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Review Article

Emerging role of competing endogenous RNA and associated noncoding RNAs in thyroid cancer

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Abstract: Cancer of the thyroid is the most common endocrine malignancy. While treatment options are limited for individuals with medullary or anaplastic thyroid cancer, understanding the underlying mechanisms is vital to developing a successful thyroid cancer treatment strategy due to the tumor's multistep carcinogenesis. Non-coding RNAs (ncRNAs) have been associated with thyroid cancer progression in several recent studies; however, the role of regulatory interactions among different types of ncRNAs in thyroid cancer remains unclear. Recently, competing endogenous RNA (ceRNA) has been discovered as a mechanism demonstrating regulatory interactions among non-coding RNAs, including pseudogenes, long non-coding RNAs (lnRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs). It has been concluded from the literature that numerous ceRNA networks are deregulated during the development, invasion, and metastasis of thyroid cancer, as well as in epithelial-mesenchymal transition (EMT) and drug resistance. Further understanding of these deregulations is important to develop diagnostic procedures for early detection of thyroid cancer and promising therapeutic options for effective treatment. The purpose of this review is to highlight the emerging roles of some newly found ceRNA members in thyroid cancer and outline the current body of knowledge regarding ceRNA, lncRNA, pseudogenes, and miRNAs.

Keywords: RNA biology, thyroid cancer, miRNA, circ RNA, ceRNA, lnc RNA

Introduction

Endocrine cancers are considered among the most devasting cancer types, where thyroid cancer is globally the most pervasive endocrine cancer [1]. Numerous high-and medium-income countries have seen a significant increase in thyroid cancer incidence among adults [2, 3]. Globally, thyroid cancer caused 255,489 new cases and 41,235 deaths in 2017 [4]. According to GLOBOCAN 2020 statistics, thyroid cancer accounted for 0.4% of the 10.0 million cancer deaths and 3.0% of the 19.3 million new cancer cases globally [5]. Thyroid cancer is the fifth most common cancer in women aged 20-84 worldwide and the third most common in women younger than 50 years [1]. Over the past few decades, the approach to diagnosing thyroid cancer has improved through advances in imaging, laboratory, and molecular techniques and knowledge [6]. Molecular advances have improved and provided individualized treatment options for some patients with aggressive thyroid cancer in addition to thyroid surgery, radioactive iodine treatment, and suppression of thyroid stimulating hormone (TSH) [6]. Considering the importance of unveiling molecular mechanism, advances in genome sequencing are considered the most important options to better understand the molecular mechanisms underlying thyroid cancer development and pathogenesis [7].

It is well known that only two percent of the transcribed genome is translated in mammals, while the remaining untranslated genes lack

the ability to code for proteins. These are known as non-coding RNAs (ncRNAs) [8] and can be divided into long and short ncRNAs. The short ncRNA are less than 200 nt in length, including microRNAs (miRNAs), transfer RNAs (tRNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), and small nuclear RNAs (snRNAs) [9]. The lncRNA are longer than 200 nt, including enhancer RNAs (eRNAs), pseudogenes, and long intergenic non-coding RNAs (lincRNAs) [10]. These lncRNAs are linked with several biological functions, such as chromatin remodeling and post-transcriptional regulation [10]. Moreover, circular RNAs (circRNAs) are another type of RNAs ranging from 200 nucleotides to over 100 kb, with an average length of 1 kb. Both lncRNAs and circRNAs play potential roles in gene regulation by interacting with competing endogenous RNAs (ceRNA) and RNA-binding proteins (RBPs). Moreover, they also play a crucial role in controlling transcription, translation, and splicing. Therefore, they have received tremendous attention from researchers [11].

CeRNAs are emerging factors in the tumorigenicity of cancer. Both coding and non-coding RNAs can regulate the expression of genes through miRNAs (sponging miRNAs) [11]. From 5' end of miRNA, the nucleotides 2-8 (especially 6 and 7) could bind with many RNAs including lncRNAs, pseudogenes, circRNAs, and mRNAs. This binding is facilitated by miRNA response elements (MREs), which are uniquely positioned in 3' untranslated regions (3' UTRs) of these RNAs. Using this binding mechanism, miRNAs are able to control other RNAs post-transcriptionally [12]. In this review, we focused first on current knowledge about non-coding RNAs and discussed the biological functions of their various components. We then specifically describe the association of pseudogenes, lncRNAS, miRNAs, and circRNAs in association with thyroid cancer. We then reviewed the prominent functions of ceRNAs and their networks during thyroid cancer progression, development, and initiation.

