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REVIEW ARTICLE

Exploring the Dual Role of MALAT1 in Thyroid Tumorigenesis: Oncogenic or Tumor Suppressor?

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Abstract: Thyroid cancer is the most prevalent form of endocrine cancer. Therefore, the administration of new therapeutic agents for thyroid cancer patients is necessary. One of the recent successes in thyroid cancer research is the identification of the role of signaling pathways in the pathogenesis of the disease. Emerging evidence reveals that long non-coding RNAs (lncRNAs) can serve as novel therapeutic approaches for the diagnosis and treatment of thyroid cancer. The lncRNA metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) plays key roles in gene expression, RNA processing, and epigenetic regulation. It is believed that MALAT1 can regulate several cancer-related processes, including tumour cell growth, proliferation, and metastasis. MALAT1 is involved in the pathogenesis of thzroid cancers by targeting multiple downstream targets and miRNA/mRNA axes. Here, we summarize the emerging roles of MALAT1 in this cancer.

Keywords: Thyroid cancer; Long non-coding RNAs; MALAT1; miRNAs; mRNAs.

1. INTRODUCTION

In the contemporary medical landscape, thyroid cancer stands as the most common form of endocrine cancer [1]. Histologically, it is classified into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), both of which are well-differentiated, as well as poorly differentiated carcinoma (PDC) and anaplastic thyroid carcinoma (ATC) [2]. According to statistics, thyroid cancer affects approximately 586,000 individuals and results in about 43,600 fatalities each year, making it the ninth most prevalent malignancy and the most common endocrine cancer [3]. Over the past 30 years, the incidence of thyroid cancer has increased in several developed countries, albeit to varying degrees across different population groups [3, 4]. Despite this rise, the fatality rate has remained low and stable, with declines observed in many developing and developed nations [5]. Various factors can elevate the risk of developing thyroid cancer, including female gender, age between 40 and 70, a family history of thyroid cancer among first-degree relatives, obesity, exposure to ionizing radiation, cold weather, use of levothyroxine, pregnancy, pre-existing thyroid diseases, diabetes, hormonal characteristics, and nutritional factors such as iodine intake [6, 7].

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides and play crucial roles in

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various biological functions, including cell cycle regulation, differentiation, development, and pluripotency. Numerous studies have highlighted the significance of lncRNAs in these processes [8]. One extensively studied lncRNA, MALAT1, is located on the forward strand of chromosome 11q13.1 and spans 8.75 kb [9]. Also known as NEAT2, LINC00047, and PRO2853, MALAT1 has been associated with tumorigenesis, metastasis, prediction, and diagnosis [10]. It is highly conserved and frequently upregulated in various solid tumours, with its differential expression linked to cancer recurrence and metastasis [11]. Furthermore, research indicates that MALAT1 promotes the proliferation and aggressiveness of thyroid cancer cells [12]. In this review, we will provide a brief overview of MALAT1's contributions to both physiological and pathological functions, concluding with a summary of the current understanding of MALAT1's roles in thyroid cancer.

2. BIOGENESIS OF MALAT1

MALAT1 was initially discovered through a microarray screening of tumours from lung cancer patients [13]. It was found that tumours with a higher propensity for metastasis exhibited upregulated expression of MALAT1 [14]. The MALAT1 gene is located on human chromosome 11q13.1 and mouse chromosome 19qA, situated within a gene-rich region that shows significant evolutionary conservation across species [15]. Specifically, MALAT1 displays considerable sequence conservation, with approximately 50% preservation in vertebrates and over 80% conservation at the 3' end of the transcript [16]. In humans, MALAT1 RNA is approximately 8.7 kb long, while the mouse version measures about 6.7 kb. It is transcribed by RNA polymerase II, and its promoter region exhibits an accessible chromatin structure, as demonstrated by various high-throughput studies and DNase sensitivity assays [16]. The expression level of MALAT1 is notably high, often compared to that of fully transcribed housekeeping genes, such as beta-actin. It is present in all tissue types, with a median expression level of around 150 transcripts per million (TPM), and is particularly abundant in the ovaries, where the median expression level reaches 287 TPM [17]. The abundance of MALAT1 in cells can be attributed to its robust promoter activity and increased stability of the transcribed RNA. MALAT1 is primarily retained in the nucleus and is localized in specific regions known as nuclear speckles [18]. These nuclear speckles contain a high concentration of factors involved in pre-mRNA processing and various transcription factors, playing a crucial role in coordinating gene regulation at both transcriptional and post-transcriptional levels. Within the nuclear speckles, MALAT1 is found in the outer regions, while pre-mRNA splicing factors are located more centrally [19]. In addition to its localization in nuclear speckles, MALAT1 is also associated with chromatin. High-throughput chromatin-RNA binding assays, such as CHART and ChIRP, have identified MALAT1 as an RNA that is preferentially enriched in chromatin and associated with actively transcribed genes [20]. Furthermore, various high-throughput investigations, including MARGI and GRID-seq, have demonstrated that MALAT1 binds to thousands of genomic loci in a cell-type-specific manner [21]. Fig. (**1**) shows the structure and biological function of MALAT1.

