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Review

Review

Recent advances of NEAT1-miRNA interactions in cancer

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Abstract

With high incidence rate, cancer is the main cause of death in humans. Non-coding RNAs, as novel master regulators, especially long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), play important roles in the regulation of tumorigenesis. lncRNA NEAT1 has recently gained much attention, as it is dysregulated in a broad spectrum of cancers, where it acts as either an oncogene or a tumor suppressor gene. Accumulating evidence shows that NEAT1 is correlated with the process of carcinogenesis, including proliferation, invasion, survival, drug resistance, and metastasis. NEAT1 is considered to be a biomarker and a novel therapeutic target for the diagnosis and prognosis of different cancer types. The mechanisms by which NEAT1 plays a critical role in cancers are mainly via interactions with miRNAs. NEAT1-miRNA regulatory networks play significant roles in tumorigenesis, which has attracted much attention from researchers around the world. In this review, we summarize the interaction of NEAT1 with miRNAs in the regulation of protein-coding genes in cancer. A better understanding of the NEAT1-miRNA interactions in cancer will help develop new diagnostic biomarkers and therapeutic approaches.

Key words NEAT1, cancer, miRNA, interaction, ceRNA

Introduction

Non-coding RNAs (ncRNAs) are divided into long non-coding RNAs (lncRNAs) and short ncRNAs, including microRNAs (miRNAs) [1]. lncRNAs are usually more than 200 nucleotides in length, may have their own promoters, and may be situated in intergenic loci [2]. lncRNAs play essential roles in various cellular and physiological processes, such as chromatin dynamics, gene expression regulation, subcellular architecture, cell differentiation, and development [3]. lncRNA NEAT1 has recently gained much attention. NEAT1 is transcribed by RNA polymerase II from a genetic locus called familial tumor syndrome multiple endocrine neoplasia (MEN) type I on the human chromosome 11 and has two distinct isoforms, i.e., NEAT1_1 (3.7 kb) and NEAT1_2 (22.7 kb). NEAT1 is important for RNA stability, isoform switching, and paraspeckle assembly, and is enriched in the nucleus, localized within paraspeckles as an essential component of the nuclear paraspeckle structure [4]. NEAT1_1 but not NEAT1_2 is needed for paraspeckle formation [5]. Interestingly, NEAT1 has been documented to be highly expressed in multiply solid malignancies, but its expression is downregulated in leukemia and multiple myeloma [6–8]. NEAT1 acts as an oncogene or tumor suppressor gene in cancers. Deregulation of NEAT1 impacts different cellular processes, including proliferation, dedifferentiation, migration, invasion, and anti-apoptosis [9–11]. As such, NEAT1 may be a potential therapeutic target in various cancers. It is also possible that NEAT1 can be utilized as a diagnostic tool for cancer at advanced stages.

As another major subset of ncRNAs, miRNAs are capable of regulating physiological and pathological processes via inhibiting target mRNA translation or promoting mRNA degradation [12]. In addition, miRNAs have pleiotropic roles in regulating cell proliferation, apoptosis, cell cycle, metastasis, angiogenesis, and metabolism, as they can target hundreds of mRNAs and inhibit mRNA translation or promote mRNA degradation [13]. Therefore, miRNAs are crucial regulators of gene expression and promising candidates for cancer biomarker development.

In this review, we summarize the interactions of NEAT1 with miRNAs in the regulation of the expression of protein-coding genes in cancer. A better understanding of NEAT1-miRNA interactions in cancer will help develop new diagnostic markers and therapeutic approaches.

NEAT1-miRNA Interactions

Numerous related studies have demonstrated that the interactions between NEAT1 and miRNAs play a key role in tumorigenesis. NEAT1-miRNA interactions are mainly divided into the following three forms: NEAT1 as a sponge for miRNA, miRNAs regulated by

NEAT1, and NEAT1 regulated by miRNAs.

