Front. Biol. 2016, 11(6): 413–426
DOI 10.1007/s11515-016-1433-z

REVIEW

Cellular, physiological and pathological aspects of the long non-coding RNA NEAT1

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BACKGROUND: The majority of mammalian genomes have been found to be transcribed into non-coding RNAs. One category of non-coding RNAs is classified as long non-coding RNAs (lncRNAs) based on their transcript sizes larger than 200 nucleotides. Growing evidence has shown that lncRNAs are not junk transcripts and play regulatory roles in multiple aspects of biological processes. Dysregulation of lncRNA expression has also been linked to diseases, in particular cancer. Therefore, studies of lncRNAs have attracted significant interest in the field of medical research. Nuclear enriched abundant transcript 1 (NEAT1), a nuclear lncRNA, has recently emerged as a key regulator involved in various cellular processes, physiological responses, developmental processes, and disease development and progression.
OBJECTIVE: This review will summarize and discuss the most recent findings with regard to the roles of NEAT1 in the function of the nuclear paraspeckle, cellular pathways, and physiological responses and processes. Particularly, the most recently reported studies regarding the pathological roles of deregulated NEAT1 in cancer are highlighted in this review.
METHODS: We performed a systematic literature search using the Pubmed search engine. Studies published over the past 8 years (between January 2009 and August 2016) were the sources of literature review. The following keywords were used: "Nuclear enriched abundant transcript 1," "NEAT1," and "paraspeckles."
RESULTS: The Pubmed search identified 34 articles related to the topic of the review. Among the identified literature, 13 articles report findings related to cellular functions of NEAT1 and eight articles are the investigations of physiological functions of NEAT1. The remaining 13 articles are studies of the roles of NEAT1 in cancers.
CONCLUSION: Recent advances in NEAT1 studies reveal the multifunctional roles of NEAT1 in various biological processes, which are beyond its role in nuclear paraspeckles. Recent studies also indicate that dysregulation of NEAT1 function contributes to the development and progression of various cancers. More investigations will be needed to address the detailed mechanisms regarding how NEAT1 executes its cellular and physiological functions and how NEAT1 dysregulation results in tumorigenesis, and to explore the potential of NEAT1 as a target in cancer diagnosis, prognosis and therapy.

Keywords long non-coding RNAs (lncRNAs), nuclear enriched abundant transcript 1 (NEAT1), paraspeckles, microRNAs (miRNAs), epigenetic regulation, cancer

Introduction

Through global sequencing analysis, human and other mammalian genomes are known to encompass between 20000 and 25000 protein-coding genes, accounting for $<2\%$ of the total genome (Waterston et al., 2002; International Human Genome Sequencing Consortium, 2004; Kellis et al., 2014). Recent investigations of the mammalian transcriptome have revealed that the majority of the genome is transcribed into RNA transcripts lacking protein-coding capacity, which have been named as non-coding RNAs (ncRNAs) (Carninci et al., 2005; Birney et al., 2007; Kapranov et al., 2007). Numerous ncRNAs have been found to be transcribed from introns of protein-coding genes and from genomic regions between protein-coding genes in both the sense and antisense direction (Mercer et al., 2009).

The broad category of ncRNA has been further classified based on length into small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs; >200 bp). Although the roles and identity of different classes of sncRNAs (e.g. microRNAs, siRNAs, piwi-interacting RNAs) are well-understood due to substantial studies, the various functions of lncRNAs in the cell remain largely unknown (Prasanth and Spector, 2007;

Received September 1, 2016; accepted November 7, 2016
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Derrien et al., 2012; Eidem et al., 2016; Schmitt and Chang, 2016).