3. MALAT1 IN HEALTH AND DISEASES

Several mechanisms have been proposed to explain the role of MALAT1 in various physiological states [22]. Based on its specific sub-nuclear localization, numerous studies suggest that MALAT1 is involved in transcription, either directly or indirectly, and may regulate alternative pre-mRNA splicing [23, 24]. MALAT1's involvement in splicing is linked to its presence in nuclear speckles, sub-nuclear bodies rich in pre-mRNA splicing factors [25]. Research has shown that knocking down MALAT1 in cells results in changes to pre-mRNA splicing [26, 27]. Furthermore, MALAT1 regulates the speckle localization and function of serine/arginine (SR) splicing factors by modulating their phosphorylation status, thereby affecting alternative splicing [28]. Other studies indicate that MALAT1 may directly participate in the pre-mRNA splicing of actively transcribed genes by recruiting splicing factors to the pre-mRNA [29]. MALAT1 has been identified as a key player in transcriptional regulation across various studies [30]. Notably, *in vivo* cross-linking experiments have shown that MALAT1 binds to the chromatin of actively transcribing genes, thereby influencing their expression at the transcriptional level [20]. Additionally, MALAT1 interacts with specific transcription factors and co-activators, such as LTBP3, FOXO1, PC2, and HMGA2, among others [22]. Despite the potential significance of MALAT1 in cellular functions, research involving three distinct knockout (KO) mouse models has revealed that the absence of Malat1 does not significantly impact normal mouse physiology or development [31]. Furthermore, MALAT1 has been shown to enhance glycolysis while inhibiting gluconeogenesis by promoting the translation of the transcription factor TCF7L2, which plays a role in metabolic stress [32]. The expression of MALAT1 is regulated by HIF1_α, a crucial transcription factor involved in the hypoxic response [33]. MALAT1 is also essential for regulating the A non-homologous end joining (NHEJ) pathway and B cell class switch recombination [34]. Studies have identified MALAT1 as a regulator of TRP53, with its knockdown leading to increased H2Ax foci, suggesting a broader role in responding to DNA damage and genotoxic stress [35]. Notably, chemotherapy drugs, known to induce genotoxic stress, significantly elevate MALAT1 expression in extramedullary myeloma, indicating its potential role as a stress-responsive gene [36]. Moreover, MALAT1 overexpression has been observed in over 20 different types of solid and lymphoid tumors, correlating with tumor progression and metastasis [37, 38]. Its association with poor outcomes in both solid and hematopoietic cancers has been documented, particularly in lung, breast, and liver cancers, where it is linked to disease spread [11, 39, 40]. Beyond tumors, MALAT1 overexpression has been implicated in a

