NEAT1 as a competing endogenous RNA in tumorigenesis of various cancers: Role, mechanism and therapeutic potential

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Abstract

The nuclear paraspeckle assembly transcript 1 (NEAT1) is a long non-coding RNA (lncRNA) that is upregulated in a variety of human cancer types. Increasing evidence has shown that the elevation of NEAT1 in cancer cells promotes cell growth, migration, and invasion and inhibits cell apoptosis. It is also known that lncRNAs act as a competing endogenous RNA (ceRNA) by sponging microRNAs (miRNAs) to alter the expression levels of their target genes in the development of cancers. Therefore, it is important to understand the molecular mechanisms underlying this observation. In this review, specific emphasis was placed on NEAT1’s role in tumor development. We also summarize and discuss the feedback roles of NEAT1/miRNA/target network in the progression of various cancers. As our understanding of the role of NEAT1 during tumorigenesis improves, its therapeutic potential as a biomarker and/or target for cancer also becomes clearer.

Key words: NEAT1, competing endogenous RNA, long non-coding RNA, microRNA, cancer, therapeutic target

Introduction

Nuclear paraspeckle assembly transcript 1 (NEAT1) is a long non-coding RNA (lncRNA) located in nuclear paraspeckles. It functions as a frame for paraspeckle formation by associating with the paraspeckle proteins, paraspeckle component 1 (PSPC1), splicing factor proline/glutamine rich (SFPQ), and 54 kDa nuclear RNA- and DNA-binding protein (p54nrb) [1,2]. Since the discovery of NEAT1 in 2007, many of its biological functions have been reported, including regulation of cell differentiation [3,4], immune response [5], and organ development [6,7]; NEAT1 also participates in the progression of a variety of disorders, such as cancer [8,9], metabolic diseases [10,11], and immunological diseases [12]. In addition, our previous studies revealed that NEAT1 is also involved in herpes simplex virus-1 (HSV-1) replication and the development of Alzheimer’s disease (AD) by epigenetically regulating the expression of HSV-1 viral genes and endocytosis-related genes, respectively [13,14]. The key role of NEAT1 is to mediate gene expression through complex mechanisms. NEAT1 regulates target genes by recruiting and/or sequestering transcriptional factors and regulators to and from promoters and transcripts of target genes, thereby influencing their transcription, splicing, RNA stability, and translation [15].

There is growing evidence that lncRNAs can act as competing endogenous RNAs (ceRNAs) by sponging microRNAs (miRNAs) to alter the expression levels of their target genes in the development of human diseases [16,17]. During tumorigenesis and cancer progression, many oncogenic lncRNAs exhibit dysregulated expression, which promotes the development of cancer and is associated with poor overall survival. This occurs through lncRNA’s enhancing of cancer cell proliferation, migration, invasion, and apoptosis.
inhibition. Researchers discovered that lncRNAs regulate the expression of tumor-related genes by interacting with lncRNA-specific miRNAs, thereby preventing the degradation of tumor-related gene transcripts and promoting their translation [18]. These findings suggest that lncRNA-mediated ceRNA networks have great potential as biomarkers and therapeutic targets for cancer.

In this review, we discuss the roles of NEAT1 in the progression of different types of tumors by describing a universal regulatory pattern of NEAT1 in tumor-related gene expression. We have focused on the function of NEAT1 as a ceRNA to upregulate these gene expression levels through sponging miRNAs. This gene upregulation results in the promotion of tumor cell proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), and cell apoptosis inhibition. We also discuss the potential clinical applications of NEAT1-mediated ceRNA networks in overcoming chemoresistance and radioresistance in cancer treatment.

**NEAT1 role in the tumorigenesis in respiratory system tumors**

In this section, we summarize the roles of the NEAT1/miRNA/target axis in respiratory system tumors, including nasopharyngeal carcinoma, sinonasal squamous cell carcinoma, laryngeal squamous cell cancer, and non-small cell lung cancer (Table 1).

**Nasopharyngeal carcinoma**

Nasopharyngeal carcinoma (NPC), a common head and neck cancer originating from the nasopharynx epithelium, is a leading cause of cancer-related deaths worldwide [19]. In a study of the underlying mechanism of NEAT1 in NPC progression, NEAT1 expression was found to be upregulated in NPC tissues and cells, and NEAT1 knockdown resulted in an inhibition of tumor cell proliferation, migration, invasion, and EMT by blocking Wnt/β-catenin signaling, a trigger for tumorigenesis [20], via targeting miR-34a-5p [21].

NF-kB signaling is another pathway that is influenced by NEAT1 in NPC progression. Cheng et al. reported that miR-124 inhibits NPC cell proliferation and promotes cell apoptosis by binding to and repressing the expression of NEAT1 and NF-kB, suggesting that NEAT1 functions as a potential ceRNA for NF-kB expression [22].

**Sinonasal squamous cell carcinoma**

Sinonasal squamous cell carcinoma (SNSCC) is the most common type of sinonasal malignancy, an aggressive tumor type characterized by late discovery and rapid progression [23,24]. A study on the molecular mechanisms of SNSCC development revealed that the expression of lncRNA NEAT1 and vascular endothelial growth factor A (VEGFA) were both upregulated in SNSCC tissues and cells, which resulted in a promotion of SNSCC cell viability and a reduction in SNSCC cell apoptosis. Moreover, upregulation of miR-195-5p in SNSCC cells decreased cell viability by directly binding with NEAT1 and VEGFA and decreasing their expression levels, suggesting an important role of the NEAT1/miR-195-5p/VEGFA axis in SNSCC progression [25].

**Laryngeal squamous cell cancer**

Laryngeal squamous cell carcinoma (LSCC) is the most common malignant tumor occurring in the head and neck, and it also is the leading cause of cancer-related deaths in this category [26]. Wang et al. [27] studied the role of NEAT1 in human LSCC progression, and the authors found that NEAT1 expression was significantly induced in LSCC with a positive relationship with grade, lymph node metastasis, and clinical stages. Moreover, NEAT1 was shown to promote LSCC cell proliferation and invasion and inhibit LSCC cell apoptosis and cell cycle arrest at the G1 phase. Further investigation of the molecular mechanism demonstrated that NEAT1 sponges miR-107 to upregulate the expression of cyclin-dependent kinase 6 (CDK6), a member of the CDK family that significantly correlates with head and neck squamous cell carcinoma progression [28].

| Table 1. Roles of NEAT1/miRNA/target axis in respiratory system tumors |
|-----------------------------|------------------|-----------------|-----------------|------------------|------------------|
| **Cancer type**             | **MiRNA**        | **Target**      | **Role**        | **Reference**    |
| NPC                         | 34a-5p           | Wnt/β-catenin   | Promoting NPC cell proliferation, migration, invasion, and EMT | [21] |
|                             | 124              | NF-xB           | Promoting NPC cell proliferation and inhibiting cell apoptosis | [22] |
| SNSCC                       | 195-5p           | VEGFA           | Enhancing SNSCC cell viability and inhibiting SNSCC cell apoptosis | [25] |
| LSCC                        | 107              | CDK6            | Promoting LSCC cell proliferation and invasion, and inhibiting LSCC cells apoptosis and cell cycle arrest at G1 phase | [28] |
| NSCLC                       | 377-3p           | E2F3            | Promoting NSCLC cells growth and metastasis | [30] |
|                             | 98-5             | MAPK6           | Promoting NSCLC cell growth, migration, and invasion | [31] |
|                             | 101-3p           | SOX9            | Promoting NSCLC cell proliferation, migration and invasion | [32] |
|                             | 376b-3p          | SURF1           | Promoting NSCLC cell proliferation, migration, and invasion and inhibiting cell apoptosis | [33] |
| LUAD                        | 193a-5p          | USF1            | Promoting LUAD cell proliferation, invasion, and migration and inhibiting cell apoptosis | [40] |

