating PTC.

Numerous evidence indicate that the three types of biomarkers mentioned above are interconnected. This review mainly investigates the correlation of lncRNAs with miRNAs and EMT-associated proteins in PTC progress (Fig. 1). In addition, we suggest some potential approaches for diagnosing and treating PTC.

2. LncRNAs-miRNAs-protein signaling axes

LncRNAs are a small subclass of transcriptional molecules, ranging in length from 200 nucleotides to 100 kilobases [24]. LncRNAs play a crucial role in tumorigenesis, angiogenesis, proliferation, migration, apoptosis, and differentiation [25]. Recently, more and more evidence has shown that lncRNAs can act as competitive endogenous RNAs (ceRNAs) to regulate the biological functions of miRNAs [26–28]. Herein, we will provide a detailed description of the regulatory mechanisms involved in PTC.

CeRNAs are RNA molecules that regulate microRNA (miRNA) activity through "sponging." This process is based on the hypothesis that different RNA molecules, such as lncRNAs, circular RNAs (circRNAs), and messenger RNAs (mRNAs), compete for binding to miRNAs response elements (MREs) on miRNAs [29,30].

MiRNAs play a crucial role in post-transcriptional gene regulation by binding to complementary sequences on target mRNAs [31]. This leads to mRNA degradation or translation inhibition, ultimately decreasing protein production. ceRNAs can sequester miRNAs by sharing MREs, preventing them from binding to their target mRNAs [32]. In this way, ceRNAs indirectly regulate gene expression by modulating the availability of miRNAs. Based on this mechanism, we summarize tumor-promoting lncRNAs in PTC (Table 1). Moreover, modern biology's molecular and genetic tools have greatly improved the understanding of the molecules and signaling axes that regulate PTC growth, proliferation, migration, and metastasis.

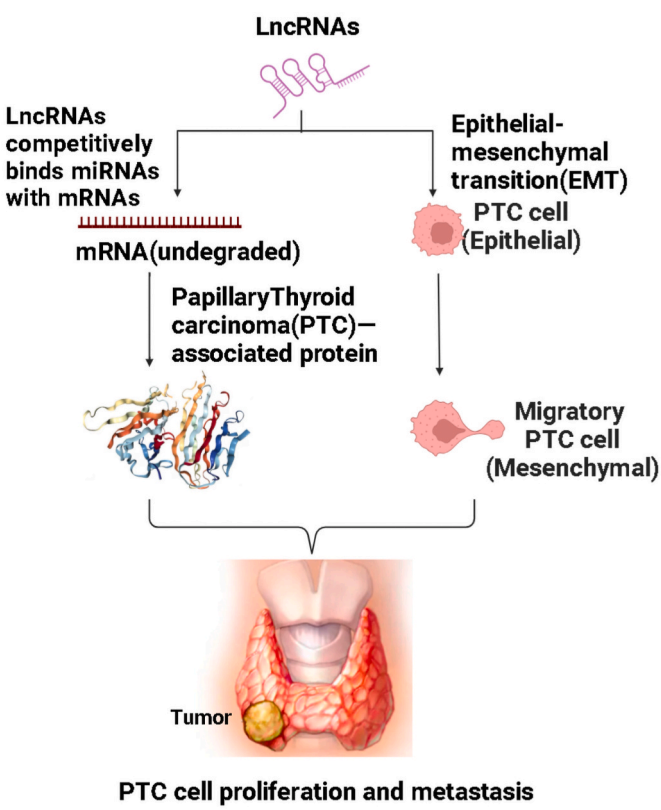

Fig. 1. LncRNAs' correlation with miRNAs and EMT-associated proteins in proliferation and metastasis of papillary thyroid carcinoma (PTC).

Table 1
Summary of tumor-promoting lncRNAs in papillary thyroid cancer(PTC).

lncRNAs	Variant	Expression	Functions	References
PWRN2	PTC	High	Sponging miR-325 to upregulate DDX5.	[33]
FAM230B	PTC	High	Sponging miR-378a-3p to upregulate WNT5A.	[35]
n384546	PTC	High	Sponging miR-145-5p to upregulate AKT3.	[39]
NORAD	PTC	High	Sponging miR-451 to upregulate IL-6R.	[40]
XIST	PTC	High	Sponging miR-101-3p to upregulate CLDN1.	[58]
NEAT1_2	PTC	High	Sponging miR-106b-5p to upregulate ATAD2.	[62]
MIAT	PTC	High	Sponging miR-150-5p to upregulate EZH2.	[71]