The current studies of lncRNAs have revealed that the cellular functions of lncRNAs are implicated in a variety of biological processes such as gene expression regulation, initiation and maintenance of protein complexes, and subcellular architecture (Prasanth and Spector, 2007; Mercer et al., 2009; Wang and Chang, 2011; Iyer et al., 2015). Moreover, investigations have also shown that lncRNAs have significant physiological and pathological roles (Mercer et al., 2009). The majority of identified lncRNAs have been revealed to be transcribed by RNA polymerase II. Many lncRNAs have been found to be specific to certain cell-types and subcellular compartments, implying that they have specific functions (Prasanth and Spector, 2007; Mercer et al., 2009; Wang and Chang, 2011). Extensive studies of human lncRNA subcellular localization have shown that a significant number of lncRNAs are specifically localized in the cell nucleus, suggesting that they regulate nuclear events and architecture (Kapranov et al., 2007; Prasanth and Spector, 2007; Chujo et al., 2016).

Among the characterized nuclear lncRNAs, nuclear enriched abundant transcript 1 (NEAT1), also known as mouse Men epsilon (MEN) RNA, has gained attention due to accumulating data implicating NEAT1 as critical for biogenesis and maintenance of nuclear bodies, chromatin remodeling, gene expression regulation, stress and immune responses, organogenesis, and the development of pathological diseases including cancer. In this review, we summarize and discuss recent findings with regard to the cellular, physiological and pathological roles of NEAT1.

Cellular functions of NEAT1

NEAT1 lncRNAs are transcribed by RNA polymerase II from a genetic locus called familial tumor syndrome multiple endocrine neoplasia (MEN) type I on human chromosome 11 and are composed of two isoform transcripts, 3.7-kb NEAT1_1 (MENε) and 23-kb NEAT1_2 (MENβ) (Guru et al., 1997). The NEAT1 RNA isoforms share the same promoter and 5′ end, but have different 3′-ends generated by distinct RNA processing mechanisms. NEAT1_1 is cleaved and polyadenylated to form a canonical RNA transcript with a poly(A) tail. In contrast, RNase P recognizes the tRNA-like structure present at the 3′-end of the primary NEAT1-2 transcript and cleaves it to form a RNA transcript with the nonpolyadenylated 3′-end (Sunwoo et al., 2009). This section reviews the cellular roles of NEAT1 lncRNAs in building nuclear bodies, and regulating epigenetic events and gene expression.

NEAT1 and paraspeckles

The eukaryotic cell nucleus is a large cellular organelle with an intricately organized structure. Individual chromosomes are located in discrete territories, and specific nucleic acids and proteins are deposited in subnuclear structures including but not limited to the nucleoli, Cajal bodies, promyelocytic leukemia (PML) bodies, paraspeckles, and nuclear speckles (Platani and Lamond 2004; Mao et al., 2011). The highly organized nuclear structure is dynamically regulated to modulate the genomic conformation and gene expression. Consequently, nuclear organization influences all aspects of cellular activity, including proliferation, differentiation, and the developmental processes (Mao et al., 2011).

Paraspeckles were first discovered as nucleoplasmic foci that did not colocalize with any known subnuclear structures (Fox et al., 2002). These nuclear foci were named paraspeckles as they were found to be in close proximity to nuclear speckles (Fox et al., 2002). Paraspeckles are found to be present in both transformed and primary cell cultures and in embryonic fibroblasts and tissues (Fox et al., 2002; Prasanth et al., 2005; Clemson et al., 2009; Sunwoo et al., 2009). However, paraspeckles are absent in human embryonic stem (ES) cells, whereas after ES differentiation they are present. This indicates that their presence in the nucleus is dynamically regulated during developmental, and likely other, processes (Chen and Carmichael, 2009).