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Table 2. Roles of NEAT1/miRNA/target axis in digestive system tumors

| Cancer type | MiRNA   | Target      | Role                                                                 | Reference |
|-------------|---------|-------------|----------------------------------------------------------------------|-----------|
| OSCC        | 365     | RGS20       | Promoting OSCC cells proliferation and invasion, and inhibiting cell cycle arrest at the G0/G1 phase and apoptosis | [45]      |
| ESCC        | 129     | CTBP2       | Promoting ESCC cell viability and invasion                           | [47]      |
| GC          | 497-5p  | PIK3R       | Promoting GC cells proliferation, and inhibited GC cells apoptosis   | [54]      |
|             | 500     | STAT3       | Promoting GC cells proliferation, migration and invasion            | [53]      |
|             | 335-5p  | ROCK1       | Promoting GC cells proliferation, colony formation, invasion, and cell cycle | [57]      |
|             | 103a    | STAMBPL1    | Promoting GC cells proliferation, migration and invasion            | [56]      |
| HCC         | 296-5p  | CNN2        | Promoting HCC cells growth, migration, and invasion                 | [60]      |
|             | 139-5p  | TGF-β1      | Promoting HCC cells growth, migration, and invasion                 | [61]      |
|             | 485     | STAT3       | Promoting HCC cells growth, migration, and invasion                 | [62]      |
| CRC         | 405-3p  | CDK6        | Promoting colon cancer cell proliferation, cell cycle, cell migration, and invasion and inhibiting cell apoptosis | [65]      |
|             | 188-5p  | IGF2        | Promoting colon cancer cell migration and invasion                  | [66]      |
|             | 34a     | SIRT1       | Promoting CRC cells proliferation, migration, and invasion          | [67]      |
|             | 196a-5p | GDNF        | Promoting CRC cells proliferation, migration, and invasion          | [68]      |
|             | 205-5p  | VEGFA       | Promoting CRC cells proliferation, migration, and inhibiting CRC cells apoptosis | [70]      |
|             | 193a    | IL17RD      | Promoting CRC cells proliferation, migration, and inhibiting CRC cells apoptosis | [72]      |
|             | 193a-3p | KRAS        | Promoting CRC cells proliferation, migration, and inhibiting CRC cells apoptosis | [71]      |
|             | 138     | SLC38A      | Promoting CRC cells proliferation, migration, and inhibiting CRC cells apoptosis | [73]      |
|             | 195-5p  | CEP55       | Promoting CRC cells proliferation, migration, and inhibiting CRC cells apoptosis | [73]      |

Non-small cell lung cancer

Lung cancer remains one of the most prevalent malignant tumors and the leading cause of cancer-related deaths all over the world [29]. The most prevalent form of lung cancer (~80%) is the non-small cell lung cancer (NSCLC). Sun et al. [30] reported that high NEAT1 expression in NSCLC is related to a short overall survival of patients with NSCLC by promoting cancer cell growth and metastasis. Further investigation revealed that NEAT1 functions as a ceRNA for E2F3, a core oncogene in promoting NSCLC progression, by sponging hsa-miR-377-3p and antagonizing its functions of binding with E2F3 to repress E2F3 expression. Furthermore, NEAT1 was found to promote growth, migration, and invasion of NSCLC by sponging miR-98-5p, miR-101-3p, and miR-376b-3p to upregulate mitogen-activated protein kinase 6 (MAPK6) [31], SRY-box transcription factor 9 (SOX9) [32], and sulfatase 1 (SULF1) [33], respectively. These targets play a vital role in cancer progression [34-36].

Lung adenocarcinoma (LUAD) is a histopathological subtype of NSCLC that accounts for nearly 40% of lung cancer cases [37,38]. Xiong et al. [39] showed that NEAT1 accelerated LUAD cell proliferation, invasion, and migration and inhibited cell apoptosis by upregulating the expression of upstream stimulating factor 1 (USF1), a basic helix-loop-helix-zipper transcription factor that promotes lung adenocarcinoma progression [40], by sponging miR-193a-3p.

NEAT1 role in the tumorigenesis in digestive system tumors

In this section, we summarize the roles of the NEAT1/miRNA/target axis in digestive system tumors, including oral squamous cell carcinoma, esophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma, and colorectal cancer (Table 2).

Oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is the most prevalent type of head and neck squamous cell carcinoma (HNSCC), the sixth most common cancer worldwide in 2018 [41,42]. In a study to determine the function and mechanism of lncRNA NEAT1 in OSCC, NEAT1 expression was found to be significantly upregulated in OSCC cells and tissues. This high expression of NEAT1 was positively correlated with advanced TNM stage (a system used to classify Tumor size, Node location, and Metastasis status) and poor survival of patients by promoting tumor cells proliferation and invasion, and inhibiting cell cycle arrest at the G0/G1 phase and apoptosis. It is proposed that NEAT1 could positively regulate the expression of the regulator of G protein signaling 20 (RGS20), an accelerator for the proliferation and migration of cancer cells [43,44], by interacting with miR-365 to suppress the repressive effects of miR-365 on the expression of RGS20 [45].

Esophageal squamous cell carcinoma

Esophageal squamous cell carcinoma (ESCC) is the predominant histological type of esophageal cancer and is one of the most common and leading aggressive malignancies, with a five-year survival rate
of less than 10% [46]. A study investigating the molecular mechanism of the NEAT1 regulatory network in ESCC progression revealed that the expression of NEAT1 and C-terminal-binding protein 2 (CTBP2) was upregulated, while expression of miR-129 was downregulated in ESCC cells. Further studies validated that miR-129 could target NEAT1 and CTBP2 to decrease their expression levels. In addition, cellular function investigation confirmed that either NEAT1 knockdown, CTBP2 knockdown, or miR-129 upregulation resulted in an inhibition of ESCC cell viability and invasion, suggesting a NEAT1/miR-129/CTBP2 regulatory network in ESCC progression [47].

**Gastric cancer**

Gastric cancer (GC) remains the third leading cause of cancer-related deaths all over the world and is the most common type of digestive malignancies [48-50]. In addition, most patients with GC exhibit malignant metastasis with poor overall survival [51,52].

Tan et al. [53] explored the detailed roles and molecular mechanisms of NEAT1 in GC progression. The authors found that the expression of NEAT1 and signal transducer and activator of transcription 3 (STAT3) were significantly upregulated in human GC cells, while expression of miR-506 was downregulated. NEAT1 and STAT3 are two targets of miR-506. Moreover, NEAT1 knockdown repressed GC cell growth, migration, and invasion by decreasing the expression level of STAT3 via miR-506 upregulation.

In addition, other NEAT1 sponging-miRNAs and targets of these miRNAs that play roles in GC progression have been discovered. For example, the NEAT1/miR-497-5p/phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) axis promotes GC cell proliferation and inhibits GC cell apoptosis [54]; the NEAT1/miR-335-5p/rho associated coiled-coil containing protein kinase 1 (ROCK1) axis promotes GC cell proliferation and inhibits GC cell apoptosis [55]; the NEAT1/miR-103a/STAM binding protein like 1 (STAMBPL1) axis promotes GC cell proliferation and cell invasion [56]; NEAT1/miR-365a-3p/ATP binding cassette subfamily C member 4 (ABCC4) axis promotes GC cell proliferation, colony formation, invasion, and cell cycle progression [57].

**Hepatocellular carcinoma**

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and seventh in women and is the second most common cause of cancer-related deaths worldwide [58,59]. Increasing evidence has demonstrated that NEAT1 expression is induced and NEAT1 upregulation promotes HCC progression. Molecular mechanism investigations have shown that NEAT1 promotes HCC cell proliferation, migration, and invasion by upregulating the expression of calponin 2 (CNN2), transforming growth factor-β1 (TGF-β1), and STAT3 by targeting miR-296-5p, miR-139-5p, and miR-485, respectively [60-62].