Important components of ceRNA

The important and structural components of ceRNA are miRNAs, lncRNAs, circRNAS, and pesudogenes. Inside the nucleus of mammalian cells, RNA polymerase II (RNA pol II) transcribes the miRNA gene into primary miRNA (pri-miRNA). DGCR-8, an RNA binding protein (RBP), and Drosha, a ribonuclease enzyme III, produce intermediate precursor miRNA (pre-miRNA) and pri-miRNA, which are 70 nt and has a stem-loop structure. The complex of Exp5/Ran-GTP is associated with pre-miRNA transportation to the cytoplasm. Subsequently, pre-miRNA is transformed to double-started RNA by Dicer/TRBP/PACT in the cytoplasm. The RISC produces mature miRNAs by incorporating only one strand [13]. The mature miRNAs are 19-25 nucleotides ncRNA, and widely regulate biological activities. The miRNAs identify their targets using miRNA response elements (MREs), which subsequently suppress gene expression [14]. In addition to regulating cellular activities, miRNAs when dysregulated contribute to aberrant cell growth and ultimately lead to tumor development and metastasis (**Figures 1** and **2**).

More than 200 nt ncRNAs are called lncRNAs, which are associated with many biological functions (**Figure 2**), such as DNA replication timing regulation, transcriptional and post-transcriptional regulation, chromosome stability, and imprinting [15]. Although for most of the lncRNAs, the nucleus is the place of biogenesis and processing, but either the nucleus or cytoplasm is the site of action for them. In many aspects, lncRNA biogenesis is similar to protein coding RNAs. RNA polymerase II transcribes most lncRNA types. It is followed by alternative splicing from exonic or intergenic regions of genes [16]. However, compared to mRNAs, splicing is less effective in lncRNAs. Furthermore, RNA polymerase III transcribed some non-polyadenylated lncRNAs [16]. The lncRNA genes promoters are rich in histone modifications such as H3K4me3, H3K9ac, and H3K27ac, which could play an important role in lnRNA synthesis [17]. In addition to their ability to regulate gene expression in many ways, lncRNAs have no specific mechanism of action [18]. LncRNAs are now known to function as scaffolds and guides for DNA, RNA, and proteins in addition to being activators and decoys [18]. Following the sequencing of increasingly more cancer transcriptomes using next-generation sequencing technology, many lncRNAs have been identified with abnormal expression [19]. Nevertheless, lncRNAs have recently gain-