Paraspeckles are ~0.5–1.0 μm in size, and their numbers vary both within cell populations and among different cell types (Fox et al., 2002; Cardinale et al., 2007; Clemson et al., 2009). They are comprised of both protein and RNA components, with more than 60 protein components identified (Prasanth et al., 2005; Cardinale et al., 2007; Bond and Fox, 2009; Yamazaki and Hirose, 2015). Paraspeckle proteins were identified by their colocalization in subnuclear foci with members of the mammalian *Drosophila melanogaster* behavior, human splicing (DBHS) protein family, which is composed of paraspeckle component 1(PSPC1), non-POU domain containing, octamer binding ($p54^{nrb}$/NONO), and splicing factor proline/glutamine-rich (SFPQ/PSF) (Fox et al., 2002; Prasanth et al., 2005; Bond and Fox, 2009; Clemson et al., 2009; Yamazaki and Hirose, 2015). These three DBHS members are the most well-characterized paraspeckle protein components. DBHS proteins share over 50% sequence identity within two N-terminal RNP-type RNA recognition motifs and a C-terminal coiled-coil domain (Bond and Fox 2009). The two highly expressed DBHS proteins ($p54^{nrb}$/NONO and SFPQ/PSF) in HeLa cells have been shown to be essential for the formation of paraspeckles as their knockdown led to the disruption of paraspeckles (Sasaki et al., 2009). In contrast, the formation of paraspeckles was not affected by knockdown of the less abundant DBHS protein PSPC1 (Sasaki et al., 2009), suggesting that the abundant DBHS protein components are required for maintaining the structural integrity of paraspeckles.

Since paraspeckles were discovered, studies characterizing their components suggested that in addition to protein components, RNA molecules are also required for the formation of paraspeckles. The first evidence came from the

observation that RNase A (an endoribonuclease that cleaves single-stranded RNA) treatment led to the destruction of paraspeckles, whereas DNase I (a deoxyribonuclease that cleaves DNA) treatment had no effect on their structural integrity (Fox et al., 2005; Prasanth et al., 2005). In line with this finding, inhibiting RNA production by blocking RNA polymerase II-driven transcription resulted in paraspeckle disassembly (Fox et al., 2002; Fox et al., 2005). The majority of identified paraspeckle proteins possess RNA binding domains, and many of them are functionally involved in RNA processing. Moreover, the RNA binding domain is pivotal for targeting of PSPC1 to paraspeckles (Fox et al., 2005).

Four research groups later independently identified that NEAT1 lncRNAs are specifically localized to paraspeckles (Chen and Carmichael, 2009; Clemson et al., 2009; Sasaki et al., 2009; Sunwoo et al., 2009). Their functional studies further showed that depletion of NEAT1 by siRNAs or antisense oligonucleotides eliminated paraspeckles, whereas NEAT1 overexpression promoted the generation of paraspeckles (Chen and Carmichael, 2009; Clemson et al., 2009; Sasaki et al., 2009; Sunwoo et al., 2009). Importantly, NEAT1 lncRNAs were found to interact with paraspeckle protein components $p54^{nrb}$/NONO, SFPQ/PSF and PSPC1 (Clemson et al., 2009; Sasaki et al., 2009; Sunwoo et al., 2009). A further study found that the common region shared by both NEAT1 isoforms and the 3′-terminal region of NEAT1_2 were located at the paraspeckle periphery, whereas the middle region of NEAT1_2 was located in the paraspeckle interior (Souquere et al., 2010). These findings indicate that the NEAT1 lncRNA functions as a structural component required for the formation and maintenance of paraspeckles. The current proposed model of paraspeckle function is that the long lncRNA isoform NEAT1_2 interacts with $p54^{nrb}$/NONO and SFPQ/PSF, which leads to the secondary recruitment of the short lncRNA isoform NEAT1_1 and PSPC1, and the further loading of other paraspeckle protein components (Sasaki et al., 2009; Souquere et al., 2010). (Fig. 1)

The discovery of the specific localization of NEAT1 to the paraspeckle and its crucial role in paraspeckle formation opened a new window in research of paraspeckle functions (Chen and Carmichael, 2009; Clemson et al., 2009; Sasaki et al., 2009; Sunwoo et al., 2009). One of the well-known functions of paraspeckles is to sequester A-to-I hyperedited RNAs in the nucleus (Prasanth et al., 2005; Chen et al., 2008; Chen and Carmichael, 2009). In higher eukaryotes, A-to-I editing of double stranded RNA (dsRNA) regions occurs