**Colorectal cancer**

Colorectal cancer (CRC) remains the second most common cause of cancer-related deaths in the United States [63]. He et al. reported that NEAT1 knockdown inhibited colon cancer cell proliferation, cell cycle, cell migration/invasion, and promoted colon cancer cell apoptosis by repressing the expression of CDK6 via interaction with miR-495-3p [64]. CDK6 is a member of the CDK family whose dysregulation in cancers results in continued proliferation and unscheduled cell cycle [65]. Moreover, the NEAT1/miR-185-5p/insulin-like growth factor 2 (IGF2) axis is another pathway that induces the invasion and migration of colon cancer [66].

In addition, NEAT1 upregulation in CRC was significantly correlated with poor TNM staging, survival, and tumor recurrence in patients with CRC. By upregulating the expression of sirtuin-1 (SIRT1) via miR-34a [67], glial cell-derived neurotrophic factor (GDNF) via miR-196a-5p [68], and VEGFA via miR-205-5p [69], NEAT1 enhanced CRC cell proliferation, colony formation, and invasive potential. By upregulating the expression of interleukin 17 receptor D (IL17RD) via miR-193a [70], solute carrier family 38 member 1 (SLC38A1) via miR-138 [71], KRAS via miR-193a-3p [72], and centrosomal protein 55 (CEP55) via miR-195-5p [73], NEAT1 promotes CRC cell proliferation, migration, and invasion and inhibits apoptosis.

**NEAT1 role in the tumorigenesis in reproductive system tumors**

In this section, we summarize the roles of the NEAT1/miRNA/target axis in reproductive system tumors, including breast cancer, ovarian cancer, cervical cancer, endometrial carcinoma, and prostate cancer (Table 3).

**Breast cancer**

Breast cancer (BC) remains the leading cause of cancer death in women and occurs in the epithelial tissue of the mammary gland [74]. Researchers found that NEAT1 overexpression in BC was correlated with poor prognosis of patients and the feedback loop of NEAT1/miR-107/carnitine palmitoyltransferase 1A (CPT1A) [75], NEAT1/miR-124/STAT3 [76], NEAT1/
miR-448/zinc finger E-box binding homeobox 1 (ZEB1) [77], and NEAT1/miR-101/enhancer of zeste homolog 2 (EZH2) [78], which promotes BC cell proliferation, migration, invasion, and cell cycle progression. In addition, NEAT1 upregulation in BC enhances EMT and inhibits cell apoptosis by sponging miR-410-3p to upregulate the expression of cyclin D1 (CCND1) [79] and spenging miR-138-5p to upregulate the expression of zinc finger protein X-linked (ZFX) [80].

Table 3. Roles of NEAT1/miRNA/target axis in reproductive system tumors

| Cancer type | MiRNA      | Target | Role                                      | Reference |
|------------|------------|--------|-------------------------------------------|-----------|
| BC         | 107        | CPT1A  | Promoting BC cells proliferation, migration, invasion and cell cycle | [75]       |
|            | 124        | STAT3  |                                            | [76]       |
|            | 448        | ZEB1   |                                            | [77]       |
|            | 101        | EZH2   |                                            | [78]       |
|            | 410-3p     | CCND1  | Promoting BC cells proliferation, migration, invasion and EMT           | [79]       |
|            | 138-5p     | ZFX    | Promoting BC cells proliferation, migration, invasion, and inhibiting apoptosis | [80]       |
| OC         | 34a-5p     | BCL2   | Promoting OC cells proliferation and inhibited apoptosis                  | [82]       |
|            | 382-3p     | ROCK1  | Promoting OC cells metastasis                                                      | [83]       |
|            | 4500       | BZW1   | Promoting OC cells proliferation, migration, invasion, and inhibiting apoptosis | [84]       |
|            | 1321       | TJP3   | Promoting OC cells proliferation, migration, and EMT                       | [85]       |
| CC         | 133a       | SOX4   | Promoting CC cells proliferation, migration, and inhibiting apoptosis         | [88]       |
|            | 9-5p       | POU2F1 | Promoting CC cells proliferation and migration                              | [87]       |
|            | 361        | HSP90  | Promoting CC cells proliferation, migration and EMT                       | [90]       |
| EC         | 214-3p     | HMGA1  | Promoting EC cells proliferation, migration and invasion                  | [93]       |
|            | 144-3p     | EZH2   | Promoting EC cells proliferation, migration and invasion                  | [94]       |
| PCa        | 98-5p      | HMGA2  | Promoting PCa cells proliferation and invasion                            | [96]       |

Ovarian cancer

Ovarian cancer (OC) is another leading cause of cancer-related deaths in the female population worldwide [81]. Ding et al. [82] reported that NEAT1 overexpression in OC promoted proliferation and inhibited apoptosis of OC cells by negatively regulating miR-34a-5p expression and positively regulating B-cell lymphoma-2 (BCL2), a target of miR-34a-5p. Moreover, NEAT1 enhanced the metastasis of OC cells by upregulating the expression of ROCK1 by sponging miR-382-3p [83].

In addition to the promotion of OC cell proliferation, migration, and invasion, NEAT1 was shown to inhibit OC cell apoptosis by upregulating the expression of basic leucine zipper and W2 domain-containing protein 1 (BZW1) via interaction with miR-4500 [84]. NEAT1 also enhanced EMT of OC cells by upregulating the expression of tight junction protein 3 (TJP3) via interaction with miR-1321 [85].

Cervical cancer

Cervical cancer (CC) remains the second most common and serious malignant tumor among women all over the world [86]. Xie et al. studied the role of NEAT1 in CC progression, and the authors reported that NEAT1 upregulation in CC tissue enhanced CC cell proliferation and migration [87]. Mechanistically, NEAT1 functions as a ceRNA to bind miR-9-5p and increase the expression level of POU class 2 homeobox 1 (POU2F1), a target of miR-9-5p. Moreover, overexpression of NEAT1 could inhibit CC cell apoptosis and EMT by targeting miR-133a, thereby increasing the expression of SRY-box transcription factor 4 (SOX4), an important epigenetic regulator in tumorigenesis [88, 89], and targeting miR-361 to increase expression of the 90-kDa heat shock proteins (HSP90s), an essential factor contributing to the tumor metastatic phenotype [90,91].

Endometrial carcinoma

Endometrial carcinoma (EC) is a commonly diagnosed gynecological cancer worldwide, and its incidence is increasing [92]. Researchers investigated the function and mechanism of IncRNA NEAT1 in EC progression, and they found that NEAT1 promotes EC cell proliferation, migration, and invasion by sponging miR-214-3p and miR-144-3p to upregulate the expression of high mobility group AT-hook 1 (HMGA1) [93] and EZH2 [94], respectively.

Prostate cancer

Prostate cancer (PCa) is the second most common tumor and the fifth leading cause of cancer-related deaths among men [42]. Guo et al. reported that NEAT1 expression was significantly upregulated in PCa tissues and PCa cell lines, and NEAT1 knockdown inhibited the growth and invasion of PCa cells [95]. Mechanistically, NEAT1 upregulates the expression of high mobility group AT-hook 2 (HMGA2), an important transcription factor for genes that modulate cell cycle process, DNA damage, apoptosis, and EMT [96], by binding miR-98-5p and decreasing the expression level of miR-98-5p.