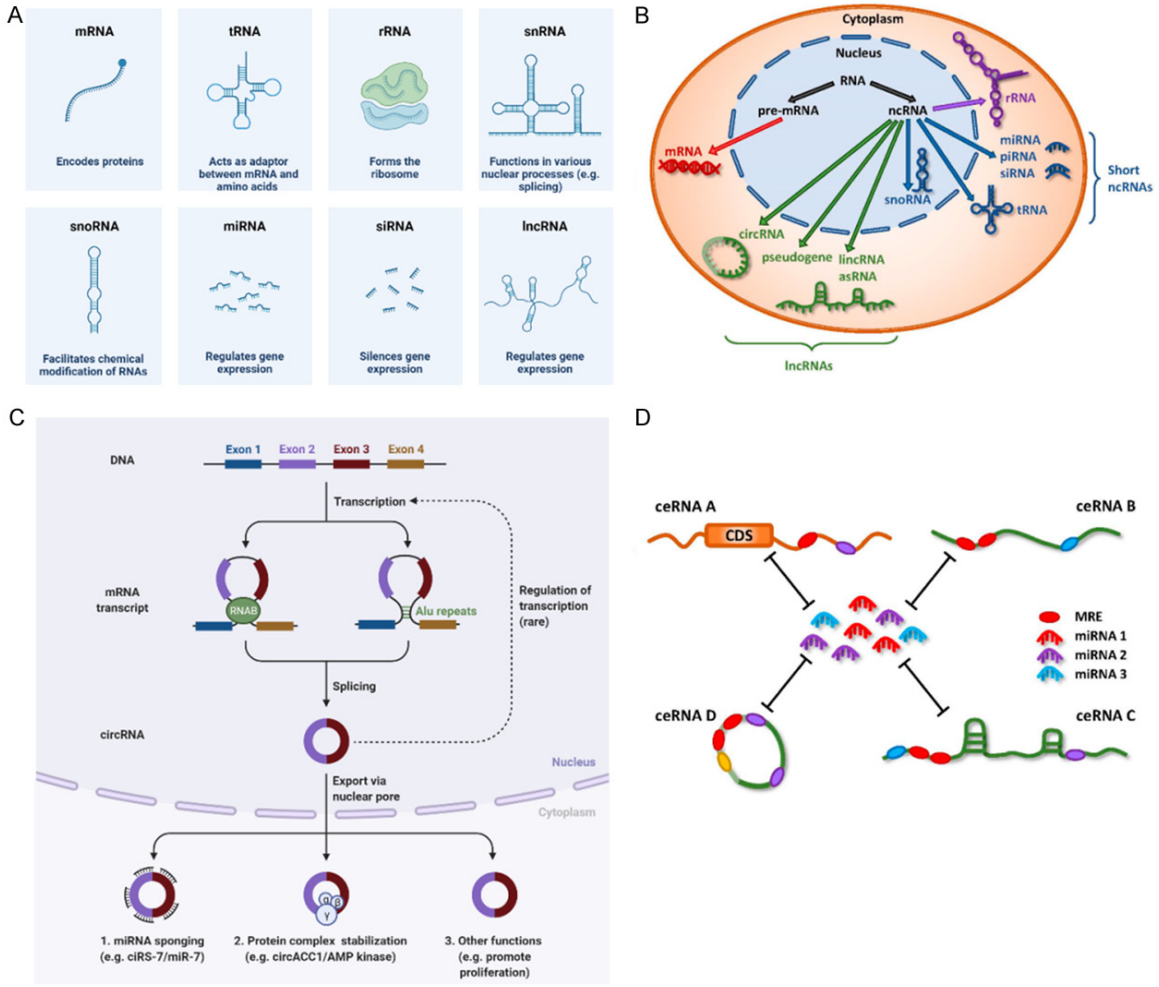

Figure 1. (A) Major RNAs produced in cells. (B) Noncoding RNAs such as lncRNAs and miRNA are subclasses of ncRNAs. LncRNAs include long intergenic ncRNA, antisense RNA, pseudogenes, and circular RNA. While, short ncRNAs consist of microRNA (miRNA), Piwi-interacting RNA, small interfering RNA, transfer RNA, aand small nucleolar RNA. The most important among these are lncRNAs and miRNAs, which are mainly involved in the regulation of gene expression. (C) CircRNAs are important players in cancer biogenesis, which are involved in cancer development, progression and regulation. (D) This part of the figures represents the binding of miRNAs to specific miRNA response elements present on ceRNA, suppresses genetic expression. In this figure ceRNA (A) represents coding transcript, while ceRNA (B-D) represent non-coding transcripts. This figure has been adapted from BioRender and a previously published article [83].

ed attention for their roles as miRNA decoys in the regulation of ceRNA.

CircRNAs are single-stranded circular structures. They lack a free 5' end cap and a 3' poly(A) tail. Mostly, they have only exons, but some have one or two introns [20]. During 1986, researchers discovered circRNAs in the hepatitis delta virus, which have gained attention since 2012 [21]. Lariat intermediate or exon skipping models, RBPs-mediated back splicing, and intron-pairing have been proposed as biogenesis models for circRNAs [22]. Unlike linear RNAs, they are more stable and cannot easily be cleaved by exonuclease enzymes which lacks a 5' end cap and 3' poly(A) tail [22]. The circRNAs sequences are highly conserved and throughout the evolutionary processes do not mutate. Numerous cancer types have been studied, and the level of expression of circRNAs in certain tumor tissues has been demonstrated to be specific [23]. The potential application of circRNAs as tumor biomarkers is thus evident. Circular RNAs contain numerous miRNAs binding sites, allowing them to bind homologous miRNAs and function as sponges. Circ-

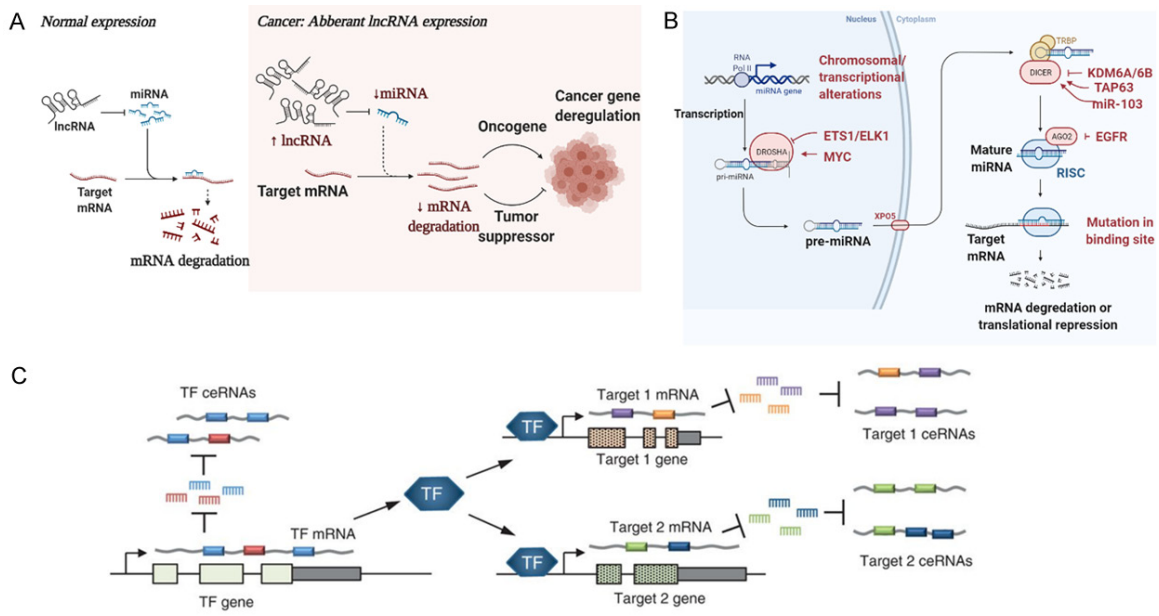

Figure 2. A. lncRNA-miRNA Gene Expression Regulation in Cancer lncRNA-miRNA Gene Expression Regulation in Cancer. This part of figure shows the effect of lncRNA expression changes on tumor behaviour depends on cannonical function of mRNA target gene. B. Depicts how miRNA function and biogenesis can be altered in cancer. This alteration can affect the availability of target mRNA. C. This figure depicts that transcription factor can act as ceRNA through correlated mRNA. Moreover, its targets transcript is stimulated by its protein which result to decoy miRNAs. This figure has been adapted from BioRender and a previously published article [84].