2.1. PWRN2-miR-325-DDX5 axis

The PWRN2-miR-325-DDX5 axis is crucial in regulating the development of PTC. Specifically, lncRNAs PWRN2 promotes proliferation and migration in PTC by upregulating DEAD-box helicase 5 (DDX5) through sponging miR-325. Overexpression of PWRN2 enhances proliferative and migratory potentials in PTC cells, but this effect can be partially reversed by overexpressing miR-325. The role of the PWRN2/miR-325/DDX5 axis in aggravating the development of PTC was confirmed through luciferase assays and rescue experiments [33]. Therefore, a potential therapeutic approach for PTC is to develop drugs or targeted therapies against critical molecules in the PWRN2/miR-325/DDX5 axis, such as miR-325 and DDX5, and finally inhibit PTC cell proliferation and migration. Furthermore, after carefully searching the relevant literature, it has not been found that PWRN2 is involved in the progression of other malignant tumors. Therefore, it may now be considered as a specific biomarker for PTC.

2.2. FAM230B-miR-378a-3p-WNT5A axis

FAM230B functions as a miRNA sponge to competitively protect WNT5A mRNA from degradation by miR-378a-3p. FAM230B, as a long noncoding RNA, can competitively bind to the 3′UTR region of WNT5A mRNA with miR-378a-3p to promote the metastasis of PTC. Elevating miR-378a-3p results in the degradation of WNT5A mRNA, which reduces the expression of the WNT5A protein involved in cell migration and invasion [34,35]. Hence, miR-378a-3p, WNT5A, and FAM230B exhibit potential as targets for hindering PTC metastasis in the future. Despite studies suggesting a potential association between FAM230B and the progression of gastric cancer [36] and colorectal cancer [37], it is more important to note that the FAM230B-miR-378a-3p-WNT5A regulatory axis appears to be specifically involved in PTC based on current research. Therefore, precision treatment approaches targeting this regulatory axis still hold great promise for PTC.

2.3. n384546-miR-145-5p-AKT3 axis

A novel lncRNA n384546 promotes PTC development by acting as a competing endogenous RNA of miR-145-5p to regulate v-akt murine thymoma viral oncogene homolog 3 (AKT3), which participates in the induction of proliferation, invasion, and metastasis of malignant tumors, and inhibition of apoptosis [38]. Specifically, lncRNA n384546 reduces the inhibitory effect of miR-145-5p on AKT3 by sequestering miR-145-5p, increasing AKT3 expression. This process can promote PTC cell proliferation and metastasis [39]. It is worth mentioning that current research has not indicated the involvement of lncRNA n384546 in

the progression of other malignant tumors. Therefore, it can potentially serve as a specific tumor biomarker for PTC.

2.4. NORAD-miR-451-IL-6R axis

In PTC, the NORAD-miR-451-IL-6R axis significantly impacts tumor development and progression [40]. NORAD is a lncRNA highly expressed in PTC cells and has a pro-oncogenic effect. Inhibition of NORAD can suppress tumor cell proliferation and metastasis. However, MiR-451, a microRNA, has low expression levels in PTC [41]. NORAD can inhibit the function of miR-451 through competitive binding with endogenous RNA molecules, known as the "ceRNA mechanism", which promotes the development of PTC since miR-451 inhibits tumor cell proliferation and migration [42]. IL-6R is a target gene of miR-451. When NORAD inhibits miR-451, IL-6R expression increases [43,44]. Increasing IL-6R may accelerate tumor development and increase tumors' invasion and metastasis [45]. After reviewing the relevant literature, we found that NORAD is also involved in the progression of other cancers, including breast cancer [46,47], gastric cancer [48,49], bladder cancer [50], osteosarcoma [51], hepatocellular carcinoma [52], pancreatic cancer [53] and colorectal cancer [54]. However, NORAD affects different downstream target molecules in each malignant tumor type. The NORAD-miR-451-IL-6R axis explicitly influences the progression of PTC. Therefore, we can consider targeting this regulatory axis for the precision treatment of PTC.

2.5. XIST-miR-101-3p-CLDN1 axis

lncRNA XIST is upregulated in PTC tissues and cell lines. Studies have shown that XIST can regulate the migration and invasion of PTC cells by acting as a sponge (competitive endogenous RNA) for miR-101-3p. CLDN1 (Claudin-1) is a tight junction protein, and its aberrant expression is associated with the proliferation, migration, and invasion of various cancers [55–57]. Research has revealed that CLDN1 is a target gene of miR-101-3p. XIST can upregulate the expression of CLDN1 by sponging miR-101-3p, thereby promoting the migration and invasion of PTC cells [58]. In summary, XIST plays a regulatory role in developing PTC through the miR-101-3p/CLDN1 axis. XIST is also proved to be involved in the progression of other malignant tumors through complex pathways [59–61].

