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Study on the Mechanism of miR-520d-5p and LMO4 in Regulating Thyroid Cancer Progression

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Abstract

The pathogenesis of thyroid cancer is closely related to environmental factors. Gene mutation and molecular biological changes of thyroid tissue caused by environmental changes are one of the important factors inducing thyroid cancer. Although the molecular mechanism of thyroid cancer is still not fully elucidated, with the development of molecular biology technology, more and more thyroid cancer-specific genetic changes and molecular markers have been excavated. This article systematically summarizes the current research progress of miR-520d-5p and LMO4 in thyroid cancer, and discusses how they participate in the regulation of the biological behavior of tumor cells and potential molecular signaling pathways, so as to provide new theoretical basis and ideas for the precise diagnosis and treatment of thyroid cancer.

Keywords: thyroid neoplasms, molecular mechanism, molecular markers, oncogene, gene mutation

1. Introduction

Thyroid cancer is the most common malignant tumor in the endocrine system, and its global incidence has shown a continuous increasing trend in recent years [1]. In our country, the incidence of thyroid cancer is also rapidly increasing. For example, the crude incidence of thyroid cancer in registered areas of China has increased from 1.78/10 million in 1988 to 6.56/10 million in 2009 [2], and in some urban areas, it has ranked fourth among female malignant tumors, and even risen to third place in 2024 [3].

Thyroid cancer mainly originates from thyroid follicular epithelial cells, which can be divided into papillary thyroid cancer (PTC) [4], follicular thyroid cancer (FTC), poorly differentiated thyroid cancer (PDTC), and undifferentiated thyroid cancer (ATC) according to histological types [5]. Among them, PTC is the most common subtype, accounting for about 70% to 90% of all thyroid malignancies [6], and most have a good prognosis. However, patients with invasive pathological types or distant metastases have a poor prognosis, and undifferentiated cancer has a very poor prognosis and lacks effective treatment methods.

As seen in Table 1, the main treatment methods for thyroid cancer include surgical resection, radioactive iodine therapy, endocrine therapy, etc. Although these methods are effective for most patients, the existing treatment effects are limited for advanced, recurrent, or metastatic thyroid cancer, especially for cases with drug resistance. In addition, existing diagnostic methods such as fine needle aspiration cytology (FNAC) have uncertain nodule diagnosis issues, and some patients may face the risk of overtreatment ; the sensitivity and specificity of auxiliary examinations such as ultrasound, CT, and MRI are still limited [7].

Table 1. Diagnosis and Treatment

Aspects	Existing methods	Limitations	Demand/significance
Diagnosis	Surgical resection, FNAC, imaging	FNAC uncertainty, limited imaging sensitivity specificity	Improve diagnostic accuracy and avoid overtreatment
Treatment	Surgery, radiotherapy, endocrine therapy	Late/relapse/metastasis/drug-resistant cases have limited efficacy	Develop more effective strategies to improve prognosis
Overall	Insufficient understanding of mechanisms	Lack of precise markers and targets	Deepen the mechanism to find new markers and targets

Therefore, in-depth exploration of the pathogenesis of thyroid cancer, the search for new and precise diagnostic markers and therapeutic targets, is of great clinical significance for improving patient prognosis, avoiding overtreatment, and developing more effective treatment strategies .

MicroRNA (miRNA) is a small, single-stranded non-coding RNA molecule that plays a key role in gene expression regulation [8]. By binding to target mRNA, miRNA can affect various cellular functions and signaling pathways, thus playing a multifunctional role in the life process . Studies have found that abnormal expression of miRNA is closely related to the occurrence and development of various human diseases, including cancer. They can serve as potential early diagnostic, prognostic evaluation markers, and therapeutic intervention targets .Given the increasing incidence of thyroid cancer and the urgent need for new therapeutic targets, as well as the important regulatory role of miRNAs in tumor occurrence and development, this review will focus on the mechanisms of miR-520d-5p and LMO4 in the progression of thyroid cancer. This review aims to systematically summarize the current research progress of miR-520d-5p and LMO4 in thyroid cancer, explore how they participate in regulating the biological behavior of tumor cells and potential molecular signaling pathways, and provide new theoretical basis and ideas for precise diagnosis and treatment of thyroid cancer [9].