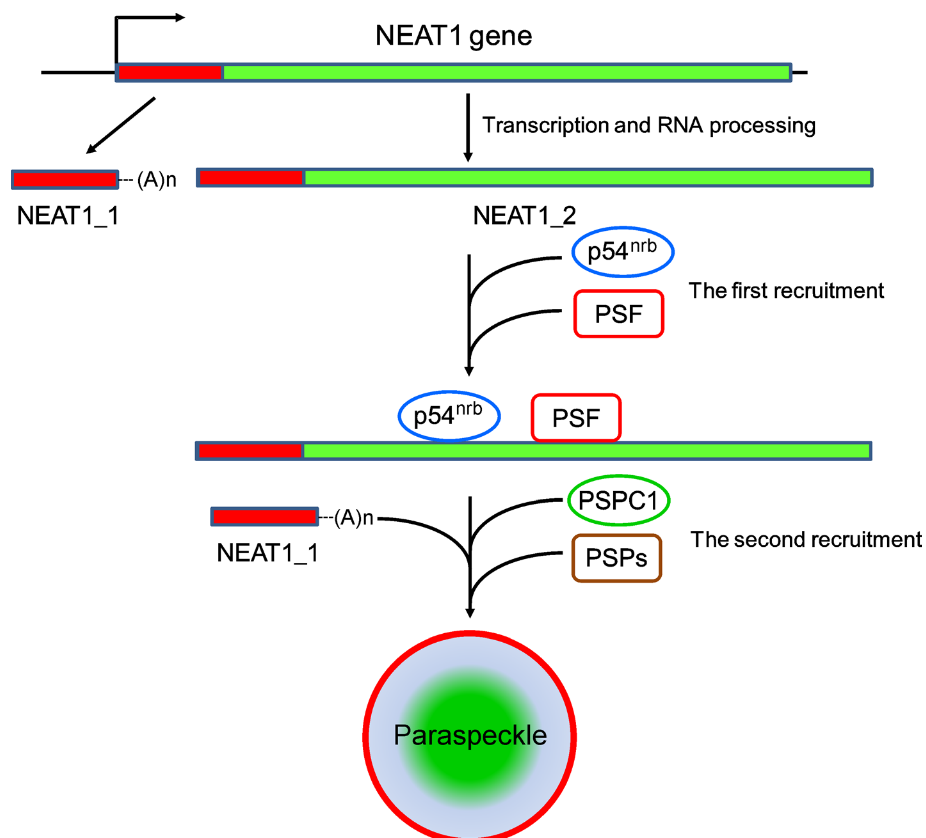

Figure 1 The hypothetical model for paraspeckle formation in the cell nucleus. The human *NEAT1* gene is transcribed into two lncRNA isoform transcripts, NEAT1_1 and NEAT1_2. Only the NEAT1_1 transcript is polyadenylated. The assembly of paraspeckles mainly involves the two steps of component recruitment. In the first recruitment, two abundant paraspeckle proteins, $p54^{nrb}$ and PSF, bind to the internal region of the NEAT1_2 transcript. The first recruitment triggers the second recruitment of PSPC1, NEAT1_1 and other paraspeckle proteins (PSPs) to form paraspeckles.

through the hydrolytic deamination of adenosines (A) to inosines (I) in the nucleus, which is catalyzed by dsRNA-dependent adenosine deaminases (ADARs) (Chen and Carmichael, 2009). ADAR editing is found to be abundant in human cells, and more than 90% of this event occurs within RNA regions composed of inverted repeated Alu elements (IRAlus) (Athanasiadis et al., 2004; Kim et al., 2004; Levanon et al., 2004)

Over 300 genes have been found to contain IRAlus in their 3′-UTR regions (Chen et al., 2008). Messenger RNAs with A-to-I hyperedited IRAlus are retained in nuclear paraspeckles via binding to paraspeckle proteins (e.g. NONO/p54^{nrb} and SFPQ/PSF) (Prasanth et al., 2005; Chen et al., 2008). Such nuclear retention prevents the export of A-to-I hyperedited mRNAs to the cytoplasm and their resulting translation. This is a cellular mechanism that prevents inappropriate translation of promiscuously edited RNAs, and is used in some regulatory mechanisms to modulate gene expression (Chen et al., 2008; Bond and Fox, 2009; Chen and Carmichael, 2010).