NEAT1 in the tumorigenesis in circulatory system tumors

In this section, we summarize and discuss the role of the NEAT1/miRNA/target axis in circulatory system tumors, including hemangioma, acute myeloid leukemia, T-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, Hodgkin’s lymphoma, and multiple myeloma (Table 4).
**Table 4. Roles of NEAT1/miRNA/target axis in circulatory system tumors**

| Cancer type | MiRNA | Target  | Role                                                                 | Reference |
|-------------|-------|---------|----------------------------------------------------------------------|-----------|
| HA          | 361-5p| VEGFA   | Promoting HemECs proliferation and migration, and inhibiting HemECs apoptosis | [100]     |
| AML         | 33-5p | HIF1α   | Promoting AML cells proliferation, decreasing the number of cells in the G2/M phase, and inducing cell apoptosis | [98]      |
|             | 23a-3p| SMC1A   | Inhibiting AML cells proliferation, migration and invasion, and enhancing AML cells apoptosis | [103]     |
|             | 338-3p| CREB3   | Inhibiting AML cells proliferation, migration and invasion, and enhancing AML cells apoptosis | [104]     |
| T-ALL       | 146b-5p| NOTCH1 | Promoting T-ALL cells proliferation                                | [107]     |
| DLBCL       | 34b-5p| GLI1    | Promoting DLBCL cells proliferation, and inhibiting DLBCL cells apoptosis | [109]     |
| HL          | 448   | DCLK1   | Promoting HL cells proliferation and invasion                      | [113]     |
| MM          | 214   | B7-H3   | Promoting M2 macrophage polarization                                | [116]     |

**Hemangioma**

Hemangioma (HA) is one of the most common benign vascular neoplasms of infancy due to the abnormal proliferation of hemangioma endothelial cells (HemECs) [97]. Yu et al. studied the roles and molecular mechanisms of NEAT1 in HA progression; the authors found that NEAT1 expression is increased in hemangiomas and depletion of NEAT1 results in the inhibition of HemEC proliferation, migration, and invasion [98]. Investigation of the mechanism revealed that NEAT1 upregulated the expression of HIF1α by sponging miR-33a-5p, thus activating NF-κB signaling, a critical pathway for tumorigenesis [99]. In addition, NEAT1 was found to inhibit the apoptosis of HemECs, thereby contributing to HA progression, by interacting with miR-361-5p to upregulate the expression of VEGFA, an essential factor in promoting cancer progression by increasing the proliferation and migration of cancer cells [100,101].

**Acute myeloid leukemia**

Acute myeloid leukemia (AML) is a representative hematologic malignancy characterized by an abnormal abundance of aberrantly differentiated myeloid cells in the bone marrow [102]. Researchers investigated the regulatory influence of the NEAT1/miRNA/target axis in AML progression; they found that NEAT1 expression was downregulated in AML cells and that overexpression of NEAT1 inhibited cell proliferation, migration, and invasion, decreased the number of cells in the G2/M phase, and significantly induced cell apoptosis through the NEAT1/miR-23a-3p/structural maintenance of chromosomes 1A (SMC1A) axis [103] and NEAT1/miR-338-3p/CREB3 regulatory factor (CREB3R) axis [104].

**T-cell acute lymphoblastic leukemia**

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive leukemia originating from T-lymphocytes in the bone marrow. Patients show symptoms of weakness, enlarged lymph nodes, fatigue, and weight loss [105]. Luo et al. studied the regulatory mechanism of NEAT1 in the process of T-ALL [106]. The authors found that NEAT1 expression levels were markedly increased in T-ALL cells. NEAT1 promotes the proliferation of T-ALL cells by upregulating the expression of NOTCH1, a driving oncogene that induces the development of pre-T cells to leukemia [107], by sponging miR-146b-5p and decreasing its expression level.

**Diffuse large B-cell lymphoma**

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, and it is typically considered an aggressive lymphoma [108]. A study to investigate the underlying mechanism of NEAT1 in DLBCL progression found that NEAT1 transcriptionally regulated by MYC was upregulated in DLBCL tissues and cell lines, and NEAT1 knockdown resulted in the inhibition of DLBCL cell proliferation and a promotion of DLBCL cell apoptosis. Mechanistically, NEAT1 functions as a ceRNA to target miR-34b-5p and, thus, increases the expression level of the GLI family zinc finger 1 (GLI1), an oncogene that contributes to cell survival of DLBCL [109, 110].

**Hodgkin's lymphoma**

Hodgkin’s lymphoma (HL) is the most common malignant lymphoma originating in the lymphoid hematopoietic system, especially in young adults [111]. Fan et al. [112] showed that NEAT1 expression was significantly enhanced in HL tissues and cell lines, and NEAT1 downregulation resulted in inhibition of HL cell proliferation and invasion through the downregulation of doublecortin-like kinase 1 (DCLK1), an accelerator in tumor cell invasion, metastasis, and EMT [113], via interaction with miR-448.

**Multiple myeloma**

Multiple myeloma (MM) is one of the most common hematological malignancies characterized...
by aberrant proliferation of plasma cells and secretion of monoclonal immunoglobulin proteins [114]. Gao et al. [115] reported that NEAT1 upregulation in MM patients promoted M2 macrophage polarization, a contributor to tumor progression that promotes angiogenesis to support tumor growth [116], by upregulating the expression and release of B7-H3 and then activating JAK2/STAT3 signaling via direct targeting of miR-214.

NEAT1 in the tumorigenesis in nervous system tumors

In this section, we summarize and discuss the role of the NEAT1/miRNA/target axis in nervous system tumors, including glioma, retinoblastoma, and neuroblastoma (Table 5).

### Table 5. Roles of NEAT1/miRNA/target axis in nervous system tumors

| Cancer type | miRNA | Target | Role | Reference |
|-------------|-------|--------|------|-----------|
| Glioma      | 107   | CDK14  | Promoting glioma cells proliferation, migration, and invasion | [118] |
|             | 132   | SOX2   |       | [119] |
|             | 449b-5| c-Met  |       | [120] |
|             | 152-3p| CCT6A  | Promoting glioma cells proliferation, migration, and invasion | [121] |
|             | 139-5p| CDK6   | Promoting glioma cells proliferation, migration, and invasion | [122] |
|             | 185-5p| DNMT1  | Promoting glioma cells proliferation, migration, and invasion | [123] |
| Retinoblastoma (RB) | 204 | CXCR4  | Promoting RB cells proliferation and migration, and inhibiting cells apoptosis | [125] |
| Neuroblastoma (NB) | 326 | JAK1, STAT3 | Promoting NB cells proliferation, and inhibiting cells apoptosis | [127] |

### Glioma

Gliomas are the most common and aggressive tumors of the central nervous system and characterized by extremely poor prognosis outcomes [117]. Researchers studied the molecular mechanisms underling gliomas. They observed that NEAT1 was upregulated in glioma tissues and cell lines, and this upregulation contributed to glioma progression by inducing glioma cell survival, promoting cell proliferation, migration, and invasion by sponging miR-107 [118], miR-132 [119], and miR-449b-5 [120] to elevate the expression levels of cyclin-dependent kinase 14 (CDK14), SRY-box transcription factor 2 (SOX2), and c-Met, respectively. In addition, NEAT1/miR-152-3p/chaperon containing the TCP1 subunit 6A (CCT6A) axis [121] and NEAT1/miR-139-5p/CDK6 axis [122] were shown to inhibit cell apoptosis, while the NEAT1/miR-185-5p/DNA methyltransferase 1 (DNMT1) axis [123] promoted EMT in glioma cells and inhibited cell apoptosis.

### Retinoblastoma

Retinoblastoma (RB) is an aggressive retinal cancer that is initiated in response to biallelic loss of the tumor suppressor gene RB1 in almost all cases and develops after additional genetic/epigenetic alterations [124]. A study on the role of NEAT1 in RB progression revealed that NEAT1 expression levels were elevated in RB tissues and cells; NEAT1 knockdown significantly inhibited RB cell proliferation and migration and promoted cell apoptosis by competitively binding with miR-204 to regulate the expression of C-X-C chemokine receptor type 4 (CXCR4) [125].