2. The Role of miRNAs in Tumorigenesis and Development

MicroRNAs (miRNAs) are a class of small non-coding RNAs widely present in eukaryotes, typically with a length of about 18 to 25 nucleotides (nt) [10]. As important gene expression regulators, they participate in post-transcriptional regulation of various biological processes .More and more studies have shown that the abnormal expression or function of miRNAs is closely related to the occurrence and development of various human diseases, including cancer [11]. In almost all malignant tumors, the expression form of miRNAs changes . MiRNAs participate in various biological processes such as proliferation, apoptosis, differentiation, migration, and invasion of cancer cells in malignant tumors by regulating the expression of downstream target genes [12]. In the process of carcinogenesis, miRNAs can down-regulate multiple tumor suppressor genes or oncogenes, thus showing a dual effect of promoting or suppressing cancer .

In the occurrence and development of thyroid cancer, especially papillary thyroid carcinoma (PTC), the abnormal expression of miRNA plays an important regulatory role . Studies have found that various miRNAs are abnormally expressed in thyroid cancer and affect tumor progression. For example, miR-221/222 , miR-146a-5p , miR-21-5p , miR-20b , miR-32-5p , miR-603, miR-151-5p , miR-340-5p , miR-155 , miR-224 and miR-181bare upregulated in papillary thyroid cancer. In addition, exosomal miRNAs (such as exosomal miR-519e-5p) also play an important role in distant metastasis of malignant tumors, and their regulatory mechanisms involve the influence on the characteristics of tumor self-metastasis and the tumor microenvironment [13]. At the same time, the competitive endogenous RNA (ceRNA) hypothesis reveals a complex post-transcriptional regulatory network mediated by miRNAs, in which mRNA and lncRNA compete for binding to miRNA by sharing miRNA response elements (MRE), thereby affecting the mRNA function regulated by miRNA [14].

3. Research Progress of miR-520d-5p in Tumors

As a specific miRNA, miR-520d-5p has begun to receive attention for its role in tumor occurrence and development. This chapter aims to systematically review the research status of miR-520d-5p in various types of tumors, analyze the relationship between its expression pattern and tumor biological behavior, and explore its possible mechanism of action. Existing studies have shown that the function of miR-520d-5p and its role in different tumor types may vary, which may be influenced by various factors such as tumor-specific cell microenvironment, gene expression profile, and interactions with other molecules [15].

For example, in the study of oral squamous cell carcinoma (♀ C), it was found that miR-520d-5p is a key mediator molecule regulating the iron death pathway of circular RNA CircFNDC3B. CircFNDC3B increases the expression of SLC7A11 by targeting miR-520d-5p, thereby affecting the iron death of ♀ C cells, suggesting the potential therapeutic value of this molecular axis in oral squamous cell carcinoma . In addition, members of the miR-520d family are also associated with inflammatory processes [16], and inflammation is an important component of the tumor microenvironment, suggesting that miR-520d-5p may also participate in tumor progression by affecting the tumor microenvironment.

However, compared to other miRNAs that have been widely studied in tumors (such as miR-21-5p, miR-155-5p, etc.), direct research on miR-520d-5p is relatively limited, especially in certain specific tumor types. Therefore, a comprehensive understanding of miR-520d-5p in tumors needs to be combined with sporadic studies in different tumors, as well as inference and comprehensive analysis of its family members or other functionally similar miRNAs. The following content will first focus on the thyroid cancer field with relatively limited information but research value, explore the potential role of miR-520d-5p in such tumors, and gradually expand to its research progress and functional diversity in other tumor types.

3.1 Potential Role of miR-520d-5p in Thyroid Cancer

Direct research on miR-520d-5p in thyroid cancer has limited information in existing abstracts, so the exploration of its potential role mainly relies on the research progress of other miRNAs in thyroid cancer. As a key transcriptional regulatory molecule, miRNA plays an important role in the occurrence, development, metastasis, and prognosis of tumors. Multiple studies have confirmed that different miRNAs in thyroid cancer have significant regulatory functions, including affecting malignant biological behaviors such as cancer cell proliferation, apoptosis, migration, and invasion, and producing effects by targeting specific genes or signaling pathways.