RNA-miRNA-mRNA regulatory axis provides valuable insight into the molecular mechanisms responsible for thyroid cancer and many other types of human cancer [24].

Role of ceRNAs in thyroid cancer

CeRNAs regulate several important genes in combination with miRNA in thyroid cancer. As a result of circRNAs, lncRNAs, and pseudogenes expressing aberrantly, miRNA levels change, affecting downstream gene expression. In the following section, we have discussed the ceRNA's role in thyroid cancer from various cross-talk perspectives (**Figure 1**).

MALAT1, SNHG3, and XIST contribute to the development of thyroid cancer

MALAT1 is has been identified as an evolutionarily conserved lncRNA, which is associated with tumor metastasis, including thyroid cancer [25]. On the other hand, IGF2BP2 is a known RBP, involved in several biological processes, including embryo development, carcinogenesis, and RNA processing. In thyroid cancer cells, IGF2BP2 and MALAT1 are upregulated in response to miR-204 downregulation [26]. Mechanistically, MALAT1 increases MYC expression by targeting miR-204 and regulating IGF2BP2 expression levels, thereby promoting cell invasion, proliferation, and migration during thyroid cancer progression and development [26]. These findings can provide the basis to understand further the roles of ceRNA based networks (MALAT1/miR-204/IGF2BP2) in the carcinogenesis of thyroid cancer.

The lncRNA SNHG3 is dysregulated in several kinds of cancers. PSMD10 or p28 is an oncogene that initiates several tumors. PSMD10 is the target of miR-214-3p. One of the important functions of SNHG3 is miRNA sponging [27]. A recent study reported the upregulation of SNHG3 in thyroid cancer, suggesting that SNHG3 can act as a ceRNA for miR-214-3p to promote PSMD10 expression. On the other hand, knockdown of SNHG3 inhibited tumor growth and dramatically reduced invasion, proliferation, colony formation, and migration. In the cell cycle, PSMD10 regulates the activity of CDK4 through protein-protein interactions [28]. Moreover, it has a high affinity for MDM2, which modulates the destruction of retinoblas-

toma and p53 proteins, all of which are cancer suppressors and known to be mutated in several types of cancers [28]. By targeting PSMD10, miR-214-3p inhibits the growth and metastasis of thyroid cancer. The miR-214-3p and PSMD10 can interact and promotes proliferation and prevents apoptosis in multiple myeloma cells [29]. In summary, it appears that ceRNA SNHG3 modulates miR-214-3p/PSMD10 axis-dependent functions of thyroid cancer, including migration, growth, and colony formation. Due to this, SNHG3 could potentially be used as a biomarker and therapeutic target for thyroid cancer.

XIST is a lncRNA that can either inhibit or promote tumor growth [30]. The lncRNA can act as a putative useful biomarker in cancers. XIST contributes to thyroid cancer malignancy through molecular sponging of miR-101-3p [31]. In addition, CLDN1 is a direct target of miR-101-3p, and the inhibition of migration and invasion of thyroid cancer cells by miR-101-3p may be reversed when CLDN1 is expressed ectopically [31]. The XIST knockdown has been reported to suppress cell invasion and migration via CLDN1 in thyroid cancer, whereas the XIST/miR-101-3p axis has been found to play a regulatory role in cancers [31]. Based on these results, XIST has a critical role in the development of thyroid cancer as an upstream regulator of the XIST/miR-101-3p/CLDN1 ceRNA network and may be exploited in clinical settings as a therapeutic and diagnostic target for thyroid cancer.

DUXAP8 and MAPKAPK5-AS1 contribute to proliferation and apoptosis

DUXAP8 is 2307 nt lncRNA. The higher expression of lncRNA in several cancers, such as, gastric, ovarian, lung, and liver cancers has been reported. Patients with parathyroid cancer who express elevated levels of DUXAP8 have worse outcome and a higher grade [32]. DUXAP8 inhibits cell apoptosis in parathyroid cancer cells by sponging miR-20b-5p and activating SOS. Knockdown of DUXAP8 reduced MEK1/2 and ERK1/2 phosphorylation, as well as cyclin D1, SOS1, and c-Myc expression levels [32]. In order to modulate RAS proteins, SOS1 coordinates the transition from GTP to GDP [58] and functions as a pacesetter for KRAS, an important oncogene in cancer, by enhancing the transition from the KRAS (off) to the KRAS (on) configuration [33]. Based on these results, DUXAP8/SOS1 cross-talk has as a critical epigenetic ceRNA role of DUXAP8 in the apoptosis and proliferation of parathyroid cancer cells through promoting miR-20b-5p downregulation. Thus, DUXAP8/miR20b5p/SOS1 could potentially be a therapeutic target for parathyroid cancer.