NEAT1 is a sponge of miRNAs

Competitive endogenous RNA (ceRNA) networks formed by lncRNA/miRNA/mRNA interactions are involved in a broad spectrum of biological processes in cancer. NEAT1 may compete with miRNA for binding to the 3′-UTR of target mRNAs, leading to the inhibition of miRNAs and the activation of target proteins (Figure 1). As a significant molecular sponge, NEAT1 competitively binds to a variety of miRNAs to modulate oncogenic factors in cancer, which plays key regulatory roles in proliferation, apoptosis, epithelial-to-mesenchymal transition (EMT), invasion, migration and metastasis.

miRNAs are regulated by NEAT1

Numerous studies have demonstrated that NEAT1 can epigenetically regulate gene expression. It has been reported that NEAT1 silences miR-129-5p expression via increased DNA methylation of miR-129 [14]. The dysregulation of the BRCA1/NEAT1/miR-129-5p/WNT4 signaling axis is involved in promoting breast tumorigenesis. Moreover, NEAT1 can positively regulate miR-17, but the specific mechanism of action requires further exploration [15].

NEAT1 is regulated by miRNAs

It has been reported that miRNAs can directly target lncRNAs and decrease the expression of lncRNAs in cancer cells. In this context, miR-124-3p inhibits NEAT1 expression, miR-124-3p is markedly decreased in ovarian cancer patients, and its tumor suppressive roles might be due to its regulation of NEAT1 expression [16] (Figure 2). Moreover, miR-370-3p, miR-548ar-3p, miR-449a, miR-384, and miR-126 induced a significant downregulation of NEAT1, confirming the interaction between the miRNAs and lncRNAs [17–21]. Some mature miRNAs may act as transcriptional regulators in the nucleus; for instance, miR-140 binds to NEAT1 at 974–998 bp in the nucleus and enhances NEAT1 stability [22]. How miRNAs contribute to and regulate NEAT1 expression warrants further investigation.

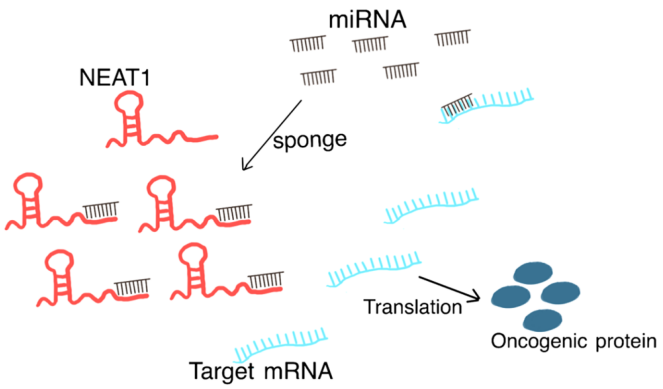

Figure 1. NEAT1 acts as ceRNA to sponge miRNA, resulting in high expression of downstream target genes

NEAT1 in Human Cancers

The present review summarizes current evidence regarding the abnormal expression of NEAT1 in human cancers. NEAT1 may serve as a potential therapeutic target and biomarker for diagnosis or prognosis due to high tissue specificity, high efficiency, and elevated stability. It has been reported that the level of NEAT1 is dynamically regulated in different cancer types, such as hepatocellular carcinoma, thyroid carcinoma, breast cancer, glioma, osteosarcoma, and prostate cancer.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC), the sixth most common cancer worldwide, has high mortality rates with poor prognosis worldwide [23]. As a result, identifying effective biomarkers is essential to predict the prognosis of HCC. Recently, a higher expression level of NEAT1 was found to be associated with larger tumor size and vascular invasion of HCC patients [24]. NEAT1 is positively associated with HCC cell growth, migration invasion, and radiosensitivity [21,25,26]. Functionally, NEAT1 enhances the tumorigenesis of HCC by directly interacting with miR-139-5p or miR-22-3p and increasing the release of miR-139-5p-targeted TGF-β1 or miR-22-3p-targeted AKT2, respectively [25,27]. Luciferase reporter and RNA-binding protein immunoprecipitation assays indicated that miR-384, miR-613, and miR-335 directly bind to the sequence of NEAT1 [21,24]. Moreover, NEAT1 also promotes the progression of HCC through sponging miR-204 [28]. ATG3 is a target of miR-204 and positively correlated with the autophagy machinery of HCC [29]. Additionally, NEAT1 functions as a ceRNA for miR-129-5p, antagonizes its function, and leads to the derepression of its endogenous target valosin-containing protein (VCP) and IκB, which is a core oncogene in the promotion of the proliferation of HCC cells [30].