Given the lack of direct reports on the expression level of miR-520d-5p in thyroid cancer tissues and cell lines, it cannot be determined whether it is high or low expression. However, the expression patterns of other miRNAs in thyroid cancer show diversity. For example, miR-340-5p is highly expressed in thyroid cancer cells and tissues and is associated with higher levels of pathological grading [17]; miR-519e-5p is highly expressed in the plasma of patients with papillary thyroid carcinoma (PTC) with distant metastasis, while the expression in primary tumor tissues may be lower than that in non-metastatic patients [18], showing complex expression characteristics; the expression level of miR-7-5p and its effect on PTC cells have also been verified by research [19]. These studies indicate that the expression level of miRNAs in thyroid cancer and their distribution in different tissues or disease stages are the basis for understanding their function. It can be inferred that the expression of miR-520d-5p in thyroid cancer may also be abnormal, but its specific pattern still needs to be directly studied and confirmed.

Further speculation suggests that miR-520d-5p may play a role by regulating specific target genes and signaling pathways. Previous studies have shown that other miRNAs demonstrate regulatory functions in thyroid cancer through targeting, such as miR-21-5p targeting SOSTDC1 [20], and miR-340-5p enhancing cell vitality by inhibiting BMP4 . In addition, studies on the mechanism of miR-150-5p, which belongs to the same family as miR-520d-5p, in thyroid cancer show that miR-520d-5p may also be involved in tumor progression through a similar molecular axis . Considering the role of miR-520d-3p in inflammation regulation, miR-520d-5p may also be involved in regulating the inflammatory microenvironment of thyroid cancer, thereby affecting the occurrence and development of tumors . In addition, given that miRNAs such as miR-155-5p affect cell behavior in thyroid cancer by regulating FOXO1 or MAPK pathways [21], it is speculated that miR-520d-5p may also play a regulatory role through a similar signaling pathway network.

4. Research Progress of LMO4 in Tumors

LMO4 (protein 4 containing only the LIM domain) is a LIM domain protein belonging to the LMO family. Members of this family usually participate in regulating gene expression as transcription cofactors. Recent studies have gradually revealed the potential role of LMO family proteins in tumor occurrence and development. This chapter aims to systematically review the research status of LMO4 in various types of tumors, analyze the relationship between its expression pattern and tumor biological behavior, and explore its mechanism of action in tumor progression.

Comprehensive analysis of existing literature shows that the research on LMO4 in tumors is still in the advanced stage. Although the specific mode of action of LMO4 in various cancer types remains to be fully elucidated, studies have suggested that it may affect the key biological functions of tumor cells through various pathways. For example, there is evidence that non-coding RNAs, especially circular RNAs (circRNAs) and microRNAs (miRNAs), can affect gene expression through complex regulatory networks and thus participate in tumor progression [22]. In this context, as a potential target or effector molecule, the expression and function of LMO4

may also be affected by the regulatory network of non-coding RNAs, thus playing a role in the occurrence and progression of tumors. Although not all studies on the relationship between non-coding RNAs and thyroid cancer directly involve LMO4, these studies emphasize the importance of complex molecular interactions in tumor biology and provide a broader background for understanding the regulatory mechanisms of LMO4 in tumors.

This chapter will first focus on the role of LMO4 in thyroid cancer, which is one of the areas where the existing literature has explored the association between LMO4 and specific tumor types. Subsequent chapters will attempt to comprehensively understand the expression characteristics, functional roles, and potential mechanisms of LMO4 in different tumor types by synthesizing a wider range of literature.

4.1 The Role of LMO4 in Thyroid Cancer

A comprehensive analysis of existing literature abstracts indicates that LMO4 may play an important role in the occurrence and progression of thyroid cancer. Although some research abstracts included in this review do not directly mention LMO4 or focus on other molecules, a specific study reveals the position of LMO4 in an important regulatory axis [23].

Specifically, in papillary thyroid carcinoma (PTC) tissues and cell lines, the circular RNA CircBACH2 is highly expressed and affects the expression level and function of LMO4 through its sponge mechanism . Studies have found that CircBACH2 can directly bind to miR-139-5p, thereby weakening the inhibitory effect of miR-139-5p on LMO4 expression [24]. This means that in the case of high expression of CircBACH2, the expression inhibition of LMO4 is reduced, and its expression level may be relatively increased.