MAPKAPK5-AS1 is an oncogenic lncRNA located on chromosome 12q24.12 [34]. It is also a ceRNA that regulates the expression of YWHAH by acting as a sponge for miR-519e-5p. The MAPKAPK5-AS1 knockdown hindered invasion, proliferation, and accelerated apoptosis. MAPKAPK5-AS1 is a negative regulator of miR-519e-5p, and YWHAH is a direct target of miR-519e-5 [35]. There are several tumor-suppressing functions of miR-519 in cancer cells, including enhancement of radiosensitivity inhibition of hypoxia-induced tumorigenesis, EMT phenomenon, and cell proliferation [36]. In summary, in thyroid cancer cells, MAPKAPK5-AS1 controls cell migration and proliferation through miR-519e-5p/YWHAH axis regulation.

AGAP2-AS1, OIP5-AS1, and HOTAIR contribute to the progression of thyroid cancer

AGAP2-AS1 is an oncogenic lncRNA having a 2117 bp length. It is upregulated in parathyroid cancer cells and increases invasion by activating NNP2 expression. There is a reported interaction between miR-628-5p and AGAP2-AS1 in certain cancers, including glioma and thyroid. A tumor suppressor, miR-628-5p, increases apoptosis while reducing invasion, migration, and proliferation in different types of cancers. AGAP2-AS1 via miR-628-5p/KLF12 promotes parathyroid cancer cell proliferation and metastasis [29]. On the other hand, knocking down AGAP2-AS1 in vivo reduces parathyroid cancer carcinogenesis. Furthermore, knockdown of AGAP2-AS1 was less effective on thyroid cancer after transfecting the cells inhibitor (miR-628-5p). In addition, miR-628-5p targets KLF12 directly and reduces its expression. MiR-628-5p inhibition increased the expression of KLF12 in parathyroid cancer cells, which enhanced cell proliferation and metastasis [29]. KLF12 is an important transcription factor that has a key role in gene expression during normal development and tumorigenesis [37]. In parathyroid cancer, the AGAP2-AS1/miR-628-5p/KLF12 axis appears to be able to perform this critical function through KLF12.

The OIP5-AS1 is a lncRNA, playing an essential role in neoplastic cell transformation and tumorigenesis through several mechanisms, including EMT regulation. The higher expression levels of OIP5-AS1 induce oncogenesis in most of the cases; however, in some malignancies, it has been found downregulated [38]. Furthermore, OIP5-AS1 is a ceRNA known to downregulate miR-429, which results in increased XIAP expression. MiR-429 inhibits T cell proliferation and promotes apoptosis in human T cells [39]. To prevent apoptosis, the XIAP protein inhibits caspases 3, 7, and 9. On the other hand, upregulation of XIAP is linked with cancer progression, poor prognosis, and therapeutic resistance. However, using antisense oligonucleotides or other advance methods, targeting the XIAP gene could have anticancer effects [40]. These studies suggest that OIP5-AS1 may be able to act as a potential treatment for thyroid cancer by improving the miR-429/XIAP axis, which may facilitate the development of thyroid cancer.

HOTAIR is a lncRNA and has been reported to be upregulated in several cancers. While it is becoming increasingly apparent that HOTAIR plays an essential role in cancer initiation, development, drug resistance, and poor survival, its function is still unknown at present [41]. Additionally, HOTAIR has been proposed as a biomarker for thyroid cancer [42]. Compared to metastasis-negative parathyroid cancer patients, metastasis-positive parathyroid cancer patients expressed more HOTAIR. This suggests that HOTAIR modulates miRNAs expression and activity and enhances tumor growth [41]. HOTAIR regulates miR-1 to increase the aggressiveness of thyroid cancer cells. Furthermore, these results indicated that HOTAIR might regulate CCND2 expression, a miR-1 downstream target, through miR-1 [43]. There was a close relationship between the higher expression of CCND2 and PITX2 in thyroid cancer tissues derived from follicular cells. Functional studies show that miR-1 reduces thyroid cancer cell proliferation and migration by targeting CCND2, consistent with CCND2 being involved in cell proliferation [44]. Collectively, through the miR-1/CCND2 axis, HOTAIR promotes proliferation, invasion, and migration of thyroid cancer cells.