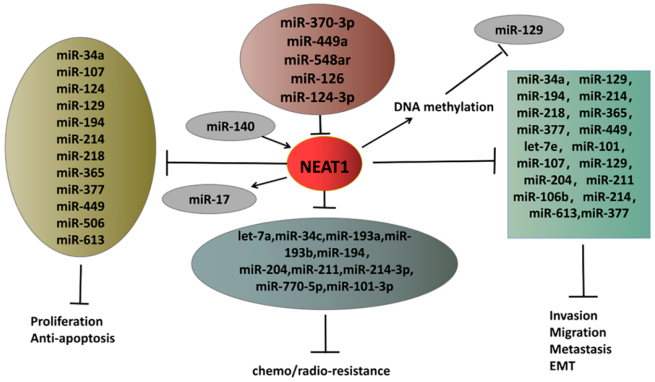

Figure 2. Schematic illustration of the interaction of NEAT1 with miRNAs miR-126, miR-370-3p, miR-449a, miR-124-3p, and miR-548ar inhibit NEAT1, while miR-140 enhances NEAT1 expression. NEAT1 regulates miRNAs to play a key role in tumorigenesis. NEAT1 suppresses the expression of miR-129 by promoting the DNA methylation of the miR-129 promoter.

We previously reported that NEAT1 mediates sorafenib resistance of HCC cells by suppression of miR-335 expression and disinhibition of the c-Met-Akt signaling pathway [31]. Another report demonstrated that NEAT1 targets the miR-149-5p/AKT1 axis to decrease the activity of sorafenib against HCC cells [32]. NEAT1 was also shown to act as a ceRNA of NEAT1/miR-199a-3p/UCK2, NEAT1/miR-485/STAT3, NEAT1/miR-296-5p/CNN2, and NEAT1/miR-320a/LAGE3, which contribute to the progression of HCC cell lines [33–36]. Repression of NEAT1 restrains $CD8^+$ T cell apoptosis and enhances the cytolysis activity against HCC, in HCC mice, through regulating the miR-155/Tim-3 pathway [37]. This provides clues for the development of new strategies for HCC immunotherapy. Furthermore, functional analysis revealed that downregulation of lncRNA NEAT1_2 radio-sensitizes HCC cells through regulation of the miR-101-3p/WEE1 axis [26]. These results indicate the potential of NEAT1 as a biomarker and possible treating target for HCC.

Thyroid carcinoma

Thyroid carcinoma is the most common malignancy in thyroid tissue, and it is also a highly invasive cancer [38]. Tan *et al.* [39] revealed that low NEAT1 expression suppressed the migration, invasion, and glycolysis in anaplastic thyroid carcinoma cells under hypoxia at least partially through modulating miR-206 and miR-599. Moreover, NEAT1 was found to bind with miR-592 to regulate neuro-oncological ventral antigen 1 (NOVA1) expression, which plays regulatory roles in thyroid cancer malignancy both *in vitro* and *in vivo* [40]. However, it has recently been found that miR-129-5p/NEAT1 negatively correlates with each other by direct target relationship, and their combination suppresses the progression of papillary thyroid cancer (PTC) [41]. Further *in vivo* and *in vitro* experiments confirmed that NEAT1 silencing reduces PTC progression by upregulating miR-129-5p, which suppresses KLK7 expression [41]. In PTC cells, NEAT1 silencing increases the level of its regulator, miR-126, and downregulates VEGFA, which sets the density of tumor vasculature [17]. In addition, NEAT1_2 serves as a ceRNA to regulate ATAD2 expression by sponging miR-106b-5p in PTC. Likewise, NEAT1 functions as a ceRNA to upregulate SPAG9 by sponging miR-9-5p, which provides new insights into molecular regulation in the resistance of anaplastic thyroid carcinoma cells to cisplatin [42]. Furthermore, silencing of NEAT1 could reverse radioactive iodine resistance of PTC cell via upregulation of miR-101-3p. Both NEAT1 silencing and miR-143 overexpression could cause a significant decrease of FN1, which is an overexpressed downstream protein in radioactivity iodine-resistance PTC tissues [43].