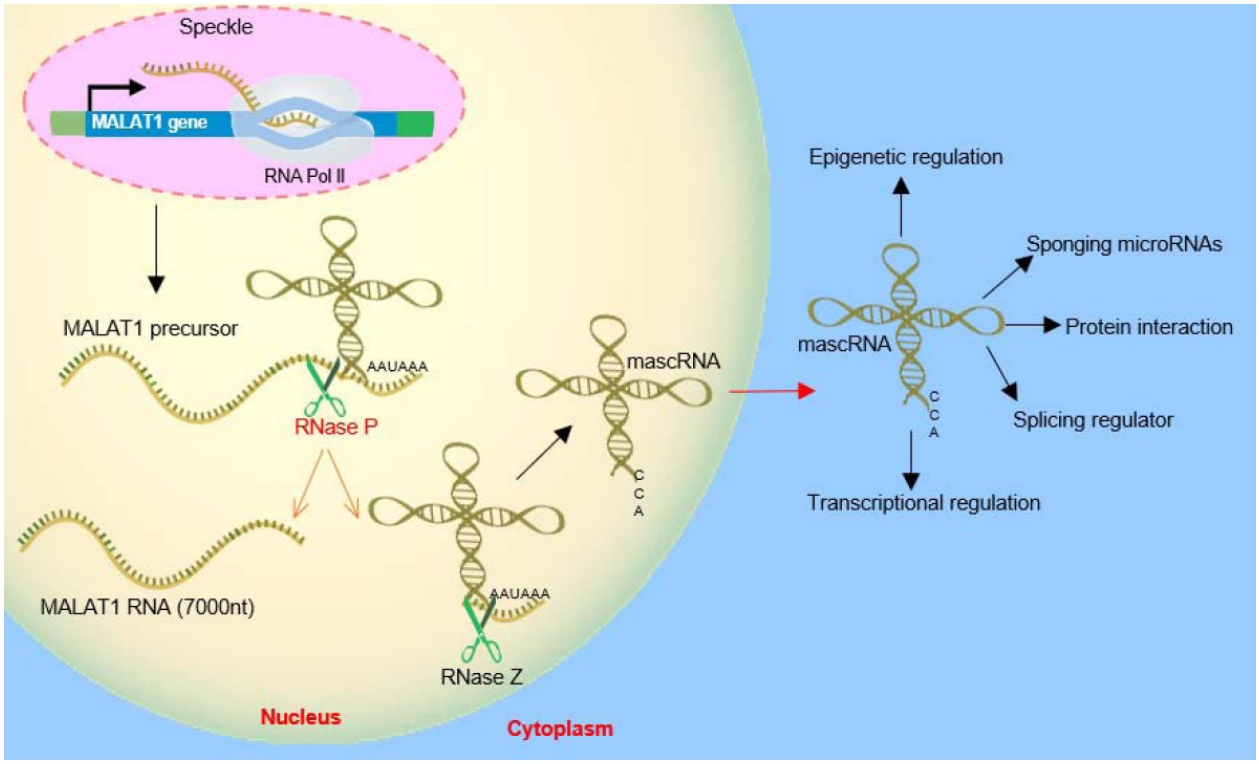

Fig. (1). The structure and biological functions of the long non-coding RNA MALAT1. MALAT1 is a highly conserved lncRNA that is retained in the nucleus and plays a crucial role in regulating alternative splicing, epigenetic modifications of gene expression, cell proliferation, survival, and organogenesis. Additionally, MALAT1 is implicated in cancer development and progression, functioning as a molecular sponge that negatively regulates microRNAs (miRNAs). Situated on human chromosome 11q13, MALAT1 is transcribed by RNA polymerase II (Pol II). Unlike typical mRNAs, it does not possess a conventional poly(A) tail at its 3' end. The primary transcript of MALAT1 undergoes processing by ribonuclease P (RNase P) and RNase Z. RNase P cleaves the transcript at a specific nucleotide, resulting in the formation of the 5' end of a smaller RNA fragment and the mature 3' end of MALAT1, which adopts a distinctive triple-helix structure. Mature MALAT1 transcripts are primarily localized in nuclear speckles, suggesting their involvement in nuclear functions. During the processing of MALAT1, shorter fragments are generated, one of which is a 61-nucleotide RNA known as mascRNA (MALAT1-associated small cytoplasmic RNA), which is subsequently transported to the cytoplasm. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

variety of pathological conditions, including diabetes and insulin signalling [41]. Research has shown MALAT1 overexpression in endothelial cells exposed to high glucose levels, and its dysregulation has been associated with several diabetic complications, such as retinopathy and atherosclerosis [42, 43].

MALAT1 plays a role in liver illnesses, specifically in liver cancer, fatty liver diseases, liver regeneration, and hepatic fibrosis. [44]. Additionally, it plays a role in pulmonary cell biology and lung inflammation, influencing acute lung injury (ALI) and chronic lung diseases [45]. MALAT1 has been shown to regulate angiogenesis and cerebrovascular pathologies, as well as induce autophagy in ischemic stroke models. Increased expression of pro-inflammatory and pro-apoptotic cytokines has been associated with MALAT1 silencing [46]. MALAT1's involvement in ocular diseases is emerging, as it regulates angiogenesis, inflammation, apoptosis, and extracellular matrix homeostasis through multiple miRNAs. However, further research is necessary to fully elucidate the mechanisms by which MALAT1 affects ocular diseases and to explore its potential as a therapeutic target [47].