2.6. NEAT1_2- miR-106b-5p- ATAD2 axis

NEAT1_2 is overexpressed in PTC tissues. In the NEAT1_2-miR-106b-5p-ATAD2 axis, NEAT1_2 upregulates the expression of ATAD2 by acting as a ceRNA to sponge miR-106b-5p. This regulatory effect promotes PTC cells' growth, invasion, and metastasis and inhibits cell apoptosis [62]. This finding reveals the important role of NEAT1_2 in the pathogenesis of PTC and provides new ideas for future therapeutic strategies targeting PTC. Meanwhile, there are studies suggesting that NEAT1_2 is associated with the sensitivity of hepatocellular carcinoma to radiation therapy [63] and also plays a role in the regulation of gastric cancer progression [64]. However, unlike its specific regulatory axis in PTC, where the mechanism is well-defined, the exact regulatory axis of NEAT1_2 in liver and gastric cancer has not yet been identified.

2.7. MIAT-miR-150-5p-EZH2 axis

The MIAT-miR-150-5p-EZH2 axis plays a significant role in the progression of PTC through molecular interactions and regulatory mechanisms. In this case, MIAT sponges miR-150-5p, which leads to the upregulation of EZH2, a critical factor in promoting tumor malignancy, invasion, and poor prognosis [65–68]. EZH2, a core component of the polycomb repressive complex 2 (PRC2), catalyzes the tri-methylation of histone 3 at lysine 27, thereby contributing to the epigenetic regulation of gene expression [69,70]. Elevated EZH2 expression is associated with various cancers, including PTC. The interaction between MIAT and mir-150-5p modulates EZH2 expression, ultimately promoting PTC tumors' development, invasion, and metastasis [71]. As a well-studied lncRNA, MIAT is currently recognized to participate in the regulation of digestive cancers, including gastric cancer [72], hepatocellular carcinoma [73], colorectal cancer [74], as well as genitourinary cancers such as ovarian cancer [75,76], breast cancer [77], cervical cancer [78], and prostate cancer [79]. The specific regulatory mechanisms of MIAT vary among different types of cancers, indicating its involvement in complex networks during cancer regulation. Thus, we suggest that targeting MIAT for future therapies or utilizing it as a cancer biomarker would yield significant benefits for various types of cancer, specifically for PTC.

3. LncRNAs impact PTC progression via EMT pathways

The impact of E-cadherin, N-cadherin, and vimentin on cancer progression is mainly related to the process of EMT [80,81]. This biological process involves cells losing their epithelial characteristics and acquiring mesenchymal properties. It is well-known that increasing the ability of cell migration and invasion can promote tumor metastasis. E-cadherin is an adhesion protein in epithelial cells that maintains tight connections between cells [82]. During EMT, E-cadherin's expression decreases, weakening intercellular connections, which makes it easier for cancer cells to detach from the primary tumor site and enter surrounding tissues or blood vessels, ultimately forming distant metastases [83,84]. N-cadherin is an adhesion protein in mesenchymal cells. When cancer cells undergo EMT, the expression of N-cadherin increases, which gives cancer cells more robust migration and invasion abilities, thereby promoting cancer progression [85–87]. Vimentin is a specific cytoskeletal protein found in mesenchymal cells. During EMT, vimentin expression increases and helps cancer cells gain higher migration ability and resistance against apoptosis Triviño López and González [88], making it easier for tumors to invade surrounding tissues and blood vessels, forming secondary tumors [89,90].

Emerging evidence has revealed a potential contribution of lncRNAs to tumor development. As shown in Table 2, we summarized the relationship between lncRNAs and EMT in PTC. Moreover, numerous studies have suggested that lncRNAs are involved in the process of EMT in PTC through a variety of pathways.

3.1. LncRNA H19-EMT

LncRNA H19 enhances the migration and invasion of PTC cells by regulating the mRNA and protein expression of E-Cadherin and vimentin, classic EMT markers. Inhibiting lncRNA H19 resulted in upregulating E-cadherin mRNA and protein levels while downregulating vimentin mRNA and protein levels [91]. These findings suggest that lncRNA H19 plays a role in PTC development through the EMT pathway. H19 is also involved in the regulation of various types of cancer through pathways other than EMT, such as colorectal cancer and lung cancer

Table 2
Summary of lncRNAs associated with EMT in PTC.

lncRNAs	Variant	Expression	Functions	References
H19	PTC	High	Facilitating the process of EMT in cells.	[91]
CASC2	PTC	Low	Inhibiting the process of EMT in cells.	[95]
ABCA1	PTC	High	Facilitating the process of EMT in cells.	[97]
LOC389641	PTC	High	Facilitating the process of EMT in cells.	[111]
DOCK9-AS2	PTC	High	Facilitating the process of EMT in cells.	[114]
MALAT1	PTC	High	Facilitating the process of EMT in cells.	[115]

[92–94]. This further illustrates that H19 can serve as an effective target for precision treatment of cancer.