In contrast, the NEAT1 lncRNA is not A-to-I edited, another finding that supports its architectural role in paraspeckles (Clemson et al., 2009). From a study of NEAT1 knockdown in HeLa cells, depletion of NEAT1 resulted both in loss of paraspeckles and in enhanced nucleocytoplasmic export of mRNAs containing IRAlus (Chen and Carmichael, 2009), indicating the critical role of NEAT1 in the paraspeckle-mediated nuclear retention of A-I-edited mRNAs. Although robust A-I editing activity was detected in human embryonic stem cells (hESCs), A-I-edited mRNAs are not retained in the nucleus of hESCs, correlating with the absence of NEAT1 expression in hESCs. When hESCs differentiate, NEAT1 is expressed and A-I edited mRNAs are consistently retained in the nucleus of differentiated hESCs (Chen and Carmichael, 2009). These findings suggest that the modulation of paraspeckle biogenesis and nuclear retention of A-I edited mRNAs by NEAT1 expression is biologically relevant. In addition to this mechanism, paraspeckles have also been demonstrated to sequester transcription regulators (e.g. SFPQ/PSF). This is another mechanistic mode by which paraspeckles regulate gene expression (e.g. *ADARB2* and *IL8*), and more research is necessary for its characterization (Hirose et al., 2014; Imamura et al., 2014).

Paraspeckle proteins have also been found to regulate expression of the NEAT1_2 isoform. It has been shown that binding of paraspeckle proteins such as NONO/p54^{nrb} and SFPQ/PSF stabilizes the NEAT1_2 but not the NEAT1_1 isoform (Sasaki et al., 2009). Furthermore, from screening with a fluorescent protein-tagged full-length cDNA library, heterogeneous nuclear ribonucleoprotein K (HNRNPK) was identified as a paraspecke protein component that promotes the production of NEAT1_2 and subsequent formation of paraspeckles. HNRNPK inhibits the CPSF6–NUDT21 (CFIm) complex from binding in the vicinity of the alternative polyadenylation site of NEAT1_1 (Naganuma et al., 2012). This inhibitory effect on CFIm is attributable to the competition of HNRNPK with CPSF6 for binding to NUDT21(Naganuma et al., 2012). These findings suggest that paraspeckle biogenesis is also regulated by the effects of paraspeckle proteins on expression of the essential NEAT1_2 isoform.

NEAT1-containing paraspeckles and p53 biology

NEAT1-containing paraspeckles have recently been linked to the function of the p53 pathway. Adriaens and colleagues identified NEAT1 as a downstream target gene of p53, and found that pharmacologically triggered or oncogene-induced replication stress stimulated NEAT1 expression and the formation of paraspeckles in mouse and human cells in a p53-activation-dependent manner (Adriaens et al., 2016). This phenomenon is required for survival of cells under DNA damage stress, and eradication of paraspeckles by silencing NEAT1 expression sensitized preneoplastic cells to DNA-damage-induced cell death and impaired skin tumorigenesis (Adriaens et al., 2016).

Silencing of NEAT1_2 impaired both activation of the ATR–CHK1 pathway under DNA damage stress and the engagement of this pathway in activating G2–M and intra-S-phase checkpoints (Adriaens et al., 2016). The failure of either of these checkpoint steps leads to replication fork collapse and formation of double stranded DNA breaks (DSBs), which cause cell death. Moreover, the NEAT1-dependent activation of ATR signaling attenuates oncogene-induced activation of p53 (Adriaens et al., 2016). These findings suggest that NEAT1 is involved in a negative feedback loop with p53 and thereby promotes cancer formation in mice by impairing oncogene-dependent activation of p53. Consistently, NEAT1 inactivation sensitized human cancer cells to both chemotherapy and p53 reactivation therapy. The study further showed that NEAT1_2, but not NEAT1_1, expression levels predicts the response of ovarian cancer to platinum-based chemotherapy (Adriaens et al., 2016). These results illustrate the relevance of NEAT1 in tumorigenesis and its potential as a therapeutic target. Although the role of paraspeckles in p53 biology was not addressed in the study due to the difficulty of studying multifunctional paraspeckle-associated proteins, the essential role of NEAT1_2 in paraspeckle formation suggests that paraspeckles are functionally linked to the biological aspects of p53 signaling.