Breast cancer

Interesting studies reported that NEAT1 played an important role in breast cancer progression, which uncovered a novel mechanism through the NEAT1/miR-410-3p/CCND1, NEAT1/miR-448/ZEB1, NEAT1/miR-21/RRM2, NEAT1/miR-101/EZH2, and NEAT1/miR-107/CPT1A axes [44–48]. Li *et al.* [49] found that NEAT1/miR-218 and NEAT1/miR-146b-5p promotes breast cancer angiogenesis, but the exact mechanism remains unclear. The expression of NEAT1 could be regulated by breast cancer susceptibility gene 1 (BRCA1), since BRCA1 and dysregulation of the NEAT1/miR-129-5p/WNT4 signaling axis contribute to BRCA1-deficiency-induced malignant phenotypes in breast cancer cells, such as increases in cell proliferation, invasiveness, anchorage-independent growth, and stemness [14]. Specifically, high expression of NEAT1 was shown to suppress the expression of miR-133b in breast cancer, and translocase of inner mitochondrial membrane 17 homolog A (TIMM17A) could be a target of miR-133b [50]. NEAT1 was also found to promote breast cancer progression by sponging miR-138-5p targeting zinc finger protein X-linked (ZFX), which acts as a transcriptional activator in multiple types of human tumors [51,52]. This reciprocal repression of miR-204 and NEAT1 highlights the significance of the interaction between lncRNAs and miRNAs, and provides new insights into the mechanisms of cell proliferation and apoptosis [53].

In addition, NEAT1 promotes 5-FU resistance in breast cancer cells via enhancement of high mobility group A2(HMGA2) by inhibiting miR-211 [54]. Furthermore, miR-548ar could regulate cell apoptosis by interacting with NEAT1. Overexpression of miR-548ar downregulates the expression of NEAT1. However, the mechanisms of miR-548ar interacting with NEAT1 remain to be further characterized, since miR-548ar does not directly bind to NEAT1 [20]. Indeed, NEAT1_1 and NEAT1_2 have distinct expression patterns among different intrinsic breast cancer subtypes [55]. In the future, the interactions between the two subtypes of NEAT1 with miRNA warrant further in-depth studies.

Glioma

Aberrant NEAT1 expression is correlated with metastasis and poor prognosis. Additionally, NEAT1 is considered to be a potential biomarker for patients with glioma. Overexpression of NEAT1 is involved in the development of glioma via inhibition of miR-132 [56]. The downstream target of miR-132 is sex-determining region Y-box protein 2 (SOX2), which positively affects cancer cell traits, such as the capacity to proliferate, migrate, invade, and metastasize [57]. Moreover, NEAT1 can promote tumor progression by suppressing the miR-107-CDK14 interaction [58]. Another study revealed that NEAT1 acts as a molecular sponge for miR-449b-5p and leads to the upregulation of c-Met [59]. NEAT1 knockdown suppresses stem-like properties in glioma stem cells by modulating the miR-107/CDK6 pathway [60]. NEAT1 also affects glioma growth by sponging miR-139-5p targeting CDK6 [61]. In another study, NEAT1 was found to sponge miR-185-5p, which promotes DNA methyltransferase 1 (DNMT1) expression and activates mammalian target of rapamycin (mTOR) signaling, thus inhibiting apoptosis and promoting glioma migration, proliferation, and the EMT process [62]. Moreover, NEAT1 enhances glioma progression by sponging miR-152-3p, which targets CCT6A [63].

Recent studies have indicated that NEAT1 is a functional oncogene in glioblastoma development. miR-370-3p exerts its function by targeting NEAT1, and NEAT1 could also inhibit the expression of miR-370-3p, promoting the upregulation of HMGA2 and HIF1A and contributing to glioblastoma progression [18]. In addition, NEAT1 promotes glioblastoma progression by the NEAT1/let-7e/NRAS axis [64]. Different from previous studies, Liu *et al.*[65] reported that NEAT1 is downregulated in glioma tissues and cells. Furthermore, NEAT1 upregulates the expression of DKK3 to inhibit proliferation and promote apoptosis of glioma cell lines by inhibiting miR-92b. NEAT1 may serve as a novel therapeutic target for glioma. Due to these inconsistent findings, the exact role of NEAT1 in glioma still needs to be further explored.