3.2. LncRNA CASC2-EMT

Overexpression of lncRNA CASC2 significantly decreases mRNA and protein expression of mesenchymal cell markers zinc finger E-box binding homeobox 1(ZEB1) and N-cadherin while increasing mRNA and protein expression of epithelial cell marker E-cadherin [95]. These findings indicate that overexpressing lncRNA CASC2 impedes PTC cell invasion by impacting the EMT pathway. CASC2 plays a crucial regulatory role in human cancer and has been validated in other types of cancer as well [96].

3.3. LncRNA ABCA1-EMT

lncRNA ABCA1 regulates the extracellular signal-regulated kinase (ERK) signaling pathway [97], which is critical in various biological processes such as cell proliferation, differentiation, migration, and survival [98]. The activation of the ERK signaling pathway leads to phosphorylation and activation of Fra-1 (Fos-related antigen 1), an immediate early gene belonging to the AP-1 transcription factor family [99,100]. Fra-1 plays a crucial role in many types of cancer, including tumor occurrence, invasion, and metastasis [101–103]. After activation, Fra-1 can further regulate the transcription of ZEB1. ZEB1 is a key EMT transcription factor that promotes the EMT process by inhibiting the expression of epithelial cell-related genes such as E-cadherin while activating the expression of mesenchymal cell-related genes such as N-cadherin and Vimentin [104–109], characterized by loss of epithelial cell characteristics, acquisition of mesenchymal cell characteristics, and the enhanced ability for cellular migration and invasion which promotes tumor metastasis. ABCA1 has been shown to play a role in other types of cancer as well, but not all through the EMT pathway [110].

3.4. LncRNA LOC389641-EMT

The downregulation of lncRNA LOC389641 suppressed PTC cell proliferation, migration, and invasion abilities [111]. Moreover, Si-LOC389641(LOC389641 gene silencing) transfected cell lines showed higher E-cadherin and lower N-cadherin and vimentin expression. These results suggest that lncRNA LOC389641 may promote EMT in PTC, associated with tumor progression. In addition to PTC, research also suggests that LOC389641 can influence the progression of pancreatic cancer and lung adenocarcinoma through other pathways [112,113].

3.5. LncRNA DOCK9-AS2-EMT

lncRNA DOCK9-AS2 plays a crucial role in influencing PTC progression through EMT by a series of interconnected mechanisms. Firstly, it is upregulated in PTC tissues and cell lines and found in exosomes of PTC patients and cell lines. Furthermore, lncRNA DOCK9-AS2 upregulation promotes PTC cell proliferation, motility, EMT, and stemness, suggesting that targeting lncRNA DOCK9-AS2 could potentially hinder PTC progression. Secondly, exosomes from PTC-CSCs increase lncRNA DOCK9-AS2 levels, facilitating PTC progression both in vitro and in vivo, which implies that lncRNA DOCK9-AS2 may affect exosome-mediated communication between non-Cancer Stem Cells (CSCs) and CSCs in PTC, ultimately driving PTC progression. Thirdly, lncRNA DOCK9-AS2 positively regulates the Wnt/β-catenin pathway by increasing β-catenin levels without affecting GSK-3β and *p*-GSK-3β. Located in both the nucleus and cytoplasm of PTC cells, DOCK9-AS2 interacts with the transcription factor SP1 in the nucleus, targeting CTNNB1, and acts as a ceRNA by sequestering miR-1972 in the cytoplasm, thereby regulating CTNNB1 [114]. As a result, lncRNA DOCK9-AS2 activates the Wnt/β-catenin pathway through SP1 and miR-1972-regulated CTNNB1, leading to accelerated PTC progression. As an emerging lncRNA, DOCK9-AS2 has only been found to promote the progression of PTC so far. However, whether it plays a role in other types of cancer remains to be further studied. Whether it can serve as a specific biomarker for PTC is interesting.