### Neuroblastoma

Neuroblastoma (NB) is the most common pediatric solid tumor that arises in the sympathetic nervous system. NB accounts for 7%-8% of childhood malignancies and ~15% of childhood cancer-related deaths [126]. Yang et al. explored the mechanism of NEAT1 in NB progression. The authors observed that NEAT1 expression was induced in neuroblastoma cell lines, and overexpression of NEAT1 resulted in an increase in NB cell proliferation and a decrease in cell apoptosis through upregulating the expression of Janus kinase 1 (JAK1) and STAT3 by sponging miR-326 [127].

### NEAT1 role in the tumorigenesis in endocrine system tumors

In this section, we summarize and discuss the role of the NEAT1/miRNA/target axis in thyroid cancer, a type of endocrine system tumor (Table 6).

### Table 6. Roles of NEAT1/miRNA/target axis in endocrine system, mobility system, and urinary system tumors

| System         | Cancer type | miRNA | Target | Role                                                   | Reference |
|----------------|-------------|-------|--------|--------------------------------------------------------|-----------|
| Endocrine system | Thyroid carcinoma | 592   | NOVA1  | Promoting thyroid cancer cells proliferation, migration, and invasion | [129] |
|                 | PTC         | 129-5p| KLK7   | Promoting PTC cells proliferation, migration, and invasion, and inhibiting cells apoptosis | [130] |
|                 |             | 106b-5| ATAD2  | Promoting PTC cells proliferation, migration, and invasion, and inhibiting cells apoptosis | [131] |
| Mobility system | OS          | 339-5p| TGF-beta | Promoting OS cells proliferation, migration, and invasion | [133] |
|                 |             | 34a-5p| HOXA13  | Promoting OS cells proliferation and inhibiting cells apoptosis | [135] |
|                 |             | 186-5p| HIF-1α  | Promoting OS cells proliferation, migration, and invasion | [134] |
| Urinary system  | Bladder cancer | 410   | HMGB1  | Promoting bladder cancer cells proliferation and inhibiting cell apoptosis and cell arrest | [137] |
|                 | RCC         | 34a   | c-Met  | Promoting RCC cells proliferation, migration, invasion, and EMT, and inhibiting cell cycle progression | [140] |
Thyroid cancer is the most commonly diagnosed endocrine tumor worldwide, with an increasing incidence in the past 20 years [128]. To date, a number of miRNAs have been reported to be aberrantly expressed in thyroid cancer and play a vital role in its progression. A study to understand the roles of miR-592 in thyroid cancer found that downregulated miR-592 in thyroid cancer exhibited a short overall survival of patients by promoting cell proliferation, migration, and invasion of thyroid cancer cells. The investigation showed that NEAT1 and neuro-oncological ventral antigen 1 (NOVA1) are targets of miR-592, and the knockdown of NEAT1 and NOVA1 effectively abolishes the promotion effects of miR-592 downregulation in thyroid cancer cells, suggesting a vital role of NEAT1/miR-592/NOVA1 axis in thyroid cancer progression [129].

Papillary thyroid cancer (PTC) is the most common form of thyroid cancer, accounting for >80% of thyroid cancer cases. Investigation of the roles of NEAT1 in PTC progression showed that NEAT1 expression was significantly upregulated in PTC tissues and cell lines, and NEAT1 overexpression promoted PTC cell proliferation, invasion, and migration, and inhibited cell apoptosis by increasing the expression level of kallikrein-related peptidase 7 (KLK7) [130] and ATPase family AAA domain-containing protein 2 (ATAD2) [131] via sponging miR-129-5p and miR-106b-5p, respectively.

NEAT1 role in the tumorigenesis in mobility system tumors

In this section, we summarize and discuss the role of the NEAT1/miRNA/target axis in osteosarcoma, a type of mobility system tumor (Table 6).

Osteosarcoma (OS) is the most common primary malignant bone tumor in children and teenagers. Somatic mutations and epigenetic mechanisms contribute to the progression of OS, such as aberrant activation of oncogenes and dysregulation of ncRNAs [132]. Several studies on the role of NEAT1 in OS progression showed that upregulation of NEAT1 in osteosarcoma tissues promoted OS cell proliferation, migration, and invasion, EMT, and inhibited cell apoptosis. Investigation of the mechanism revealed that NEAT1 acts as a ceRNA to regulate the expression of TGF-β1 [133], human hypoxia-inducible factor 1α (HIF-1α) [134], and homeobox A13 (HOXA13) [135] by sponging miR-339-5p, miR-186-5p, and miR-34a-5p, respectively.

NEAT1 role in the tumorigenesis in urinary system tumors

In this section, we summarize and discuss the role of the NEAT1/miRNA/target axis in urinary system tumors, including bladder cancer and renal cell carcinoma (Table 6).

Bladder cancer

Bladder cancer is a common urological malignant tumor in men worldwide and is characterized by a high rate of early systemic dissemination and nearly 170,000 deaths annually [136]. Shan et al. [137] revealed that the upregulation of NEAT1 in bladder cancer promotes bladder cancer cell proliferation and inhibits cell apoptosis and cell arrest by sponging miR-410, thereby upregulating the expression of high mobility group box 1 (HMGB1), an accelerator for tumor progression by its immune protective and suppressive functions [138].

Renal cell carcinoma

Renal cell carcinoma (RCC) is the most common type of kidney cancer and accounts for nearly 95% of all kidney cancer diagnoses [42]. In a study to determine the role of NEAT1 in RCC progression, Liu et al. [139] found that NEAT1 expression is upregulated in RCC tissue and cell lines, and high NEAT1 expression is correlated with poor prognosis. Further investigation revealed that NEAT1 enhanced RCC cell proliferation, migration, invasion, and EMT, and inhibited cell cycle progression by sponging miR-34a, thus increasing the expression level of c-Met, a potential therapeutic target in cancers [140].

NEAT1 in cancer therapy

Conventional treatments for cancer include surgery, chemotherapy, and radiotherapy. However, there is a subset of cancer patients that exhibit metastases and are unresponsive to chemotherapy or radiotherapy owing to tumor heterogeneity, tumor microenvironment, and dysfunction of therapeutic resistance-related genes [141-143]. To date, dozens of studies have reported an association between NEAT1 and resistance to chemotherapy or radiotherapy in various cancers (Table 7). They found that knockdown of NEAT1 could sensitize cancer cells to radiation or chemical drugs through NEAT1-mediated ceRNA networks. Therefore, targeting the feedback loop of NEAT1/miRNA/target may be a potential pathway to overcome therapeutic resistance in cancer.

Conclusions

The effect of malignant cancers is devastating across all physiological systems. The interplay between uncontrolled cancer cell growth, migration, invasion, and inhibition of apoptosis results in inevitable metastasis affecting all organ systems. To
date, lncRNA NEAT1 has been reported to be aberrantly expressed in different types of cancers. This review extensively summarized all existing information available on NEAT1’s contribution in their development, as NEAT1’s role as a ceRNA influences the miRNA environment during tumorigenesis (Figure 1). NEAT1 knockdown studies have revealed a therapeutic potential by redirecting the feedback loop between NEAT1/miRNA/target, thereby increasing efficacy of radio- and chemotherapy. It therefore highlights that NEAT1 is of relevant research interest and its role in therapeutic knockdown to enhance cancer therapies should be considered. However, as a nuclear enriched lncRNA, it should be clarified how NEAT1 sponges so many miRNAs to regulate expression of tumorigenesis-related genes, and whether NEAT1 in the peripheral blood could act as a biomarker for the diagnosis of cancers. In addition, more studies are needed in the future to characterize the role of NEAT1 in tumor microenvironments, such as whether NEAT1 affects the function of tumor infiltrating lymphocytes (TILs), and whether NEAT1 could function as a “messenger lncRNA” for the communication between tumor cells and these immune cells. Overall, this review summarizes and discusses the roles of the NEAT1-miRNA-target axis in the progression of various cancers and provides insight into its potential clinical utility in cancer treatment.