4. EXPLORING THE ROLE OF MALAT1 IN THYROID CANCER PATHOGENESIS

A growing body of research indicates that MALAT-1 is dysregulated in a variety of malignancies; it primarily acts as an oncogene with variable effects on tumorigenesis. In non-small cell lung cancer (NSCLC) [14], cervical cancer [48], osteosarcoma [49], hepatocellular carcinoma [50], colorectal cancer [51], glioblastoma [52], and other malignancies [53], MALAT-1 is elevated. By regulating autophagy, apoptosis, and the epithelial-mesenchymal transition (EMT), MALAT-1 contributes to tumor development. Here, we focus on the emerging roles of this lncRNA in thyroid cancer (Table **1**). Research indicates that MALAT1 can function as both an oncogene and a tumor suppressor in thyroid cancers, highlighting its complex role in tumor biology (Fig. **2**).

4.1. Dual Roles of MALAT1 in Different Types of Thyroid Tumors

MALAT1 is highly expressed in normal thyroid tissues (NT) and thyroid tumors, with levels increasing

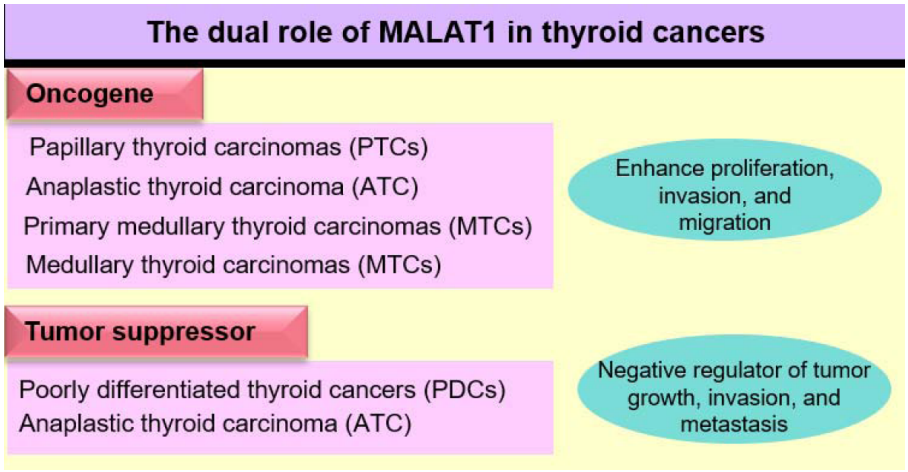

Fig. (2). MALAT1 can exhibit dual functionality in thyroid cancers, acting as both an oncogene and a tumor suppressor. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. MALAT1 function in thyroid cancer.

lncRNA	Expression Level	Types of Cancer/Cell Line	Conclusion	References
MALAT1	Upregulation	ATC cell lines	BI-847325 which inhibits both MEK and Aurora kinase family can regulate the genes involved in cell cycle and apoptosis including MALAT1 and its downstream genes such as miR-363-3p, Mcl1, and cyclin D1 and could be effective against ATC	[58]
	Upregulation	FTC tumor tissue, ATC cell lines, and FTC cell line	MALAT1 promoted the proliferation and invasion of thyroid cancer cells *via* regulating the expression of IQGAP1	[59]
	Upregulation	Primary MTCs and MTC-derived cell line	There was increased expression of miR-21 and MALAT1 in MTCs and overexpression of miR-21 and MALAT1 may regulate MTC progression	[60]
	Upregulation	FTC tumor tissues, ATC cell lines and FTC cell line	MALAT1-mediated FGF2 protein secretion from TAMs inhibited inflammatory cytokines release, promoted proliferation, migration and invasion of FTC133 cells and induced vasculature formation	[10]
	Upregulation	ATC tissues and human ATC cell lines	MALAT1 knockdown suppressed ATC progression by regulating miR-200a-3p/FOXA1	[61]
	Upregulation	Thyroid cancer cell lines	MALAT1 contributes to thyroid cancer progression through the upregulation of IGF2BP2 by binding to miR-204	[62]
	Upregulation	PTC cell lines	miR-146b-5p can promote MALAT1 expression by negatively regulating DNMT3A in PTC	[63]

during the progression from NT to papillary thyroid carcinomas (PTCs). However, its expression is downregulated in poorly differentiated thyroid cancers (PDCs) and ATCs compared to NT. The elevated MALAT1 expression observed in a PTC cell line (TPC1) is attributed to TGF-beta-induced EMT, indicating a potential role for MALAT1 in EMT within thyroid tumors. This study provides the first evidence that certain thyroid malignancies may exhibit downregulated MALAT1 levels. The findings suggest that ATCs may have distinct molecular characteristics compared to lower-grade thyroid malignancies, indicating that MALAT1 could play dual roles in different types of thyroid tumours-functioning both as a tumour suppressor and as an oncogene [54].