3.6. LncRNA MALAT1-EMT

lncRNA MALAT1, a well-known lncRNA, has been shown to impact the progression of PTC through the EMT pathway in several ways. In normal thyroid tissue and thyroid neoplasms, MALAT1 expression increases during the progression from normal tissue to benign neoplasms and then to well-differentiated thyroid cancers, such as PTCs and follicular carcinoma (FCs). Notably, lncRNA MALAT1 expression is upregulated in PTC cells during TGF-β-induced EMT. Previous studies have demonstrated that EMT in thyroid cell lines is associated with increased cell proliferation, cell migration, tumor growth in immunodeficient mice, and the number of cancer stem cells [115]. As a result, lncRNA MALAT1 could play a vital role in cancer stem cell proliferation in thyroid tumors, thereby influencing the progression of PTC through the EMT pathway. MALAT1 can regulate multiple steps in tumor development, and its diagnostic and prognostic significance has been demonstrated in various types of cancer [116].

4. Therapeutic approaches

LncRNAs-miRNAs-protein signaling axes are shown in Fig. 2. These findings shed light on the complex molecular mechanisms underlying PTC tumorigenesis and provide valuable insights for developing novel diagnostic and therapeutic strategies for PTC. Based on the above, potential treatment options could be considered: utilize gene editing techniques (such as CRISPR-Cas) to modify ceRNAs and regulate their binding ability with miRNAs [117]. This approach enables the development of gene therapy methods that accurately control the interactions between ceRNAs and miRNA (Fig. 3). Gene therapy also involves introducing a vector encoding for a particular miRNA into cells to regulate its expression [118]. This method can increase the expression of specific miRNAs, affecting tumor biology processes (Fig. 3). Specific proteins derived from miRNA transcription can promote tumor progression, while others have the opposite effect [119–121]. Therefore, we can use miRNA inhibitors to simulate the "ceRNA" mechanism and

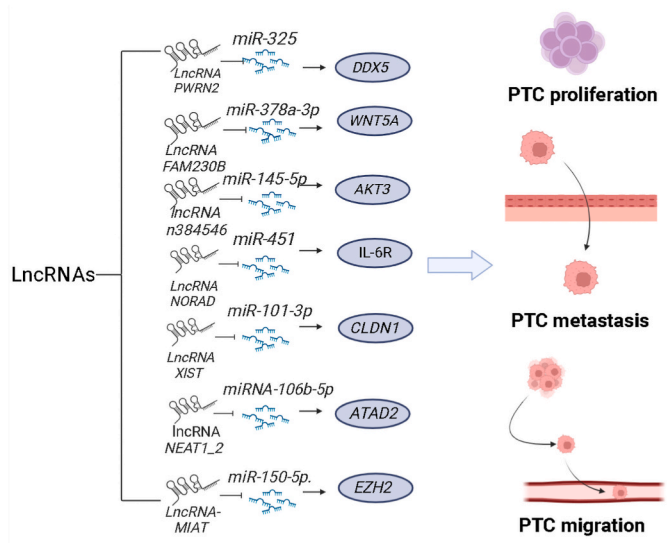

Fig. 2. Seven types of lncRNAs-miRNAs-proteins and their effects on PTC. LncRNAs competitively bind miRNAs with mRNA, resulting in the mRNAs of tumor-associated proteins not being degraded, thereby promoting the proliferation, migration, and metastasis of PTC.