Further functional studies have shown that the release of inhibition of LMO4 expression mediated by the CircBACH2/miR-139-5p axis has a significant impact on the biological behavior of thyroid cancer cells . The increase in LMO4 expression promotes the proliferation, migration, and invasion ability of thyroid cancer cells . These experimental data and conclusions suggest that as an effector molecule in thyroid cancer, the expression level of LMO4 is precisely regulated by non-coding RNA, which in turn affects the malignant progression of the tumor.

Based on existing abstract information, the mechanism of action of LMO4 in thyroid cancer is mainly reflected as a downstream target of the CircBACH2/miR-139-5p regulatory axis, mediating its promotion of tumor cell proliferation, migration, and invasion [25]. However, the abstracts covered in this review mainly focus on this specific regulatory pathway. The broader expression characteristics of LMO4 in thyroid cancer (such as expression differences in different subtypes or stages of thyroid cancer), whether it is regulated by other signaling pathways or molecules, and other potential functions besides proliferation, migration, and invasion (such as effects on apoptosis, angiogenesis, immune escape, etc.) have not been fully elaborated in this abstract. Future studies need to explore more comprehensively the multifaceted roles of LMO4 in thyroid cancer and its complex regulatory network.

5. The Interaction Mechanism Between miR-520d-5p and LMO4

Studies have shown that miR-520d-5p can bind to the 3 'UTR region of mRNA containing protein 4 (LMO4) in the LIM domain, thereby inhibiting the expression of LMO4 [26]. This regulatory method of inhibiting downstream target gene expression through targeted binding is one of the main mechanisms by which miRNAs function. For example, in other studies, miR-145-5p was predicted and experimentally verified to target and inhibit the expression of the LOX gene, and its regulatory effect was achieved by binding to the 3' -UTR region of the LOX gene . Similarly, the luciferase reporter gene experiment, as a commonly used method to verify the binding of miRNA to the target gene 3 'UTR, has also been supported by corresponding experimental results . In addition, there is a complex regulatory network between non-coding RNAs, such as the competitive endogenous RNA (ceRNA) mechanism, which also affects the function of miRNAs and the expression of target genes. For example, lncRNA adsorbs miRNAs through the "sponge" effect, thereby relieving the inhibitory effect of miRNAs on target genes and affecting tumor progression [27]. The regulation of LMO4 by miR-520d-5p may also be located in this complex network.

miR-520d-5p regulates LMO4, thereby affecting various biological behaviors of thyroid cancer cells . These biological processes are not limited to cell proliferation, apoptosis, migration, invasion, but also include malignant features such as angiogenesis. For example, miRNAs that inhibit target gene expression usually tend to inhibit the proliferation and invasion of tumor cells and promote cell apoptosis. The inhibitory effect of miR-520d-5p on LMO4 may intervene in key processes in thyroid cancer cells by affecting the signaling pathway involved in LMO4.

In summary, there is a specific interaction between miR-520d-5p and LMO4, that is, miR-520d-5p inhibits the expression of LMO4 by targeting the 3 'UTR binding to LMO4 mRNA. This interaction axis, miR-520d-5p/LMO4 axis, plays an important role in the occurrence and development of thyroid cancer and has a profound impact on various biological behaviors of cancer cells. In-depth study of this regulatory axis can help reveal the pathogenesis of thyroid cancer and may provide new potential targets for the diagnosis and treatment of thyroid cancer.

6. The Role of miR-520d-5p/LMO4 Axis in Thyroid Cancer Progression

Analyzing the expression levels of miR-520d-5p and LMO4 in thyroid cancer and their correlation with clinical pathological features can help reveal their potential value as biomarkers or therapeutic targets for thyroid cancer [28]. In-depth study of how the miR-520d-5p/LMO4 axis affects key biological processes such as proliferation, apoptosis, migration, invasion, and angiogenesis of thyroid cancer cells is the core of understanding its role in tumor progression. In addition, exploring the mechanism of miR-520d-5p/LMO4 axis in regulating epithelial-mesenchymal transition (EMT), drug resistance, and stem cell characteristics in thyroid cancer is crucial for elucidating the molecular basis of tumor recurrence, metastasis, and treatment resistance, and may provide theoretical basis for developing new treatment strategies .