Role of Circ-RNAs in thyroid cancer

CircRASSF2 and CircHIPK3 contribute to cancer development

The circRASSF2 or circ_0059354 derived from the RASSF2 gene. It was first discovered as an oncogene in laryngeal squamous cell carcinoma [45]. Highly expressed circRASSF2 in parathyroid cancer cells has also been reported, which can further affect the advancement of parathyroid cancer via the miR-1178/TLR4 pathway. Exosomes from parathyroid cancer patients were shown to have higher levels of circRASSF2, suggesting the possible role of exosomes in the ceRNA network. Knockdown of circRASSF2 induces apoptosis and G1 arrest in parathyroid cancer cells. A mouse xenograft model has shown parathyroid cancer growth inhibition in response to knockdown of circRASSF2, indicating that circRASSF2 can serve as a potential therapeutic target for parathyroid cancer. The circHIPK3 is important for the initiation and development of several kinds of cancers. It could also be used as a potential prognostic marker or therapeutic target for cancers [46]. Analysis of human cancer tissues indicated that circHIPK3 could regulate multiple miRNAs by sponging multiple cell proliferation signals [47]. CircHIPK3 sponges miR-338-3p and increase RAB23 expression in thyroid cancer cells, promoting cancer and invasiveness. Knockdown of circHIPK3 significantly reduced migration, invasion, and proliferation of thyroid cancer cells [48]. These findings suggest that circHIPK3 may be used as a potential therapeutic target in thyroid cancer since it increases tumor-promoting activities in ceRNA networks.

Circ_0005273 and Circ_0058124 contribute to cancer progression

The Circ_0005273 is a miRNA sponge for miR-1183 via the miR-1183/circ_0005273/SOX2 axis. This circRNA is found to promote TC and implies a poor prognosis. By sponging miR-1183, Circ_0005273 knockdown inhibited PTC development. Furthermore, miR-1183 directly targets SOX2 and suppresses its expression. Several thyroid hormone response elements have been detected upstream of the SOX2 promoter, which is inevitable for the self-renewal process of undifferentiated/primary embryonic

stem cells. SOX2 has been demonstrated to contribute to the stemness of TC cells [49], and therefore, the clinical importance of circ_0005273/miR-1183/SOX2 is significant for TC. The Circ_0058124 is derived from FN1. FN1 is a precursor mRNA [49]. Higher levels of this circRNA are found in PTC tissues [49]. Knockdown of circ_0058124 increased apoptosis. Circ_0058124 modulates the miR-370-3p/LMO4 axis to promote PTC development [50]. The levels of miR-370-3p are lower in various cancers, and are therefore, a tumor suppressor [51]. Studies have shown that circRNAs target miR-370-3p in TC. These findings indicate that Cir0058124 plays a crucial role in TC development and invasion, implying that it may be useful as a diagnostic biomarker or a treatment option for PTC.

CircFAT1(e2) and CircITGA7 modulate thyroid cancer

CircFAT1(e2) is a novel circRNA with dual roles as anti-tumor or oncogenic. In PTC cells, circFAT1(e2) is upregulated, resulting in tumorigenesis [52]. Circafat1(e2) targets miR-873 and suppresses its expression, increasing ZEB1 expression, influencing the proliferation, invasion, and metastasis of parathyroid cancer [52]. The network of CircFAT1(e2)/miRNA-873/ZEB1 contribute to parathyroid cancer progression via circFAT1(e2), indicating its therapeutic potential for parathyroid cancer. The CircITGA7 has dual roles; it can act as both an oncogenic and a tumor suppressor. In thyroid cancer, it acts as oncogenic by activating FGFR1 through its sponging activity for miR-198. Additionally, knockdown of circITGA7 inhibited the migration and invasion of TC in TPC1 and CAL-62 cells [53]. Thyroid, gastric, and lung cancers show aberrant regulation of the miR-198/FGFR1 axis. MiR-198 inhibits the aggressive biological properties of parathyroid cancer by inhibiting FGFR1 [54]. These observations indicate that circITGA7 plays a crucial role in the circITGA7/miR-198/FGFR1 complex, which may unveil the process of how ceRNA networks contribute to the modulation of thyroid cancer.

Role of pseudogenes in thyroid cancer

LGMN, HMGA1P6, and HMGA1P7 contribute to the progression of thyroid cancer

Legumain (LGMN) contains a pseudogene that has protease activity. LGMN is highly expressed in various solid human tumors [55]. On the other hand, knocking down LGMN suppresses the progression of TC. In particular, LGMN depletion inhibited the proliferation of TC cell lines as well as the tube-formation ability of HUVECs. Furthermore, the knock down of LGMN leads to higher expression levels of miR-495, meaning that LGMN-pseudogene could target miR-495 [56]. The microRNA-495 is an autophagy regulator, increasing p62 expression and decreasing ATG3 expression [57]. In fact, LGMN-pseudogene controls autophagy signaling through p62 and LGMN/miRNA-495/ATG3 networks. The high expression levels of the HMGA1P7, HMGA1P6, and HMGA1 pseudogenes have been linked to tumor growth. Cell proliferation and migration increases by acting as sponges for a number of miRNAs that target the HMGA1 gene. Moreover, the expression of several proteins associated with cancer such as S1pr3, Pde3B, Epha3, and Hjurp are also increased by preventing their production from being maintained by miR-214, miR-761, miR-15, and miR-16. HMGA1P6 and HMGA1P7 are found in lower levels in less aggressive PTC cancers. As for ATC, extremely high HMGA1P levels are found, one of the most aggressive tumors [58]. These findings suggest that TC severity is related to the upregulation of HMGA1P6, HMGA1P7, and HMGA1. These findings have significant implications for understanding the role of HMGA1P7 and HMGA1P6 in TC aggressiveness and could lead to new therapeutic approaches to improving various aspects of TC features.