4.2. MALAT1 as a diagnostic marker for PTC

MALAT1 expression was greater in PTC tissues when compared to paired, comparable noncancerous tissues. Additionally, upregulated MALAT1 expression was correlated with tumor size, lymph node metastases, and WHO disease stage. According to this research, MALAT1 may have an oncogenic function in PTC and could be used as a diagnostic marker for this cancer [55].

4.3. MALAT1 polymorphisms

Wen *et al*. conducted a case-control study involving 1,134 patients with papillary thyroid carcinoma (PTC)

and 1,228 controls from the Chinese population to investigate the potential association between genetic variations in MALAT1 and the risk of developing PTC. Their findings revealed that the MALAT1 SNP rs619586 significantly reduces susceptibility to PTC. Furthermore, functional experiments indicated that the G allele of rs619586 notably decreases MALAT1 expression, inhibits PTC proliferation, and promotes apoptosis in PTC cells. The researchers concluded that MALAT1 SNP rs619586 may serve as a potential biomarker for PTC pathogenesis and susceptibility [56].

4.4. MALAT1 regulation of stemness behaviors

Mahdiannasser *et al*. conducted an exploratory study to investigate the role of lncRNAs ROR and MALAT1, along with their related genes, in the stemness of cancer stem cells (CSCs) in ATC. Using magnetic-activated cell sorting (MACS), the researchers separated CD133-positive and CD133-negative subpopulations from the ATC cell lines SW1736 and C643. They then analyzed the expression profiles of the CD133 marker, MALAT1, and its associated genes (CCND1, NESTIN, MYBL2, MCL1, IQGAP1), as well as ROR and its related genes (POU5F1, SOX2, NANOG). The findings revealed significant upregulation of ROR, POU5F1, SOX2, NANOG, CD133, MALAT1, IQGAP1, and MCL1 in CD133-positive SW1736 cells compared to CD133-negative cells. Similarly, in CD133-positive C643 cells, CCND1, IQGAP1, POU5F1, SOX2, NANOG, and NESTIN were significantly upregulated compared to CD133-negative cells. The researchers concluded that these lncRNAs in CD133-positive SW1736 and C643 cells may play a role in regulating stemness behaviours in ATC [57].

4.5. MALAT1-miRNA/mRNA signaling pathways in thyroid cancer

4.5.1. MALAT1/miR-363-3p/Mcl1/cyclin D1

Samimi *et al*. ascertained how the anticancer drug BI-847325, a dual MEK/Aurora kinase inhibitor, affects the molecular mechanisms of MALAT1-mediated gene regulation in ATC. In ATC cell lines, MALAT1 gene expression was markedly downregulated after BI-847325 treatment. On the other hand, BI-847325 markedly increased the expression of miR-363-3p. Also, Mcl1 expression was markedly downregulated. After treatment, there was a significant downregulation in the expression of cyclin D1. This suggests that BI-847325, known for its inhibition of MEK and the Aurora kinase family, could potentially combat ATC by modulating genes related to apoptosis and cell cycle regulation, including MALAT1 and its downstream targets [58].

4.5.2. MALAT1/IQGAP1

Researchers also found that in comparison to the control group, thyroid cancer tissues and cells had higher expression of MALAT1 and higher levels of IQGAP1, which is a crucial protein that controls cell adhesion and motility. When MALAT1 was knocked down, invasion and proliferation of FTC-133 thyroid cancer cells were significantly suppressed. Furthermore, MALAT1 appeared to enhance IQGAP1 expression in thyroid cancer cells. Notably, the knockdown of IQGAP1 counteracted the effects of MALAT1 on the proliferation and invasion of these cells. Ultimately, *in vivo*, investigations confirmed that MALAT1 promotes tumor growth in thyroid cancer [59].

4.5.3. MALAT1/miR-21

In a study of primary medullary thyroid carcinomas (MTCs), strong expression of miR-21 was observed in 17 out of 39 samples, accounting for 44% of the cases. In contrast, a remarkable 37 out of 39 primary MTCs, or 95%, exhibited strong expression of MALAT1. Real-time PCR analysis revealed that both MALAT1 and miR-21 levels were significantly higher in primary MTCs compared to normal thyroid cells. Further experiments conducted using an MTC-derived cell line demonstrated that silencing miR-21 and MALAT1 with siRNA resulted in significant reductions in cell invasion and proliferation. These findings suggest that the overexpression of miR-21 and MALAT1 may play a critical role in the progression of MTC, highlighting their potential as targets for therapeutic intervention [60].