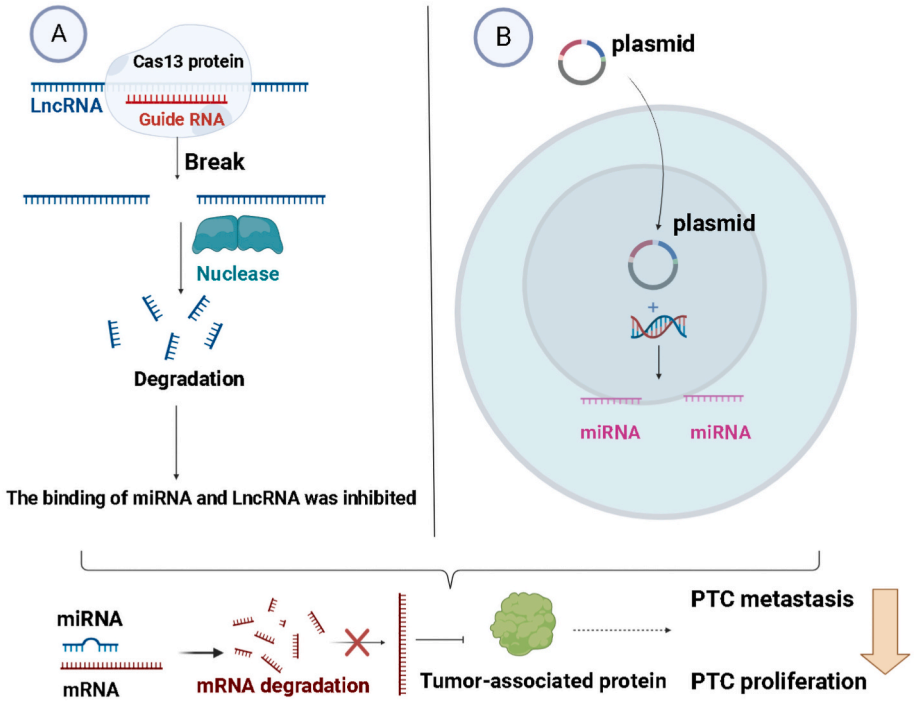

Fig. 3. LncRNA and miRNA can decrease mRNA stability or suppress its translation, further influencing the proliferation and metastasis of PTC. A. Upon recognition and binding to the target RNA through its guide RNA (gRNA), Cas13 induces site-specific cleavage of the target RNA molecule. Subsequently, the cleaved RNA fragments are typically degraded by cellular nucleases. B. Upon entry into the target cells, the viral vector introduces the miRNA sequence into the cell's genome. This miRNA sequence is recognized by the cellular transcription machinery and transcribed into miRNA.

increase the number of tumor-suppressing proteins, thereby controlling tumor progression. This approach shows promise as a potential therapeutic strategy for cancer. MiRNA inhibitors bind to miRNAs and prevent them from binding to target mRNAs, inhibiting their biological function [122], which can hinder the growth and spread of cancer cells. (Fig. 4). Furthermore, miRNA mimics are artificially synthesized molecules that mimic natural miRNAs' function [122]. Introducing them into cells can increase the activity of specific miRNAs, finally regulating gene expression related to tumors.

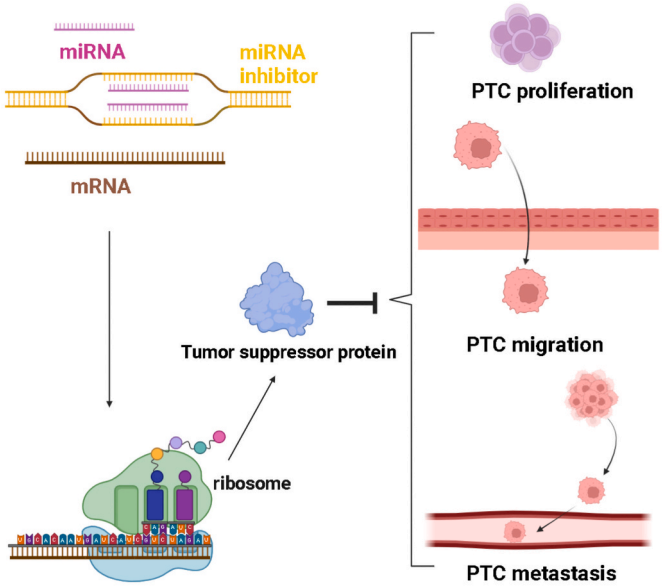

Fig. 4. miRNA regulates PTC proliferation, migration, and metastasis. miRNA inhibitors bind to particular miRNA molecules, preventing their complementary interaction with target mRNAs and restoring tumor suppressor protein. This restoration may inhibit PTC proliferation, migration, and metastasis, ultimately contributing to an anti-tumor effect.

We have also summarized the role of lncRNAs-EMT pathways in PTC progression. However, further research is required to fully understand the association between lncRNAs and EMT in PTC, which may have diagnostic and prognostic implications. Previous research indicates that lncRNAs can induce EMT through the PI3K-AKT and Wnt/β-catenin pathways, thereby promoting tumor invasion, metastasis, and prognosis. Based on the above, some potential therapeutic strategies could be considered: 1. Inhibitors targeting EMT-induced pathways: developed drugs target the vital EMT signaling pathways, such as transforming growth factor beta (TGF-β) signaling pathway [123,124], Wnt/β-catenin signaling pathway (Fig. 5), PI3K/Akt signaling pathway (Fig. 6), to prevent tumor cell invasion and metastasis [125]. 2. Targeted therapy: antibody or small molecule drugs target the specific cell surface markers on tumor cells like N-cadherin and vimentin [126,127].

5. Conclusions and perspectives

PTC, the most common type of thyroid cancer, accounts for about 80% of all thyroid cancers [128]. Although PTC generally has a good prognosis, 10% of patients suffer from local recurrence and distant metastasis. Thus, it is essential to clarify the mechanisms of PTC and identify the latent biomarkers for improving the prognosis of PTC.