Table 7. Roles of NEAT1/miRNA/target axis in therapeutic resistance of cancers

| Cancer type | MiRNA   | Target        | Chemical-/radio- resistance | Reference |
|-------------|---------|---------------|-----------------------------|-----------|
| BC          | 211     | HMGA2         | 5-fluorouracil (5-FU)       | [144]     |
| CRC         | 150-5p  | CPSF4         |                             | [145]     |
| OC          | 770-5p  | PARP1         | Cisplatin (CDDP)           | [146]     |
| ATC         | 9-5p    | SPAG9         |                             | [147]     |
| OS          | 34c     | BCL-2         |                             | [148]     |
| PCA         | 204-5p  | ACSL4         | Docetaxel                   | [149]     |
| Bladder cancer | 214-3p | Wnt/β-catenin | Doxorubicin (DOX)           | [150]     |
| OC          | 194     | ZEB1          | Paclitaxel (PTX)            | [151]     |
| EC          | 361     | STAT3         |                             | [152]     |
| HCC         | 204     | ATG3          | Sorafenib                   | [153]     |
| RCC         | 335     | c-Met         |                             | [154]     |
| NPC         | 34a     | c-Met         |                             | [150]     |
| NPC         | 129     | Bcl-2         | Suberoylanilide hydroxamic acid (SAHA) | [155]     |
| HCC         | 204     | ZEB1          | Radiation                   | [156]     |
| CC          | 193b-3p | CCND1         |                             | [157]     |
| Abbreviations | NEAT1: nuclear paraspeckle assembly transcript 1; LncRNA: Long non-coding RNA; CeRNA:
competing endogenous RNA; MiRNAs: MicroRNAs; PSCP1: Paraspeckle component 1; SFPQ: Splicing factor proline/glutamine rich; P54rnb: 54 kDa nuclear RNA- and DNA-binding protein; AD: Alzheimer’s disease; EMT: Epithelial-mesenchymal transition; NPC: Nasopharyngeal carcinoma; SNCC: Sinonasal squamous cell carcinoma; VEGFA: Vascular endothelial growth factor A; LSCC: Laryngeal squamous cell carcinoma; CDK6: Cyclin-dependent kinase 6; NSCLC: Non-small cell lung cancer; MAPK6: Mitogen-activated protein kinase 6; LUAD: Lung adenocarcinoma; USF1: Upstream stimulator factor 1; OSCC: Oral squamous cell carcinoma; TNM: Tumor size, Node location, and Metastasis; RGS20: G protein signaling 20; ESCC: Esophageal squamous cell carcinoma; CTBP2: C-terminal-binding protein 2; GC: Gastric cancer; STAT3: Signal transducer and activator of transcription 3; PIK3R1: Phosphoinositide-3-kinase regulatory subunit 1; ROCK1: Rho associated coiled-coil containing protein kinase 1; STAMP1L: STAM binding protein 1; ABCCA4: ATP binding cassette subfamily C member 4; HCC: Hepatocellular carcinoma; CNN2: Calponin 2; TGF-β1: Transforming growth factor-β1; CRC: Colorectal cancer; IGF2: Insulin-like growth factor 2; SIRT1: Sir3tun-1; GDNF: Glial cell-derived neurotrophic factor; IL17RD: Interleukin 17 receptor D; EMT: Epithelial-mesenchymal transition; P54nrb: 54 kDa nuclear-retained protein; OS: Osteosarcoma; HIF-1α: Hypoxia-inducible factor 1α; HOXA13: Homeobox A13; HMGB1: High mobility group box 1; RCC: Renal cell carcinoma; TILs: tumor infiltrating lymphocytes.

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**Authors’ contributions**

KL, TY, YZ and WL drafted the manuscript. ZW contributed to conception, designed the figure, and revised the manuscript. All authors read and approved the final manuscript.

**Competing Interests**

The authors have declared that no competing interest exists.

**References**

1. Mao YS, Sunwoo H, Zhang B, et al. Direct visualization of the co-transcriptional assembly of a nuclear body by noncoding RNAs. Nat Cell Biol. 2011; 13(1): 95-101.
2. Clement CM, Hutchinson JN, Sara SA, et al. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. Mol Cell. 2009; 33(6): 717-26.
3. Mercer TR, Qureshi IA, Gokhan S, et al. Long noncoding RNAs in neuronal-glial fate specification and oligodendrocyte lineage maturation. BMC Neurosci. 2010; 11: 14.
4. Sunwoo H, Dinger ME, Wilusz JE, et al. MEN epsilon/beta nuclear-retained non-coding RNAs are up-regulated upon muscle differentiation and are essential components of paraspeckles. Genome Res. 2009; 19(3): 347-59.
5. Morchikh M, Cribier A, Raffel R, et al. HEXIM1 and NEAT1 Long Non-coding RNA Form a Multi-subunit Complex that Regulates DNA-Mediated Inmate Immune Response. Mol Cell. 2017; 67(3): 387-399.e5.
6. Nakagawa S, Shimada M, Yanaka K, et al. The IncRNA Neat1 is required for corpus luteum formation and the establishment of pregnancy in a subpopulation of mice. Development. 2014; 141(23): 4618-27.
7. Standaert L, Adriaens C, Radaelli E, et al. The long noncoding RNA Neat1 is required for mammary gland development and lactation. RNA. 2014; 20(12): 1844-9.
8. Li Y, Cheng C. Long noncoding RNA NEAT1 promotes the metastasis of osteosarcoma via interaction with the G9a-DNMT1-Small complex. Am J Cancer Res. 2018; 8(1): 81-90.
9. Li W, Zhang Z, Liu X, et al. The FOXN3-NEAT1-SIN3A repressor complex promotes progression of hormonally responsive breast cancer. J Clin Invest. 2017; 127(9): 3421-3440.
10. Wang X. Down-regulation of IncRNA-NEAT1 alleviated the non-alcoholic fatty liver disease via mTOR/S6K1 signaling pathway. J Cell Biochem. 2018; 119(2): 1567-1574.
11. Lin Z, Li X, Zhan X, et al. Construction of competitive endogenous RNA network reveals regulatory role of long non-coding RNAs in type 2 diabetes mellitus. J Cell Mol Med. 2017; 21(12): 3204-3213.
12. Zhang F, Wu L, Qian J, et al. Identification of the long noncoding RNA NEAT1 as a novel inflammatory regulator acting through MAPK pathway in human lupus. J Autoimmun. 2016; 75: 96-104.
13. Wang Z, Fan P, Zhao Y, et al. NEAT1 modulates herpes simplex virus-1 replication by regulating viral gene transcription. Cell Mol Life Sci. 2017; 74(6): 1117-1131.
14. Wang Z, Zhao Y, Xu N, et al. NEAT1 regulates neuroglial cell mediating Aβ clearance via the epigenetic regulation of endocytosis-related genes expression. Cell Mol Life Sci. 2019, 76(15): 3005-3018.
15. Wang Z, Li K, Huang W. Long non-coding RNA NEAT1-centric gene regulation. Cell Mol Life Sci. 2020; 77(19): 3769-3779.
16. Moreno-Garcia L, Lopez-Royo T, Calvo AC, et al. Competing Endogenous RNA Networks as Biomarkers in Neurodegenerative Diseases. Int J Mol Sci. 2020; 21(24): 9582.
17. Niu ZS, Wang WH, Dong XN, et al. Role of long noncoding RNA-mediated competing endogenous RNA regulatory network in hepatocellular carcinoma. World J Gastroenterol. 2020; 26(29): 4240-4260.