4.5.4. MALAT1/FGF2

Thyroid cancer tissues and cells exhibited elevated levels of MALAT1 and fibroblast growth factor-2 (FGF2) compared to the control group. Additionally, the culture medium from tumour-associated macrophages (TAMs) showed a significant increase in TNF-α and IL-12, while IL-10 levels decreased when MALAT1 was silenced with si-MALAT1. When MALAT1 was downregulated in TAMs, there was a notable reduction in the proliferation, migration, and invasion of FTC133 cells, along with suppressed angiogenesis. However, the effects of MALAT1 siRNAs on cell migration, invasion, and angiogenesis were reversed by the overexpression of FGF2. These findings suggest that MALAT1 and FGF2 could serve as promising biomarkers and potential therapeutic targets in the fight against thyroid cancer progression [10].

4.5.5. MALAT1/miR-200a-3p/FOXA1

In ATC tissues and cells, researchers observed decreased levels of miR-200a-3p alongside increased expression of MALAT1. When MALAT1 was knocked down or miR-200a-3p was overexpressed in ATC cells, there was a notable enhancement in autophagy and apoptosis, along with a reduction in cell proliferation, migration, and invasion. Interestingly, miR-200a-3p was found to directly bind to MALAT1, and inhibiting miR-200a-3p reversed the suppressive effects of MALAT1 knockdown on ATC progression. Additionally, FOXA1 was identified as a target of miR-200a-3p, and restoring FOXA1 expression diminished the anti-cancer effects of miR-200a-3p in ATC cells. MALAT1 also acted as a competing endogenous RNA (ceRNA), sponging miR-200a-3p to relieve the repression of FOXA1 expression. By downregulating FOXA1 and upregulating miR-200a-3p, interference with MALAT1 effectively reduced tumor growth. Overall, the

knockdown of MALAT1 inhibited the progression of ATC by modulating the miR-200a-3p/FOXA1 pathway, suggesting a potential new therapeutic strategy for treating this aggressive cancer [61].

4.5.6. MALAT1/miR-204/IGF2BP2/m6A-MYC

MALAT1 and insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) were found to be highly expressed in thyroid cancer, while miR-204 exhibited low expression levels. It has been confirmed that IGF2BP2 is a target of miR-204. Research revealed that MALAT1 upregulates IGF2BP2 and enhances MYC expression through m6A modification recognition by competitively binding to miR-204. This interaction ultimately accelerates the proliferation, invasion, and migration of thyroid cancer cells while inhibiting apoptosis. Silencing MALAT1 was shown to decrease MYC expression and inhibit tumour growth *in vivo* by downregulating IGF2BP2. Understanding the specific processes behind the MALAT1/miR-204/IGF2BP2/m6A-MYC axis is a key step towards the advancement of targeted therapies for thyroid cancer [62].

4.5.7. MALAT1/miR-146b-5p/DNMT3A

It was discovered that MALAT1 expression was markedly upregulated in both PTC tissues and cell lines. In contrast, the knockdown of MALAT1 resulted in a marked inhibition of cellular activity, migration, and invasion in the B-CPAP and K1 cell lines. Furthermore, a positive correlation was observed between miR-146b-5p and MALAT1, while a negative correlation existed between miR-146b-5p and DNA methyltransferases 3A (DNMT3A). Notably, a binding site for miR-146b-5p was identified in the 3′ untranslated region of DNMT3A. This suggests that miR-146b-5p can enhance MALAT1 expression by negatively regulating DNMT3A in PTC [63].

CONCLUSION

It can be concluded that high expression of MALAT1 by suppressing various miRNAs, including miR-363-3p, miR-21, miR-200a-3p, miR-204, and miR-146b-5p play critical roles in the pathogenesis of thyroid cancer. Besides, this lncRNA by targeting Mcl1/cyclin D1, IQGAP1, FGF2, FOXA1, IGF2BP2/m6A-MYC, and DNMT3A can regulate key cellular processes such as proliferation, invasion, and apoptosis in thyroid cancer. Understanding these mechanisms is crucial for developing targeted therapies in thyroid cancer.

AUTHOR CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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