Numerous pieces of evidence have identified some biomarkers that could assist in diagnosing PTC. Zhang et al. suggested that the downregulation of lncRNA DANCR could be a diagnostic biomarker for PTC [129]. Lan et al. proposed that lncRNA NONHSAT037832 has high diagnostic value in distinguishing PTC from non-cancerous diseases and identifying PTC with lymph node metastasis and larger tumors (≥3 cm) [130]. Generally, combining several biomarkers can increase the accuracy of diagnosis. For example, Kim et al. found that the combination of LRRC52-AS1, LINC02082, and UNC5B-AS1 lncRNAs accurately diagnose PTC [131]. To improve the diagnostic accuracy of PTC more conveniently and increase its clinical utility, Wu et al. identified seven

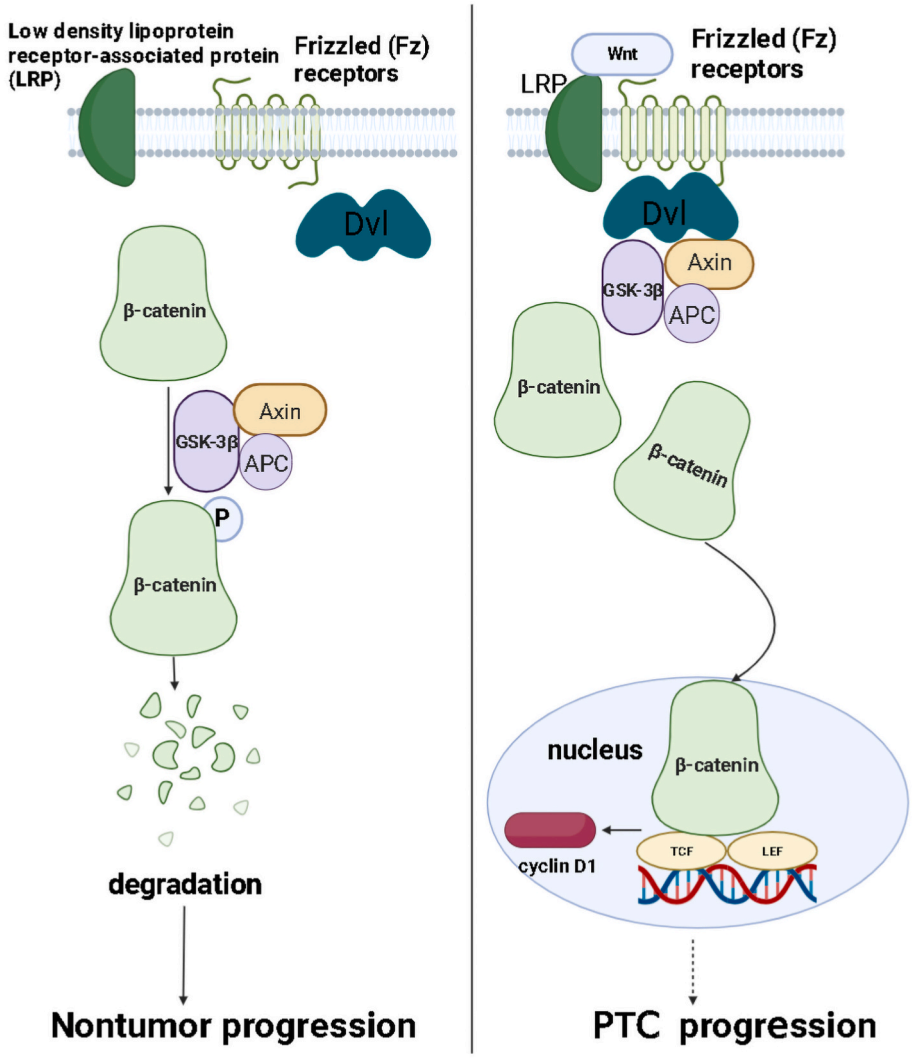

Fig. 5. The Wnt/β-catenin signaling pathway potentially contributes to PTC progress. β-catenin is phosphorylated and degraded when the Wnt signal is absent. However, upon activation of the Wnt signal by binding to Frizzled family proteins and its ligand Wnt, the protein tyrosine kinase Dishevelled (Dvl) gets activated, protecting phosphorylated β-catenin from degradation. The β-catenin then enters the nucleus through nuclear pore complexes where it binds with TCF/LEF transcription factors to promote transcription of target genes such as c-Myc and cyclin D1 involved in cellular proliferation.

downregulated circulating lncRNAs (TCONS_00516390, TCONS_00336559, TCONS_00311568, TCONS_00321917, TCONS_00336522, TCONS_00282483, and TCONS_00494326) with the ability to predict the occurrence of PTC [132]. In addition to lncRNAs, miRNAs are also considered necessary in the diagnosis and prognosis of PTC [133].