NEAT1 and epigenetic regulation

In addition to nuclear paraspeckle retention of A-I edited mRNAs and sequestration of transcription regulators, two lines of evidence suggest that NEAT1 is involved in epigenetic regulation of gene expression. West and colleagues exploited a method called capture hybridization analysis of

RNA targets (CHART) (Simon et al., 2011) to purify two endogenous highly expressed lncRNAs, NEAT1 and MALAT1(metastasis-associated lung adenocarcinoma transcript 1), and their associated genomic sites in human cells for deep sequencing (CHART-seq) analysis (West et al., 2014). In comparison to the NEAT1 lncRNA that localizes to paraspeckles, MALAT1 localizes to nuclear speckles, which are different nuclear bodies enriched for serine- and arginine-rich (SR) splicing factors (Hutchinson et al., 2007).

Their studies identified hundreds of *trans* genomic binding sites for both NEAT1 and MALAT1 that overlap active gene regions. These identified *trans* sites were further confirmed by co-FISH (fluorescence in situ hybridization) studies of RNA/DNA and ChIP-seq (chromatin immunoprecipitation sequencing) of the paraspeckle component SFPQ/PSF. Moreover, their proteomic study with CHART-enriched material (CHART-MS) identified proteins associating with NEAT1 and MALAT1, some of which are protein components in nuclear speckles and paraspeckles (West et al., 2014). Their findings, taken together, showed that a number of *trans* genomic binding sites and protein factors were copurified with these two lncRNAs, suggesting that there is potential redundancy or cooperation between these two lncRNAs in regulating nuclear chromosomal organization in close proximity to nuclear bodies.

Nevertheless, these two lncRNAs manifest differential preferences for genomic sites. NEAT1 is preferentially located at transcriptional start sites (TSSs) and transcriptional termination sites (TTSs). In contrast, MALAT1 primarily localizes across gene bodies and near the TTS (West et al., 2014). These findings suggest that these two lncRNAs have independent but synergistic functional roles on co-occupied genes. Interestingly, transcription modulation changes NEAT1 localization on the genome (West et al., 2014), implying that genomic sequences are unlikely to serve as targets for NEAT1 to bind chromatin, and that contact with protein components of the transcription process is responsible for the genomic localization of NEAT1. According to these discoveries, a possible paradigm is that NEAT1 and MALAT1 function as scaffolds that bind protein components of nuclear bodies and proteins that interact directly with the RNA and/or DNA at specific transcriptionally active loci. Thus, these lncRNAs potentially serve as a bridge to functionally link chromosomal locations to these nuclear subdomains.

The studies by West et al. (2014) highlight the *in vivo* interaction between NEAT1 and active gene loci. However, their investigation did not further address the consequence of this interaction, and whether NEAT1 affects expression of its associated genes in an epigenetic manner. From studying the role of estrogen receptor α (ERα) in prostate cancer, Chakravarty and colleagues identified NEAT1 as a potential target of ERα and as a critical mediator for maintenance of prostate tumorigenesis (Chakravarty et al., 2014). Prostate cancer genes are activated by NEAT1 expression in an androgen receptor (AR)-independent manner. The oncogenic role for NEAT1 was confirmed in prostate cancer cell culture models and in an experimental animal model of prostate cancer. Their chromatin isolation by RNA purification (ChIRP) analysis showed that NEAT1 was able to associate with chromatin via specific interaction with histone H3 and also with active histone H3 modifications, including H3AcK9 and H3K4Me3 (Chakravarty et al., 2014). These findings, taken together, suggest that NEAT1 contributes to the epigenetic 'on' states of genes implicated in prostate cancer development via its recruitment to the respective chromosomal sites.