Non-small cell lung cancer (NSCLC)

NEAT1 overexpression positively correlates with malignant features

of NSCLC, including TNM stage, tumor size, and lymph node metastasis, as well as poor prognosis [66]. NEAT1 promotes cisplatin sensitivity of NSCLC by sponging miR-98-5p targeting copper transporter 1 (CTR1) [67]. Similarly, NEAT1 inhibits miR-98-5p to induce CTR1 expression, resulting in increased chemosensitivity [68]. Moreover, Wu *et al.* [69] showed that NEAT1/hsa-mir-98-5p/MAPK6 is involved in the development and progress in NSCLC. NEAT1 functions as ceRNA against miR-377-3p, and E2F3 may be a direct target of miR-377-3p [66,70]. In another study, NEAT1 was found to sponge miR-101-3p, which targets the transcription factor SOX9 to promote the invasion of NSCLC [71]. SOX9 plays an important role in cancer cell proliferation, migration, and angiogenesis by activating the Wnt/β-catenin signaling pathway [72]. NEAT1 plays an oncogenic role in NSCLC progression through activating the miR-101-3p/SOX9/Wnt/β-catenin and has-miR-376b-3p/SULF1 axes [73]. For instance, NEAT1 upregulates the HMGB2, the target gene of miR-181a-5p through acting as a competitive sponge of miR-181a-5p [74]. Thus, NEAT1 could be a potential therapeutic target for NSCLC.

Osteosarcoma

Osteosarcoma is the most common primary bone sarcoma and has poor prognosis and high disability rates in adolescents [75]. Upregulated NEAT1 reduces the sensitivity of cisplatin (DDP) and inhibits DDP-induced apoptosis and cell cycle arrest via miR-34c [76]. Moreover, Wang *et al.* [77] reported that knockdown of NEAT1 inhibits proliferation, invasion, and induces apoptosis in osteosarcoma cells by suppressing miR-194 expression. NEAT1 serves as a sponge of miR-186-5p and miR-339-5p to upregulate HIF-1α and TGF-β1, thereby regulating the proliferation, invasion, and EMT process of osteosarcoma cells [78,79]. It has also been verified that NEAT1 competitively binds to miR-34a-5p and thus mediates HOXA13 expression [80].

Colorectal cancer

NEAT1 functions as an oncogene influencing cell viability and invasion in part by serving as a ceRNAs which modulate miR-205-5p, miR-196a-5p, miR-185-5p, and miR-495-3p expression, leading to subsequent repression of the miR-205-5p/VEGFA, miR-196a-5p/GDNF, miR-185-5p/IGF2, and miR-495-3p/CDK6 axes [68,81–83]. Similarly, NEAT1 sponges miRNA-34a expression, leading to subsequent upregulation of silent information regulator T1 (SIRT1)expression and activation of the Wnt/β-catenin signaling pathway [84]. NEAT1 functions as a ceRNA for miR-193a, resulting in the upregulation of KRAS in cancer cells [85,86]. As suggested previously, much more research is needed to understand the roles of NEAT1 in colorectal cancer metastasis.

Cervical cancer

Patients with higher NEAT1 levels have poorer clinical characteristics and a shorter survival time compared to those that exhibit lower NEAT1 expression levels [87]. NEAT1 binds to miR-361 to regulate SOX4 expression, which induces EMT and sphere formation in cervical cancer cells [88]. NEAT1 could function as a ceRNA to regulate cyclin D1 through sponging miR-193b-3p in cervical cancer [89]. However, it has recently been found that NEAT1 can serve as a sponge for miR-9-5p, miR-101, and miR-361 to inhibit their expression, thereby promoting miR-361 [87,88,90]. Further studies on the mechanism are needed to explore the downstream targets of miRNA. In addition, NEAT1 could negatively regulate its target miR-124, and miR-124 could reverse the effects of NEAT1 on the migration, invasion, EMT, and NF-κB pathway of cells [91].

Pancreatic cancer

Pancreatic cancer is the most malignant type of human cancers, and its prognosis is extremely poor with a 5-year relative survival rate of 5% [92]. Researchers have shown that NEAT1 is highly expressed in pancreatic cancer relative to normal pancreatic tissues and is associated with tumor size, TNM stage, lymph node, and distant metastasis, and also predicts poor prognosis [93–95]. NEAT1 upregulates the expression of c-Met to promote cell growth, migration, invasion, and apoptosis by sponging miR-335-5p [94]. Moreover, NEAT1 can also bind to miR-506-3p [93], but further investigation of this mechanism is needed. In another study, specifically focused on pancreatic ductal adenocarcinoma (PDAC), RELA, as components of the NF-κB pathway, could bind to the promoter region of NEAT1 to induce its expression [96]. However, RELA is also a direct downstream target of miR-302a-3p, and NEAT1 could serve as a sponge for miR-302a-3p [96]. In summary, RELA, NEAT1, and miR-302a-3p form a feedback loop in PDAC to modulate PDAC cell proliferation and migration [96].