Taken together, we not only describe lncRNAs as novel candidate biomarkers for the clinical diagnosis of PTC and potential indicators for prognosis. Moreover, miRNAs have potential use as biomarkers for diagnosis, prognosis, and treatment of PTC. EMT-associated proteins can also be biomarkers to facilitate PTC diagnosis and prognostic evaluation. Specifically, we investigate lncRNA's interaction with miRNAs and EMT-associated proteins. More importantly, we can comprehensively analyze pivotal mechanisms in PTC, including lncRNAs-miRNAs-protein signaling axes and lncRNAs-EMT pathways. These signaling pathways can help understand thyroid cancer's development mechanisms better while providing new strategies for diagnosis or treatment.

In recent years, personalized treatment for patients diagnosed with solid tumors has resulted in several advancements [134]. Personalized cancer medicine can have fewer side effects than other types of therapy because it is designed to be more specific [135]. Personalized treatment may affect healthy cells less and cells involved in cancer more and improve the patient's prognosis [136,137]. As mentioned in the previous section on treatment modalities, we summarize the mechanisms of lncRNA involvement in the progression of PTC. Based on these findings, we have provided some feasible or worthy of further research strategies for clinical diagnosis and treatment. These include regulating the expression of lncRNAs targeting miRNAs in vivo and developing drugs that target EMT-related pathways. Delightfully, our findings can provide a reference for PTC patients' clinical treatment and serve as a valuable resource for clinical researchers in this field. Furthermore, developing personalized treatment plans based on PTC patient-specific information such as gene expression profiles, genetic mutations, and pathological subtypes is beneficial. Correspondingly, combining the therapeutic methods could achieve a more effective treatment outcome.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

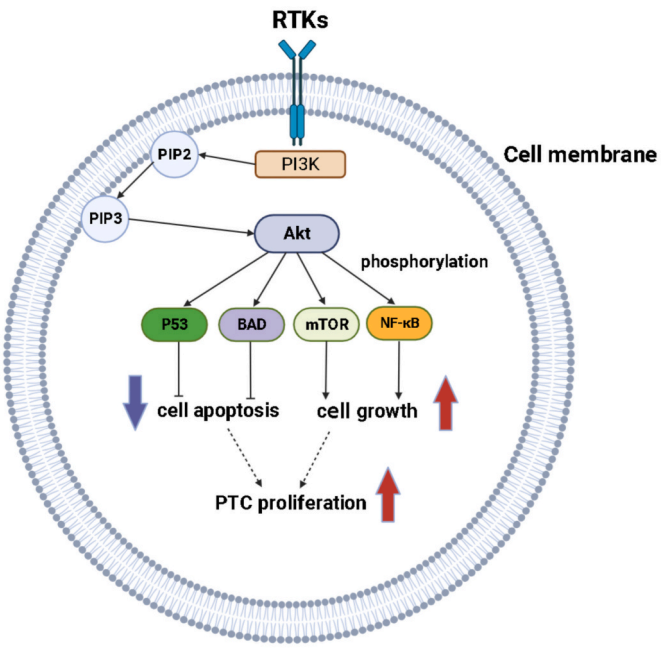

Fig. 6. The PI3K/Akt signaling pathway induces PTC proliferation. The associated protein initially binds to its cell surface receptor(receptor tyrosine kinases, RTK). RTK activates protein kinases like PI3K, a crucial signaling molecule in cellular growth, proliferation, and migration. Once activated by PI3K, Akt produces phosphatidylinositol-3,4,5-triphosphate (PIP3), a serine/threonine kinase found in cells. Akt is essential in regulating cellular processes, including cell growth, apoptosis, and proliferation through phosphorylation of downstream target proteins(p53/BAD/mTOR/NF-κB), finally promoting PTC proliferation via inhibiting apoptosis and increasing growth.

Availability of data and materials

Not applicable.

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Data availability

Data will be made available on request.

CRediT authorship contribution statement

Yuanhao Su: Writing – original draft. **Lin Mei:** Validation. **Tiantian Jiang:** Validation. **Zhidong Wang:** Writing – review & editing. **Yuanyuan Ji:** Writing – review & editing, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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