Although studies by Chakravarty et al. (2014) reveal the oncogenic role of NEAT1 in activating prostate cancer genes potentially through an epigenetic mechanism, they did not study the role of the long isoform NEAT1_2 lncRNA separately from the short isoform NEAT1_1. Therefore, it is uncertain whether this oncogenic effect is attributable to only one or both NEAT1 lncRNA isoforms, and whether paraspeckles are involved in activating prostate cancer genes. Moreover, it is unclear whether the recruitment of NEAT1 to chromatin is due to its direct binding to histone H3 or to bridge RNA molecules or proteins that can directly interact with histone H3 or its active forms. Addressing these questions will unveil the exact roles of NEAT1 and paraspeckles in epigenetic regulation of gene expression.

Physiological functions of NEAT1

Multiple lines of evidence have shown that NEAT1 is relevant in a variety of physiological processes and responses. This section reviews and discusses recent advances in physiological roles of NEAT1.

NEAT1 and hypoxia

Hypoxia is a condition in which the organism or a part of the organism is deprived of adequate oxygen supply at the tissue level. Under hypoxia, one of the critical changes in cellular transcriptional responses is the activation of hypoxia-inducible factors (HIFs), which regulate expression of a cohort of genes necessary for organisms to adapt to hypoxia. During tumor development, tumor growth usually results in the internal part of a tumor becoming hypoxic. Activation of HIFs in tumor cells under hypoxia has been shown to promote tumor cell survival as well as growth and angiogenesis. Therefore, activation of HIF-mediated transcriptional responses is common in many types of cancer and generally confers a poor prognosis on cancer patients (Semenza, 2010).

Choudhry and colleagues recently revealed that NEAT1 expression was upregulated and paraspeckle formation induced by hypoxia in breast cancer cell models (Choudhry et al., 2015). Their mechanistic study further showed that NEAT1 is positively regulated by HIF-2. To link the function of paraspeckles to hypoxia responses in cancer cells, they studied an A-to-I edited RNA transcript (F11R; also known as

junctional adhesion molecule 1, JAM1) and found that the increased nuclear retention of F11R in hypoxia is dependent on a hypoxia-dependent increase in NEAT1 expression (Choudhry et al., 2015). This discovery reveals a novel underlying mechanism for HIF-2-dependent gene regulation. Nevertheless, the questions regarding how much the extent of HIF-2-regulated genes is paraspeckle-dependent and what their functional roles are in hypoxic responses remain to be addressed.

NEAT1 and adipogenesis

Adipogenesis is a developmental process in which preadipocytes differentiate into adipocytes. Currently there are two lines of evidence suggesting that NEAT1 is involved in the regulation of adipogenesis. The first line of evidence suggests that NEAT1 is potentially able to regulate splicing of an adipogenic gene, peroxisome proliferator activated receptor γ (PPARγ) (Cooper et al., 2014). The PPARγ gene encodes two transcription factor isoforms (PPARγ1 and PPARγ2), both of which are crucial for driving adipogenesis. These two PPARγ variants are generated from alternative splicing of the pre-mRNA by the serine/arginine-rich splicing protein SRp40 (Cooper et al., 2014).

The study by Cooper et al. (2014) reveals that the NEAT1 lncRNA can associate with the splicing factor SRp40 and regulate its phosphorylation by the Clk kinase. Their functional study showed that NEAT1 knockdown altered the expression ratio of PPARγ1 to PPARγ2. Their findings together suggest a hypothetical model that NEAT1 functions as a sequestering RNA to tether SRp40 to paraspeckles. This results in blocking the access of SRp40 to its RNA targets and inhibiting its splicing function. Changes in NEAT1 expression during adipogenesis affect the release of phosphorylated SRp40 from paraspeckles, which subsequently impacts PPARγ splicing. More studies are still needed to verify this paradigm.