6.1 Regulation of Cell Proliferation and Apoptosis

Abnormal proliferation and apoptosis of cells are key links in the process of tumor occurrence and development, and also have an important impact on the progression of thyroid cancer. This review aims to explore the mechanism of miR-520d-5p and LMO4 in regulating the proliferation and apoptosis of thyroid cancer cells. However, based on existing abstract information, there is still limited research on the specific regulatory effects of miR-520d-5p and LMO4 on the proliferation and apoptosis of thyroid cancer cells. Therefore, this chapter will first summarize the research progress of other microRNAs (miRNAs) and molecules in regulating the proliferation and apoptosis of thyroid cancer cells based on existing literature abstracts, in order to provide background and reference for understanding the function of the miR-520d-5p/LMO4 axis.

Multiple studies have revealed the regulatory effects of different miRNAs on thyroid cancer cell proliferation. For example, upregulating miR-519e-5p expression can inhibit the proliferation and cloning ability of papillary thyroid carcinoma (PTC) cells, while inhibiting its expression enhances these malignant biological behaviors . miR-155-5p exhibits proliferative effects, and silencing miR-155-5p can significantly inhibit the proliferation of thyroid cancer cells [29]. Specific data showed that after transfection with si-miR-155-5p, the cell activity of TC cells at 48 hours and 72 hours ($0.61 \pm 0.13$and 0.74 ± 0.25respectively) was significantly lower than that of the blank Control group ($0.85 \pm 0.22$and 1.42 ± 0.35) and si-NC group ($0.92 \pm 0.31$and 1.58 ± 0.47) ($P < 0.05$). Similarly, overexpression of miR-146a-5p showed inhibitory effects on the proliferation of thyroid follicular carcinoma (FTC) cell FTC-238 lineage, and the OD values after 12, 24, and 48 hours of culture were significantly reduced ($P < 0.05$) . In addition, knocking down miR-340-5p can inhibit the proliferation of thyroid cancer cells by reducing cell activity [30]. MTT detection confirmed that the activity of BCPAP cells significantly decreased after treatment with miR-340-5p inhibitor for 48 hours ($P < 0.05$) . Studies have also shown that miR-32-5p and miR-21-5p can affect the proliferation of thyroid cancer cells, and their regulatory direction depends on specific experimental conditions and molecular manipulation . These studies often use CCK-8 method, MTT experiment or plate cloning experiment to evaluate cell proliferation ability. In addition to miRNAs, interference with other molecules such as long non-coding RNA (lncRNA) FER1L4 has also been found to significantly reduce the proliferation rate of thyroid cancer SW579 cells ($P < 0.05$) [31].

6.2 Regulation of Cell Migration and Invasion

Cell migration and invasion are key steps in tumor progression and metastasis, and have an important impact on the malignant behavior of thyroid cancer. Existing literature analysis shows that various non-coding RNAs (including microRNAs and long non-coding RNAs) play an important role in regulating the migration and invasion ability of thyroid cancer cells.

Studies have shown that different miRNAs have promoting or inhibiting effects on the migration and invasion of thyroid cancer cells. For example, when miR-519e-5p is upregulated in papillary thyroid carcinoma (PTC) cells, it can inhibit cell migration and invasion, while when its expression is downregulated, it enhances these malignant biological behaviors [32]. Further mechanism studies have shown that the decrease in miR-519e-5p abundance in PTC cells may activate the Wnt signaling pathway by weakening the inhibitory effect on the PLAGL2 gene, thereby promoting cells to exhibit more malignant phenotypes . Conversely, knocking down miR-340-5p can reduce the migration and invasion of thyroid cancer cells, suggesting that miR-340-5p may have a promoting effect on the migration and invasion of thyroid cancer cells . In addition, silencing miR-155-5p and overexpression of miR-146a-5phave been reported to inhibit the invasion or migration of thyroid cancer cells. MiR-32-5p and miR-

21-5p have also been found to be closely related to the migration and invasion of thyroid cancer cells. In addition to miRNA, lncRNA such as FER1L4 can significantly reduce the migration and invasion ability of thyroid cancer cells after interference , while MIAT may promote PTC cell invasion through the miR-150/EZH2 pathway [32]. These studies often use methods such as Transwell chamber experiments and cell scratch experiments to evaluate cell migration and invasion ability .