18. Braga EA, Forte MV, Moscovitz AA, et al. LncRNAs in Ovarian Cancer Progression, Metastasis, and Main Pathways: ceRNA and Alternative Mechanisms. Int J Mol Sci. 2020; 21(22): 8855.

19. Lee VH, Lam KO, Chang AT, et al. Management of Nasopharyngeal Carcinoma: Current Therapy and Future Practice. Int J Radiat Oncol Biol Phys. 2018; 101(5): 1194-1201.

20. Fodde R, Brabletz T. Wnt/beta-catatin signaling in cancer stemness and malignant behavior. Curr Opin Cell Biol. 2007; 19(2): 150-8.

21. Ji Y, Wang M, Li X, et al. The Long Noncoding RNA NEAT1 Targets miR-36a-5p and Promotes Nasopharyngeal Carcinoma Progression through Wnt5a/B-Catenin Signaling. Oncol Rep. 2019; 40(6): 594-602.

22. Cheng N, Guo Y. Long noncoding RNA NEAT1 promotes nasopharyngeal carcinoma progression through regulation of miR-124-3P/NEK pathway. Onco Targets Ther. 2017; 10: 5843-5852.

23. Oliver JR, Lieberman SM, Tam MM, et al. Human papillomavirus and survival for 2499-509. Int J Cancer. 2003; 104(4): 385-392.

24. Sun C, Li S, Zhang F, et al. Long non-coding RNA NEAT1 promotes non-small-cell lung cancer development. J Cell Biochem. 2019; 120(3): 763-775.

25. Oliver JR, Lieberman SM, Tam MM, et al. Human papillomavirus and survival for 2499-509. Int J Cancer. 2003; 104(4): 385-392.

26. Braga EA, Forte MV, Moscovitz AA, et al. LncRNAs in Ovarian Cancer Progression, Metastasis, and Main Pathways: ceRNA and Alternative Mechanisms. Int J Mol Sci. 2020; 21(22): 8855.

27. Lee VH, Lam KO, Chang AT, et al. Management of Nasopharyngeal Carcinoma: Current Therapy and Future Practice. Int J Radiat Oncol Biol Phys. 2018; 101(5): 1194-1201.

28. Fodde R, Brabletz T. Wnt/beta-catatin signaling in cancer stemness and malignant behavior. Curr Opin Cell Biol. 2007; 19(2): 150-8.

29. Ji Y, Wang M, Li X, et al. The Long Noncoding RNA NEAT1 Targets miR-36a-5p and Promotes Nasopharyngeal Carcinoma Progression through Wnt5a/B-Catenin Signaling. Oncol Rep. 2019; 40(6): 594-602.

30. Cheng N, Guo Y. Long noncoding RNA NEAT1 promotes nasopharyngeal carcinoma progression through regulation of miR-124-3P/NEK pathway. Onco Targets Ther. 2017; 10: 5843-5852.

31. Oliver JR, Lieberman SM, Tam MM, et al. Human papillomavirus and survival for 2499-509. Int J Cancer. 2003; 104(4): 385-392.

32. Sun C, Li S, Zhang F, et al. Long non-coding RNA NEAT1 promotes non-small-cell lung cancer development. J Cell Biochem. 2019; 120(3): 763-775.

33. Oliver JR, Lieberman SM, Tam MM, et al. Human papillomavirus and survival for 2499-509. Int J Cancer. 2003; 104(4): 385-392.
Yu L, Shu H, Xiong H, et al. LncRNA NEAT1 accelerates breast cancer progression through regulating miR-410-3p/CCND1 axis. Cancer Biomark. 2020; 29(2): 277-290.

Yao L, Chen L, Zhou H, et al. Long Non-coding RNA NEAT1Promotes the Progression of Breast Cancer by regulating miR-138-5p/ZFX Axis. Cancer Biother Radiopharm. 2020. doi: 10.1089/cbr.2019.315.

Torre LA, Trabert B, Desantis CE, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018; 68(4): 284-296.

Ding N, Wu H, Tao T, et al. NEAT1 regulates cell proliferation and apoptosis of ovarian cancer by miR-34a-5p/BCL2. Onco Targets Ther. 2017; 10: 4905-4915.

Liu Y, Wang Y, Fu X, et al. Long non-coding RNA NEAT1 promoted ovarian cancer cell’s metastasis through regulation of miR-382-3p/ROCK1 axis. Int. J. Biol. Sci. 2020; 17: 2190-2198.

Xu H, Sun X, Huang Y, et al. Long non-coding RNA NEAT1 modifies cell proliferation, colony formation, apoptosis, migration and invasion via the miR-4500/B2W1 axis in ovarian cancer. Mol. Med. Rep. 2020; 22(4): 3347-3357.

Luo M, Zhang L, Yang H, et al. Long non-coding RNA NEAT1 promotes ovarian cancer invasion and migration by interacting with miR-1231 and regulating tight junction protein 3 expression. Mol. Med. Rep. 2020; 22(4): 3429-3439.

Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020; 70(5): 321-346.

Xie Q, Lin S, Zheng M, et al. Long noncoding RNA NEAT1 promotes the growth of cervical cancer cells via sponging miR-9-5p. Biochem Cell Biol. 2019; 97(7): 100-108.

Yuan LY, Zhou M, Lv H, et al. Involvement of NEAT1/miR-133a axis in promoting cervical cancer progression via targeting SOX4. J Cell Physiol. 2019; 234(10): 10898-10909.

Hanafi HA, Ahmed EA, Vishnubhalaji R, et al. SOX4: Epigenetic regulation and role in tumorigenesis. Semin Cancer Biol. 2020. 67(Pt 1): 91-104.

Xu D, Dong P, Xiong Y, et al. MicroRNA-361-Mediated Inhibition of HSP90 Expression and EMT in Cervical Cancer Is Counteacted by Oncogenic Intrinsic NEAT1. Cell Death Dis. 2019; 10(9): 6320.

Das JK, Xiong X, Ren X, et al. Heat Shock Proteins in Cancer Immunotherapy. J Oncol. 2019; 2019: 3262707.

Brooks RA, Fleming GF, Lastra RR, et al. Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin. 2019; 69(4): 258-279.

Wang J, Zhao X, Guo Z, et al. Regulation of NEAT1/miR-214-3p on the growth, migration and invasion of endometrial carcinoma cells. Arch Gynecol Obstet. 2017; 295(6): 1469-1475.

Yi H, Hao T, Li Y, et al. LncRNA NEAT1 promotes endometrial cancer cell proliferation, migration and invasion by regulating the miR-144-5p/ENZ axis. Radiol Oncol. 2019; 53(4): 432-439.

Guo Z, He C, Yang F, et al. Long non-coding RNA NEAT1, a sponge for miR-146b-5p, can regulate cell apoptosis in glioma. Cancer Biol Ther. 2019; 20(6): 299-312.

Zhang H, Cai Y, Zheng L, et al. Long noncoding RNA NEAT1 regulate proliferation, colony formation, apoptosis, migration and invasion via the miR-34a-5p/BCL2 pathway. Cell Death Dis. 2018; 9: 3358-3366.

Zhan Y, Hao T, Zhang J, et al. MicroRNA-592 suppresses the malignant progression of glioma through sponging miR-107 and inhibiting CDK14. J Cell Physiol. 2019; 234(7): 10871-10879.