Gastric cancer

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer deaths globally [97]. NEAT1 promotes GC cell proliferation and migration by inhibiting miR-1224-5p [98]. Remodeling and spacing factor 1 (RSF1) is a downstream target of miR-1224-5p and is associated with TNM stage and poor prognosis in cancer [98]. NEAT1 can also promote cell growth in GC by regulating the miR-497-5p/PIK3R1 axis [99]. NEAT1 can be recognized as a competing endogenous RNA to modulate STAT3, ROCK1, and ABCC4 by sponging miR-506, miR-335-5p, and miR-365a-3p in GC, respectively [100–102]. Moreover, NEAT1 affects PI3K/AKT/mTOR signaling pathway via regulating miR-1294 and AKT1 [103]. Jiang *et al.* [104] suggested that NEAT1 functions as a ceRNA to suppress miR-27b-3p expression, thereby inhibiting the radiation-mediated inhibition of tumor growth and is associated with poor overall survival. NEAT1 could regulate STAMBPL1 expression through regulating miR-103a [105]. Additionally, NEAT1 regulates radio-sensitivity via miR-27b-3p in gastric cancer [104]. However, NEAT1 enhances cell viability and migration through upregulating miR-17 [15].

Nasopharyngeal carcinoma (NPC)

Cox regression analyses and a meta-analysis suggested that high expression of NEAT1 is an independent unfavorable prognostic factor in patients with nasopharyngeal carcinoma (NPC) [106]. Further research is required to verify the prognostic value of NEAT1 in patients with NPC. NEAT1 interacts with miR-124, thereby modulating the metastasis of NPC cells through NF-κB [107]. In addition, NEAT1 knockdown exerts suppression effects on cell proliferation, migration, invasion, and EMT by miR-34a-5p and miR-204 [108,109]. NEAT1 targets miR-34a-5p at least partly to drive NPC progression by regulating Wnt/β-catenin signaling [108]. NEAT1 contributes to NPC cell growth, invasion, and radiation resistance *in vitro* and cancer metastasis *in vivo* by directly interacting with miR-101-3p and decreasing the binding of miR-101-3p to the 3′ UTR of epithelial membrane protein 2 expression (EMP2) [110]. The

NEAT1/let-7a-5p axis regulates cisplatin resistance by targeting Rsf-1 and modulating the Ras-MAPK signaling pathway [111].

Ovarian cancer

Ovarian cancer is one of the most frequently diagnosed malignancy in females worldwide. Chai *et al.* [16] discovered that the expression of NEAT1 is significantly increased in ovarian cancer tissues compared with that in adjacent non-tumor tissues. With regard to clinicopathological parameters, increased NEAT1 levels are closely associated with the International Federation of Gynecology and Obstetrics (FIGO) stage and lymph node metastasis. In general, NEAT1 displays advantageous characteristics as a novel biomarker for early diagnosis, prognosis evaluation, and as a therapeutic target in ovarian cancer. NEAT1, stabilized by LIN28B, promotes ovarian cancer cell proliferation and migration via sponging miR-506 [112]. Additionally, NEAT1 modulates the expression of well-known oncogenes, such as Rho-associated coiled-coil containing protein kinase 1 (ROCK1), tight junction protein 3 (TJP3), basic leucine zipper W2 domain-containing protein 1 (BZW1), and B-cell lymphoma-2 (BCL2), by competing for miR-382-3p, miR-1321, miR-4500, and miR-34a-5p, respectively. This leads to a consequent increase in metastasis, invasion, and EMT [113–117]. Interestingly, a few studies have implicated different NEAT1 ceRNA axes in chemoresistance (cisplatin resistance and paclitaxel resistance), including miR-194/ZEB1 and miR-770-5p/poly adenosine diphosphate-ribose polymerase 1 (PARP1) [114,118].