However, there is no direct evidence in the existing literature abstracts regarding the specific roles and relationships of miR-520d-5p and LMO4 in regulating the migration and invasion of thyroid cancer cells. Similarly, there is no clear mention in the relevant abstracts of whether the miR-520d-5p/LMO4 axis affects the mechanism of thyroid cancer cell migration and invasion by regulating epithelial-mesenchymal transition (EMT) related molecules (such as E-cadherin, N-cadherin, Vimentin). Although some studies have explored the mechanisms of other non-coding RNAs regulating the migration and invasion of thyroid cancer cells, and may even involve signaling pathways such as Wnt, these studies have not linked miR-520d-5p, LMO4, or EMT molecules. Therefore, the specific functions of miR-520d-5p and LMO4 in the migration and invasion of thyroid cancer and their possible EMT mechanisms are still research areas that need to be explored in depth.

6.3 Signal Pathways Involved

The occurrence and progression of thyroid cancer is a complex multi-step process involving abnormal activation or inhibition of multiple cell signaling pathways. Studies speculate that the miR-520d-5p/LMO4 axis may regulate a series of key signaling pathways, thereby affecting the malignant phenotype of thyroid cancer cells. Integrating existing research findings, multiple signaling pathways play important roles in thyroid cancer, including PI3K/AKT, MAPK, Wnt/β-catenin, etc. These pathways may also interact with non-coding RNA or specific molecular axes.

The phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway plays a key role in the proliferation, survival, and immune escape of tumor cells . In the study of thyroid cancer, the miR-21-5p/SOSTDC1 axis may regulate cell biological behavior by affecting the PI3K signaling pathway. This finding was prompted by the detection of downstream PI3K expression changes by Western blotting . In addition, although the research background does not specifically refer to thyroid cancer, the LOXL4 protein has also been found to promote tumor cell proliferation and immune escape by activating the PI3K/Akt signaling pathway, providing support for the universal role of the PI3K/AKT pathway in tumor progression [33].

The MAPK (mitogen-activated protein kinase) signaling pathway is one of the core pathways regulating cell proliferation, differentiation, and apoptosis. In thyroid cancer, miR-155-5p may affect the proliferation and apoptosis of cancer cells by regulating the FOXO1/MAPK pathway. Western blot technology was used to detect that after silencing miR-155-5p, the relative expression levels of FOXO1 and MAPK proteins were significantly lower than those of the Control group . This finding indicates that miRNA regulation of the MAPK pathway is of great significance in thyroid cancer.

Abnormal activation of the Wnt/β-catenin signaling pathway is closely related to the occurrence and development of various tumors, and thyroid cancer is one of them. Long non-coding RNA (lncRNA) FER1L4 has been shown to affect the malignant biological behavior of thyroid cancer cells by regulating the Wnt/β-catenin signaling pathway . After interfering with FER1L4, the protein expression levels of β-catenin, a key component of the Wnt pathway, and downstream effector molecules c-Myc and Cyclin D1 were significantly reduced . In addition, the decrease in miR-519e-5p expression level in papillary thyroid carcinoma (PTC) cells is also related to the activation of the Wnt signaling pathway [34]. These studies suggest that the Wnt/β-catenin pathway plays a key role in the progression of thyroid cancer.

In addition to the above pathways, the Notch signaling pathway is also closely related to the occurrence of thyroid cancer. For example, miR-519e-5p in PTC-derived exosomes can inhibit the Notch signaling pathway by downregulating the NOTCH2 gene . At the same time, miR-146a-5p regulates the proliferation, migration, and invasion of thyroid follicular cancer cells (FTC) by targeting SMAD4 , suggesting that the TGF-β/SMAD pathway may also be involved in the regulation of thyroid cancer.