Zhou K, Zhang C, Yao H, et al. Knockdown of long non-coding RNA NEAT1 inhibits glioma cell migration and invasion via modulation of SOX2 targeted. Mol. Cell. 2018; 71(1): 105.

Zhou L, Yun-Hui L, Hong-Yu D, et al. Long non-coding RNA NEAT1 promotes glioma pathogenesis by regulating miR-449p-5p/c-Met axis. Tumour Biol. 2016; 37(1): 673-83.

Li B, Lu X, Ma C, et al. Long non-coding RNA NEAT1 promotes human glioma tumor progression via miR-152-3p/CCT6A pathway. Neurosci Lett. 2020; 722: 133806.

Wu DM, Wang S, Wen X, et al. Long noncoding RNA nuclear enriched abundant transcript 1 impacts cell proliferation, invasion, and migration of glioma through regulating miR-139-5p/ CDK6. J Cell Physiol. 2019; 234(5): 5960-5967.

Yu H, Xu A, Wu B, et al. Long noncoding RNA NEAT1 promotes progression of glioma as a ceRNA by sponging miR-185-5p to stimulate DNM1/tmTOR signaling. J Cell Physiol. 2021; 236(1): 121-130.

Kaurkhwaja R, Rojanaporn D. Retinoblastoma: Etiology, Modeling, and Treatment. Cancers (Basel). 2020; 12(8): 2304.

Zhong W, Yang J, Li M, et al. Long non-coding RNA NEAT1 promotes the growth of human retinoblastoma cells via regulation of miR-204/ CXCR4 axis. J Cell Physiol. 2019; 234(7): 11567-11576.

Zafar A, Wang W, Liu G, et al. Molecular targeting therapies for neuroblastoma: Progress and challenges. Med Res Rev. 2021; 41(2): 961-1021.

Yang B, Ye X, Wang J, et al. Long noncoding RNA nuclear-enriched abundant transcript 1 regulates proliferation and apoptosis of osteosarcoma cells treated by cisplatin by targeting miR-326 through Janus kinase/signal transducer and activator of transcription 3 pathway. Neurooncot. 2020: 31(17): 1189-1198.

Fabbri P, Ferrari SM, Galliandro MR, et al. Molecular targets of tyrosine kinase inhibitors in thyroid cancer. Semin Cancer Biol. 2020; 51: 101447.

Luo Y, Hao T, Zhang J, et al. MicroRNA-592 suppresses the malignant phenotypes of thyroid cancer by regulating lncRNA NEAT1 and miR-125b. Cancer Sci. 2020; 111(12): 2814-2822.

Gao Y, Fang P, Li WJ, et al. LncRNA NEAT1 sponges miR-214 to regulate M2 macrophage polarization by regulation of B7-H3 in multiple myeloma. Mol Oncol. 2020; 14(7): 1102-1116.
138. Rapoport BL, Steel HC, Theron AJ, et al. High Mobility Group Box 1 in Human Cancer. Cells. 2020; 9(7): 1664.
139. Liu F, Chen N, Gong Y, et al. The long non-coding RNA NEAT1 enhances epithelial-to-mesenchymal transition and chemoresistance via the miR-34a/c-Met axis in renal cell carcinoma. Oncotarget. 2017; 8(38): 62927-62938.
140. Pothula SP, Xu Z, Goldstein D, et al. Targeting HGF/c-MET Axis in Pancreatic Cancer. Int J Mol Sci. 2020; 21(23): 9170.
141. Kuczynski EA, Sargent DJ, Grothey A, et al. Drug rechallenge and treatment beyond progression—implications for drug resistance. Nat Rev Clin Oncol, 2013; 10(10): 571-587.
142. Gottesman MM, Lavi O, Hall MD, et al. Toward a Better Understanding of the Complexity of Cancer Drug Resistance. Annu Rev Pharmacol Toxicol. 2016; 56: 85-102.
143. Reubucci M, Michielis C. Molecular aspects of cancer cell resistance to chemotherapy. Biochem Pharmacol. 2013; 85(9): 1219-1226.
144. Li X, Wang S, Li Z, et al. The IncRNA NEAT1 facilitates cell growth and invasion via the miR-211/HMGA2 axis in breast cancer. Int J Biol Macromol. 2017; 105(Pt 1): 346-353.
145. Wang X, Jiang G, Ren W, et al. LncRNA NEAT1 Regulates 5-Fu Sensitivity, Apoptosis and Invasion in Colorectal Cancer Through the MiR-150-5p/CPSF4 Axis. Onco Targets Ther. 2020; 13: 6373-6383.
146. Zhu M, Yang L, Wang X. NEAT1 Knockdown Suppresses the Cisplatin Resistance in Ovarian Cancer by Regulating miR-770-5p/PARPi Axis. Cancer Manag Res. 2020; 12: 7277-7289.
147. Yan P, Su Z, Zhang Z, et al. LncRNA NEAT1 enhances the resistance of anaplastic thyroid carcinoma cells to cisplatin by sponging miR-9-5p and regulating SPAC9 expression. Int J Oncol. 2019; 55(3): 988-1002.
148. Hu Y, Yang Q, Wang L, et al. Knockdown of the oncogene IncRNA NEAT1 restores the availability of miR-34c and improves the sensitivity to cisplatin in osteosarcoma. Biosci Rep. 2018; 38(3): BSR20180375.
149. Jiang X, Guo S, Zhang Y, et al. LncRNA NEAT1 promotes docetaxel resistance in prostate cancer by regulating ACSL4 via sponging miR-34a-5p and miR-204-5p. Cell Signal. 2020; 65: 109422.
150. Guo Y, Zhang H, Xie D, et al. Non-coding RNA NEAT1/miR-214-3p contribute to desorubicin resistance of urothelial bladder cancer preliminary study. J Exp Clin Cancer Res. 2018; 37(1): 437-4380.
151. An J, Lu W, Zhang Y. LncRNA NEAT1 contributes to paclitaxel resistance of ovarian cancer cells by regulating ZEB1 expression via miR-194. Oncotarget. 2017; 10: 5377-5390.
152. Dong P, Xiong Y, Yue J, et al. Long non-coding RNA NEAT1 drives aggressive endometrial cancer progression via miR-361-regulated networks involving STAT3 and tumor microenvironment-related genes. J Exp Clin Cancer Res. 2019; 38(1): 295.
153. Li X, Liu L, Yang L, et al. LncRNA NEAT1 promotes autophagy via regulating miR-204/ATG3 and enhanced cell resistance to sorafenib in hepatocellular carcinoma. J Cell Physiol. 2020; 235(4): 3402-3413.
154. Chen S, Xia X. Long non-coding RNA NEAT1 suppresses sorafenib sensitivity of hepatocellular carcinoma cells via regulating miR-335-c-Met. J Cell Physiol. 2019. doi: 10.1002/jcp.27567.
155. Xue F, Cheng Y, Xu L, et al. LncRNA NEAT1/miR-129/Bcl-2 signaling axis contributes to HDAC inhibitor tolerance in nasopharyngeal cancer. Aging (Albany NY). 2020; 12(14): 14174-14188.
156. Lu Y, Li T, Wei G, et al. The long non-coding RNA NEAT1 regulates epithelial to mesenchymal transition and radioresistance in through miR-204/ZEB1 axis in nasopharyngeal carcinoma. Tumour Biol. 2016; 37(9): 11733-11741.
157. Chen X, Zhang N. Downregulation of IncRNA NEAT1_2 radiosensitizes hepatocellular carcinoma cells through regulation of miR-101-3p/WEE1 axis. Cell Biol Int. 2019; 43(1): 44-55.
158. Han D, Wang J, Cheng G. LncRNA NEAT1 enhances the radio-resistance of cervical cancer via miR-193b-3p/CCL3 axis. Oncotarget. 2017; 9(9): 2395-2409.