Endometrial cancer

Endometrial cancer is an aggressive cancer without effective therapies. A recent study indicated that NEAT1 promotes proliferation, migration, and invasion of endometrial cancer by sponging the miR-144-3p-targeting EZH2 [119]. In addition, NEAT1 promotes proliferation, invasion, sphere formation, and paclitaxel resistance of endometrial cancer through sponging miR-361, whose downstream target is the oncogene *STAT3* [120]. Progesterone exerts suppressive influence on endometrial cancer progression by regulating the NEAT1/miR-146b-5p-mediated Wnt/β-catenin signaling pathway [121]. NEAT1 sponges the tumor suppressor miR-214-3p, which regulates HMGA1 to promote the growth, migration, and invasion of cancer cells [122].

Prostate cancer

Prostate cancer is the most common noncutaneous cancer in men worldwide, with incidence and mortality steadily rising [92,123]. NEAT1 was found to be expressed at high levels in prostate cancer cell lines and in docetaxel-resistant prostate cancer clinical samples or related cell lines [124–126]. Prostate cancer patients with higher expression of NEAT1 are also significantly associated with poorer TNM stage, lymph nodes metastasis, distant metastasis, and Gleason score, showing shorter overall survival [124]. Additionally, NEAT1 modulates the expression of ACSL4 by competing for miR-34a-5p and miR-204-5p in prostate cancer, with a consequent increase in the docetaxel resistance [125]. Guo *et al.* [127] demonstrated that NEAT1 promotes the proliferation ability of prostate cancer cells by acting as an endogenous sponge of miR-98-5p and regulating the expression of the miR-98-5p target gene HMGA2.

Conclusions and Perspectives

NEAT1 has emerged as a novel master regulator of cancer. In most solid tumors, NEAT1 is highly expressed and plays an oncogenic role, promoting the occurrence and development of tumors (Table 1). However, NEAT1 is significantly repressed in acute promyelocytic leukemia and acts as a tumor suppressor gene, which is different from its role in solid malignancies. In the future, research concerning the interaction between NEAT1 and miRNA should be carried out, primarily in the context of cancer. The establishment of a comprehensive NEAT1–miRNA regulatory network is of great significance to the development of targeted anti-tumor drugs. However, NEAT1 and miRNA dysregulation has also been identified in non-cancerous diseases, such as viral infections and neurodegeneration diseases. We expect that there will be more research works associated with various signaling pathways linked to non-cancerous diseases to be identified in near future. The ratio of NEAT1_1 and NEAT1_2 isoforms dynamically changes in a cell type-specific manner.

Despite such crucial roles for NEAT1_1, its expression levels are much lower in most tissues compared to the other isoform. In adult mouse tissues, NEAT1_2 is only expressed in specific types of cell, such as the epithelial layers of digestive tissues. However, NEAT1_1 is expressed in a broader range of cell types and also has a variety of NEAT1_2/paraspeckle-independent functions [128]. NEAT1_2 has been detected in several nonparaspeckle loci. Such localization patterns imply the paraspeckle-independent roles for this isoform. We should particularly investigate the functional differences in expression, function, and cellular localizations of both NEAT1 isoforms. Future research on NEAT1 should be isoform-specific and build up the missing link between the regulatory role of the lncRNA-miRNA interaction and cancer progression. At present, most experiments are still at the cellular level, and animal models should be further established to better realize “bench to bedside” translational research via integrating computational analysis, perfect experimental equipment, and robust clinical tools.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1. miRNAs sponged by NEAT1 s in different cancer types