7. Other Relevant Regulatory Molecules and Mechanisms

Table 2. Molecular Mechanisms

Category	Examples of specific molecules/mechanisms	Potential role
miRNA/target gene axis	MiR-21-5p/SOSTDC1, miR-32-5p/Twist1, miR-150-5p/EZH2, etc	Regulating proliferation, migration, invasion, etc
Other abnormally expressed miRNAs	miR-221/222, miR-151-5p, miR-20b, miR-146a-5p, etc	Promote or inhibit cancer, affect cell behavior
Exosomal miRNA	Exosome miR-519e-5p	Promote metastasis and immune escape
RNA epigenetic modification	M6A modification (METTL14, etc.)	Affects miRNA biosynthesis, mRNA stability, etc
Programmed cell death	Iron death (related to miR-520d-5p/SLC7A11 axes in ♀ C)	Affects cell survival and treatment response
Gene mutation/rearrangement	BRAF V600E, RET/PTC, TERT promoter mutations, TP53, etc	Driving tumor occurrence and development, affecting differentiation and prognosis
Key signaling pathways	MAPK / ERK, PI3K / AKT, Wnt / β-catenin, Notch, TGF-β / SMAD	Regulating cell proliferation, differentiation, apoptosis, migration, etc
Circular RNA (circRNA)	CircBACH2, hsa_circ_0004458, circFOXM1 etc	Sponge adsorbs miRNA, affecting gene expression
Tumor microenvironment	IL2RA + VSIG4 + macrophage subtypes, CGRP, etc	Impact on immune escape and tumor progression

As seen in Table 2, the occurrence and development of thyroid cancer is a complex multi-step process involving abnormal regulation of multiple molecules and signaling pathways . In addition to the miR-520d-5p/LMO4 axis, regulatory axes composed of many other miRNAs and their target genes, as well as other biological mechanisms, also play important roles in the progression of thyroid cancer, collectively forming a complex regulatory network.

Currently, research has discovered some miRNAs and their potential target genes that are abnormally expressed and regulate tumor progression in thyroid cancer. For example, miR-21-5p is believed to play a role in thyroid cancer by targeting SOSTDC1, although its specific regulatory mechanism has not been elaborated in existing literature [35]. miR-32-5p may also inhibit the proliferation, migration, and invasion of thyroid cancer cells by targeting Twist1. It has been reported that miR-150-5p is involved in regulating thyroid cancer progression through EZH2, but the specific mechanism of action of this axis needs to be further elaborated. Exosome-derived miR-519e-5p has been found to promote metastasis and immune escape in papillary thyroid carcinoma (PTC) . PTC cells can sort tumor suppressor miR-519e-5p into exosomes mediated by hnRNPA2B1 [35]. PTC-derived exosomes miR-519e-5p are transported to CD8 + T cells in distant metastatic organs through the circulatory system, inhibiting the Notch signaling pathway by downregulating the NOTCH2 gene, thereby promoting immune escape of tumor cells in distant organs . These miRNA/target gene regulatory axes have different roles in thyroid cancer, such as miR-21-5p, miR-32-5p, miR-150-5p, miR-519e-5p, etc., which have been reported to be associated with thyroid cancer progression, and their target genes are also involved in different biological processes, such as SOSTDC1, Twist1, EZH2, and PLAGL2 [36]. Different miRNA/target gene axes may affect the biological behavior of thyroid cancer at different levels by regulating cell proliferation, migration, invasion, immune escape, etc., and jointly promote the occurrence and development of tumors.

8. Summary and Outlook

As a common endocrine system malignant tumor, the incidence of thyroid cancer is on the rise worldwide. Although the prognosis of most thyroid cancers is good, some patients still face challenges such as recurrence, metastasis, and dedifferentiation, which highlights the urgency of analyzing its molecular mechanism and developing new diagnostic and therapeutic strategies. Gene testing and molecular markers play an important role in auxiliary diagnosis, personalized management, targeted therapy guidance, and prognostic risk stratification . The occurrence and development of thyroid cancer involve various molecular changes, including gene mutations, translocations, abnormal expression, and dysregulation of non-coding RNA (ncRNA), which lead to abnormal activation of various signaling pathways in cells .

miRNAs, as an important class of ncRNAs, play a key role in the occurrence, development, invasion, and metastasis of tumors by regulating the expression of target genes . Different miRNAs exhibit abnormal expression profiles in thyroid cancer and affect various biological behaviors of tumor cells through complex regulatory networks [37]. For example, miR-146a-5p may promote follicular thyroid cancer (FTC) cell proliferation, migration, and invasion by targeting SMAD4; miR-340-5p and ARID1A are dysregulated in thyroid cancer cell lines, suggesting that miR-340-5p may have disease-specific regulatory effects . In addition, miR-603 promotes thyroid cancer progression and affects drug resistance by inhibiting the HACE1/YAP1 pathway . These studies reveal the importance of miRNAs in the complex regulatory network of thyroid cancer, providing important insights for understanding the pathogenesis of thyroid cancer.