Thyroid cancer signaling pathways are regulated by CeRNA

Numerous signaling pathways have been identified in cells, and they play an important role in gene regulation and a variety of biological processes. Many studies indicate that ceRNA networks play a role in human cancer signaling pathways [59]. Signaling pathways such as PI3K/AKT/mTOR have important roles in regulating cell proliferation and survival [60]. Several evidence suggests that miR-34a suppresses tumor growth by targeting MET (receptor tyrosine kinase) responsible for promoting tumor growth. This process is carried out by transmitting extracellular stimuli to intracellular signaling mediated through a known pathway (PI3K/AKT). Researchers found that the XIST/miR-34a network affects TC cell proliferation and tumor growth via the MET-PI3K-AKT

pathway [61]. Hippo signaling has been implicated in a range of malignancies, including cancer, in addition to controlling cell proliferation. SNHG15, a novel lncRNA, has been identified as a key modulator of cancer growth and development and results in poor prognosis in parathyroid patients. The SNHG15 if knockdown results in the suppression of migration and growth and promotes apoptosis in parathyroid cancer cells. Additionally, SNHG15 induces oncogenicity in parathyroid cancer via upregulating YAP1 and sponging miR-200a-3p [62]. In short, the SNHG15 ceRNA modulates the YAP1-Hippo signaling pathway of parathyroid cancer by targeting miR-200a-3p directly.

Mutations in the APC gene can develop thyroid cancer due to inappropriate Wnt pathway signaling. The lncRNA, PTCSC3 inhibits the progression of parathyroid cancer via the Wnt/β-Catenin pathway [63]. PTCSC3 if overexpressed, decreases migration and proliferation of parathyroid cancer cells. In addition, it stimulates SCAI expression and inhibits β-catenin expression. In summary, the network comprised of PTCSC3/miR-574-5p/Wnt/β-catenin determines the aggressiveness of PTC, which will be of critical importance for PTC treatment in the future. Furthermore, lncRNA CASC15 promotes tumorigenesis through the Wnt/catenin signaling pathway by sponging miR-7151-5p and upregulating WNT7A. The WNT5A, a member of the WNT family, is reported to be deregulated in cancer; by sponging the miR-378a-3p/WNT5A axis, the lncRNA FAM230B induces migration, invasion, and metastasis in PTC cells [64]. CircRNAs are known to play a regulatory role in the Wnt/β catenin signaling pathway [65]. CircNEK6 promotes TC growth by increasing FZD8 expression levels and by targeting miR-370-3p, which activates the Wnt/β catenin pathway. The Circ-ITCH acts as a tumor suppressor and is derived from the multiple exons of the ITCH [66]. Through sponging miR-22-3p, circ-ITCH increases the CBL, an E3 ligase of nuclear β-catenin levels. Thus, CBL upregulation inhibits the Wnt/β-catenin pathway, thereby slowing PTC growth [67].

Transition of tumor epithelial-to-mesenchymal is regulated by CeRNA

Acquiring mesenchymal characteristics by epithelial cells leads to the appearance of epithelial-mesenchymal transition (EMT), which affects cancer cells and makes them more aggressive, invasive, have stem-like characteristics, and resist apoptosis. NcRNAs, such as miRNAs and lncRNAs, can directly target EMT-inducing transcription factors (such as E-cadherin) [68], which are generally deregulated in thyroid cancer. Observations regarding EMT's function in thyroid cancer indicate that they are involved in the transition from PTC and FTC to ATC and PDTC [69]. The lncRNA TUG1 is upregulated in thyroid cancer cells and modulates invasion, proliferation, migration, and EMT phenotypes by activating ZEB1 and sponging miR-145. Furthermore, knocking down TUG1 reversed EMT into MET [70]. Another study found that LINC-00460 modulates the miR-485-5p/Raf1 axis, thus accelerating the progression of PTC. The LINC00460 knockdown inhibits the EMT process by enhancing E-cadherin protein levels and reducing N-cadherin, MMP9, and vimentin levels [71]. Previous research has indicated that the lncRNA HOXA-AS2 is upregulated in PTC, activating the EMT process through miR-520c-3p/S100A4 regulation [72].

CiRS-7 is a novel circRNA that regulates miRNA, mRNA, and RBP functions to influence certain physiological processes [73]. As an oncogene, ciRS-7 suppresses miR-7 and promotes tumor growth in several cancer types. Furthermore, circRNA ciRS-7 has been implicated in promoting EMT in PTC cells [74], and via modulating the miR-7/EGFR axis, ciRS-7 enhances PTC cell proliferation and migration [74]. In TC, another study suggested the possible role of Circ_0001681 in the EMT process. In TC cells, Circ_0001681 is usually found in the cytoplasm and has a much higher expression level than in normal cells. Moreover, miR-942-5p in TC downregulates and inversely related to circ_0001681 level [75]. By targeting miR-942-5p and increasing the expression of TWIST1, knockdown of circ_0001681 significantly inhibited TC progression [75]. These findings indicate that circ_0001681 is an important treatment candidate in TC.