Cancer type	Expression	Functions	Role	Related molecules	Ref.
Hepatocellular carcinoma	Upregulated	Proliferation Anti-apoptosis Migration Invasion	Oncogenic	miR-129-5p↓, VCP↑, IκB↑, miR-101-3p↓, WEE1↑, miR-199a-3p↓, UCK2↑, miR-155↓, Tim-3↑, miR-320a↓, LAGE3↑, miR-204↓, ATG3↑, hsa-mir-139-5p↓, TGF-β1↑, miR-485↓, STAT3↑, miR-296-5p↓, CNN2↑, let-7b↓, IGF-1R↑	[25,26,28,30,33–37]
Thyroid carcinoma	Upregulated	Migration Migration Enhances cisplatin resistance	Oncogenic	miR-101-3p↓, FN1↑, miR-9-5p↓, SPAG9↑, miR-214↓, B-catenin↑	[42,43]
Breast cancer	Upregulated	Proliferation Anti-apoptosis Metastasis	Oncogenic	miR-101↓, EZH2↑, miR-410-3p↓, CCND1↑, miR-138-5p↓, ZFX↑, miR-146b-5p↓, miR-129↓, ZEB2↑, miR-211↓, HMGA2↑, miR-124↓, STAT3↑, miR-107↓, CPT1A↑, miR-133b↓, TIMM17A↑, miR-448 ↓, ZEB1↑, miR-21↓, RRM2↑, miR-204↓	[44–46,48–51,53,54]
Glioma	Upregulated	proliferation Metastasis Anti-apoptosis	Oncogenic	miR-107↓, CDK14↑, miR-139-5p↓, CDK6↑, miR-185-5p↓, DNMT1↑, miR-132↓, SOX2↑, miR-152-3p↓, CCT6A↑, miR-449b-5p↓, c-Met↑	[56,58,59,61-63]
Glioma	Downregulated	Apoptosis	Anti-oncogene	miR-92b↑, DKK3↓	[65]
Glioblastoma	Upregulated	Cell growth Migration Invasion	Oncogenic	miR-370-3p↓, HMGA↑, HIF1A↑, let-7e↓, NRAS↑	[18,64]
Non-small cell lung cancer	Upregulated	Proliferation Invasion Migration Anti-apoptosis	Oncogenic	miR-376b-3p↓, SULF1↑, miR-377↓, E2F3↑, miR-181a-5p↓, HMGB2 ↑, miR-377-3p↓, E2F3↑	[66,70,73,74]
Osteosarcoma	Upregulated	Anti-apoptosis Invasion Migration	Oncogenic	miR-34c↓, BCL-2↑, CCND1↑, Ki-67↑, miR-186-5p↓, HIF-1α↑, miR-339-5p↓, TGF-β1↑, miR-34a-5p↓, HOXA13↑	[78–80]
Colorectal cancer	Upregulated	Proliferation Migration Invasion	Oncogenic	miR-205-5p↓, VEGFA↑, miR-185-5p↓, IGF2↑, miR-495-3p↓, CDK6↑, miR-34a↓, SIRT1↑, miR-196a-5p↓, GDNF↑ miR-193a-3p↓, KRAS↑	[68,81–83,86]
Cervical cancer	Upregulated	Invasion Proliferation Anti-apoptosis Enhance the radio-resistance	Oncogenic	miR-9-5p↓, miR-133a↓, SOX4↑, miR-101↓, miR-124↓, miR-193b-3p↓, CCND1↑	[87,89–91]
Pancreatic cancer	Upregulated	Proliferation Migration	Oncogenic	miRNA-335-5p↓, c-met↑	[94]
Gastric cancer	Upregulated	Proliferation Invasion Migration Cell cycle	Oncogenic	miR-27b-3p↓ miR-1224-5p↓, RSF1↑, miR-497-5p↓, PIK3R1↑, miR-506↓, STAT3↑, miR-365a-3p↓, ABCC4↑, miR-1294↓, AKT1↑, miR-335-5p↓, ROCK1↑, miR-103a↓, STAMBPL1↑	[98–100,102–105]

(*Continued*)

Cancer type	Expression	Functions	Role	Related molecules	Ref.
Ovarian cancer	Upregulated	Metastasis Enhance cisplatin and paclitaxel resistance Invasion Migration	Oncogenic	miR-382-3p↓, ROCK1↑, miR-770-5p↓, PARP1↑, miR-506↓, miR-1321↓, TJP3↑, miR-4500↓, BZW1↑, miR-34a-5p↓, BCL2↑	[112–117]
Endometrial cancer	Upregulated	Migration Invasion Proliferation	Oncogenic	miR-144-3p↓, EZH2↑, miR-361↓, STAT3↑, miR-146b-5p↓, miR-214-3p↓, HMGA1↑	[119–122]
Prostate cancer	Upregulated	Migration Invasion Proliferation	Oncogenic	miR-34a-5p↓, miR-204-5p↓, ACSL4↑, miR-98-5p↓, HMGA2↑	[125,127]

Arrows indicate upregulation (↑) or downregulation (↓) of the respective factor.

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