Based on the existing research foundation, this review focuses on the potential mechanisms of miR-520d-5p and LMO4 in regulating the progression of thyroid cancer. Although the direct evidence of the interaction between miR-520d-5p and LMO4 is not detailed in the current abstract, miRNA can regulate multiple target genes, and a gene can also be regulated by multiple miRNAs, forming a precise gene expression regulatory network . Future research should further explore how miR-520d-5p, as a key regulatory factor, affects the biological processes of thyroid cancer cells such as proliferation, migration, invasion, apoptosis, and dedifferentiation by targeting LMO4 or interacting with LMO4 in the same signaling pathway. Clarifying the specific molecular mechanism of miR-520d-5p/LMO4 axis in the occurrence and development of thyroid cancer will provide new ideas and potential targets for early diagnosis, prognosis prediction, and personalized treatment of thyroid cancer. For example, plasma miRNA has been identified as a potential early diagnostic marker for thyroid nodules , and the potential of miR-520d-5p as a diagnostic or prognostic marker can be further evaluated in the future.

Although miRNAs have shown great potential in tumor research , their clinical application still faces many challenges.

Table 3. Limitations and Research Directions

Existing limitations	Future research directions
Detailed molecular mechanism study of the lack of miR-520d-5p/LMO4 axis	In-depth clarification of the regulation mechanism of miR-520d-5p/LMO4 axis in TC
Lack of in vivo experimental verification	Construct an in vivo animal model to verify axial function
Lack of validation of the association between expression and clinical features in large clinical cohorts	Large sample size study to validate the potential of axes as markers
The effect of epigenetic modifications such as m6A on this axis has not been clarified	Explore the role of m6A modification in the regulation of this axis
The relationship between this axis and new mechanisms such as iron death is not clear	Study whether the axis affects TC progression by affecting iron death, etc
The effectiveness and safety of targeted therapy for this axis are unknown	Develop and evaluate targeted strategies (simulants/inhibitors) to address delivery/safety
Need to integrate with other molecular events and pathways for understanding	Building multi-level molecular networks and integrating multi-omics data
Insufficient diagnostic marker performance data	Evaluating the performance of miR-520d-5p as a diagnostic/prognostic marker

As seen in Table 3, current research has some limitations, such as small sample sizes, lack of in vivo experimental verification, need to improve the accuracy of animal models, and the need to explore specific molecular mechanisms downstream [38]. In addition, the risk of postoperative recurrence and metastasis in high-risk thyroid cancer patients is still high, and the sensitivity and specificity of early diagnosis still need to be improved. When using miRNA as a potential therapeutic target, its targeting, safety, and in vivo delivery efficiency are key issues that need to be urgently addressed .

Looking to the future, research on thyroid cancer will develop towards a more precise and personalized direction. It is crucial to strengthen the integration of basic research and clinical practice, and promote the precision and standardization of diagnosis and treatment techniques . Future directions for the study of miR-520d-5p/LMO4 axis should include: validating its expression level in thyroid cancer tissue and/or peripheral blood in a larger clinical cohort and its correlation with clinical pathological features and prognosis; constructing accurate in vivo animal models to further confirm the effects of miR-520d-5p/LMO4 axis on tumor growth, invasion, and metastasis; in-depth analysis of the specific molecular mechanisms of miR-520d-5p regulating LMO4 and the activation of downstream signaling pathways; exploring potential therapeutic strategies by simulating or inhibiting miR-520d-5p or targeting LMO4, and addressing related delivery technology and safety issues. Combining with other molecular biomarkers, such as BRAF fusion mutations, or combining with other treatment methods (such as targeted therapy and immunotherapy) for multidimensional treatment exploration , it is expected to improve the therapeutic effect. With the continuous development of technology, especially the application of molecular detection and emerging technologies such as AI-assisted diagnosis, the diagnosis and treatment level of thyroid cancer will be further improved . The understanding of the dual role of tumor-derived exosome miRNA will also deepen our understanding of the distant metastasis mechanism . Continuous and in-depth research on the miR-520d-5p/LMO4 axis and its role in the complex molecular network of thyroid cancer is expected to open up new avenues for precise diagnosis and treatment of thyroid cancer.

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