Drug resistance of TC is regulated by ceRNA

New advances in cancer therapy have significantly improved cancer patients' quality of life as well as their survival rate [76]. The fact is, in plenty of other cases, a favorable response to therapy can change later on, leading to the recurrence of cancer. Resistance to therapy is

one of the biggest issues in preparing efficient cancer therapies [76]. In drug resistance of TC cases, ncRNAs play a significant role as components of ceRNA networks. In TC drug resistance, the lncRNA NEAT1 is one of a good example of lncRNAs functions. NEAT1 makes ATC cells more resistant to cisplatin [77]. Mechanistically, ATC developed resistance to cisplatin when NEAT1 targets miR-9-5p and increases SPAG9 expression. Moreover, knockdown of NEAT1 via the miR-9-5p/SPAG9 network inhibited cisplatin resistance in ATC [77]. Radioiodine is a common treatment choice for PTC patients [78]. It has been previously reported that CASC2 ectopic overexpression can promote radioiodine sensitivity in resistant PTC cells, suggesting the possible role of ncRNAs in radioiodine sensitivity. Specifically, CASC2 enhances radioiodine sensitivity of the PTC through miR-155 sponging [78]. The miR-155 has been reported to be oncogenic in many types of cancer, such as breast cancer, lung cancer, and thyroid cancer. The lncRNA MEG3 also stimulates radioiodine sensitivity in TC cells [79]. Patients with decreased MEG3 expression in TC patients receiving radioiodine treatment have much lower survival rates. Additionally, MEG3 increased radioiodine sensitivity in TC cells via miR-182 sponging, suggesting that MEG3 may be a useful biomarker and therapeutic option in TC patients with radioiodine resistance [79]. An additional study demonstrated that NEAT1 is upregulated in radioiodine-resistant PTC cells, enabling them to resist radioiodine by increasing cell proliferation and reducing apoptosis. In radioiodine-resistant PTC cells, NEAT1 targets miR-101-3p and enhance the expression of FN1, a highly expressed downstream protein [80].

The FN1 overexpression induced an increase in the levels of p-ERK, p-AKT, and p-PI3K while depletion of the NEAT1 reversed this effect and prevented activated PI3K/AKT signaling. NEAT1 knockdown has been shown to disrupt radioiodine resistance in PTC cells via miR-101-3p/FN1/PI3K-AKT axis [80]. Research indicates that circRNAs contribute to chemo- and radiation-resistance in cancer cells [81]. In addition, the circEIF6 may increase cisplatin-induced autophagy, which may reduce apoptosis, increasing the resistance of PTC and ATC cells to cisplatin [82]. Modulating the miR-144-3p/TGF-α network, the circleEIF6 increased autophagy, resulting in increased resistance to cisplatin in parathyroid cancer and ATC cells [82].

Conclusions

Over the last decade, more effective molecular tools have been developed for early thyroid cancer diagnosis and identifying the genetic basis of thyroid cancer. Even so, some aggressive subtypes of thyroid cancer patients do not have a sufficiently improved survival rate, emphasizing the need for more fundamental research leading to personalized treatments-using RNA transcripts may be one such option. The function of various types of RNA, including miRNAs, pseudogenes, lncRNAs, and circular RNAs, in diverse physiological conditions, has been determined in the past years. Scientists anticipate a boom in the reporting of ceRNA function of diverse RNA molecules in view of advances in whole-genome transcript datasets. Only 2% of human genes code for proteins while the rest are non-coding regions. The MiRNAs, lncRNAs, pseudogenes, and circRNAs are most commonly transcribed from these non-protein-coding regions. Many of them compete for binding to miRNAs with certain mRNAs, as discussed in the present review. However, the specific mechanisms they contribute to tumorigenesis remain largely unknown. Understanding how multiple genes and pathways are modified using ceRNAs provides a deeper insight into the basic biological mechanisms of thyroid cancer pathogenesis. In this study, we discuss the development of thyroid cancer characteristics by deregulating ceRNA networks, including cell metastasis, apoptosis, proliferation, invasion, and migration, as well as resistance to therapeutics or treatments. In addition, the development in understanding prognosis and discovery of diagnostic biomarkers for thyroid cancer may be made possible with further studies related to unveiling the mechanism that how EMT progress is affected by ceRNA networks at molecular levels. Moreover, future investigations aimed at understanding the mechanisms of noncoding RNA-induced thyroid cancer cell resistance to chemotherapeutic treatments might provide insight into the possibility of curing thyroid cancer. Overall, we suggest that studying the molecular mechanisms underlying thyroid cancer development with a specific focus on ceRNAs, lncRNAs, and miRNAs are necessary to

develop advanced level effective therapeutic options and promising preventive measures.

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Disclosure of conflict of interest

None.

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