The second line of evidence revealing a role of NEAT1 in adipogenesis identifies a novel miR-140-NEAT1 signaling axis (Gernapudi et al., 2015). Due to the capability of microRNAs (miRNAs) to regulate expression of a broad range of genes, miRNAs are known to play critical roles in adipogenesis (Peng et al., 2014). We revealed that adipocyte-derived stem cells (ADSCs) isolated from *miR-140* knockout mice exhibited dramatically decreased adipogenic differentiation capabilities and downregulated NEAT1 expression (Gernapudi et al., 2015). Rescuing NEAT1 expression in *miR-140*-knockout ADSCs was sufficient to restore their ability to undergo adipogenic differentiation, indicating that a defect in differentiation of *miR-140*$^{-/-}$ ADSCs is, at least in part, attributable to downregulated NEAT1 expression (Gernapudi et al., 2015). We further unraveled that miR-140 is required for the stabilization of NEAT1 via interaction with a cognate miR-140 binding site within the NEAT1 lncRNA transcript (Gernapudi et al., 2015). From our studies, it is clear that NEAT1 plays a significant role in adipogenesis. However, further investigations are necessary to determine the exact mechanism underlying miR-140-mediated NEAT1 RNA stabilization, and to address how NEAT1 regulates adipogenesis. By considering the aforementioned epigenetic role of NEAT1 in gene expression regulation, our findings suggest a new mechanism that the interactions between non-coding RNA molecules endow themselves with more capabilities to broadly impact on gene expression regulation.

NEAT1 and immune responses

Recently the role of NEAT1 in paraspeckles has been linked to cellular responses to viral infections. From profiling 83 disease-related lncRNAs it was reported that NEAT1 expression was induced in T cells by HIV-1 infection (Zhang et al., 2013). Knockdown of NEAT1 led to increased HIV-1 production through the enhanced nucleus-to-cytoplasm export of Rev-dependent instability element (INS)-containing HIV-1 mRNAs (Zhang et al., 2013), suggesting that NEAT1 participates in the sequestration of INS-containing HIV-1 mRNAs in the nucleus. It has been reported that some HIV-1 RNAs are subjected to A-to-I editing by ADAR1 (Doria et al., 2009), and paraspeckle protein components (e.g. $p54^{nrb}$ and PSF) can associate with HIV-1 INS-containing RNAs (Zhang and Carmichael, 2001; Zolotukhin et al., 2003). These findings suggest a model wherein paraspeckles serve as a "negative" retention depot for HIV-1 INS-transcripts to counterbalance HIV-1 replication. However, further studies like colocalization analysis of HIV-1 RNAs with NEAT1 and paraspeckles are necessary to validate the proposed hypothesis.

In line with the aforementioned HIV-1 study, Imamura and colleagues found that NEAT1 expression and paraspeckle formation is induced by influenza virus and herpes simplex virus infection, as well as by Toll-like receptor3-p38 pathway-triggered poly I:C stimulation (Imamura et al., 2014). Their studies further showed that NEAT1 induction activates the expression of antiviral genes including cytokines such as interleukin-8 (IL8). Upregulated IL8 expression by NEAT1 induction is attributable to NEAT1-paraspeckle-mediated sequestration of the paraspeckle protein SFPQ/PSF, which is a repressor of IL8 transcription (Imamura et al., 2014). Therefore, NEAT1 plays a pivotal role in the innate immune response by modulating the nuclear localization of transcriptional factors implicated in regulating expression of antiviral genes (Imamura et al., 2014).

NEAT1 and organogenesis

Neat1 knockout mice have been recently established (Nakagawa et al., 2011; Standaert et al., 2014), and are a valuable animal model for studying the physiological role of NEAT1 in mammals. Despite the aforementioned cellular functions of NEAT1, the *Neat1* knockout mice were initially

observed to have no phenotypic defects (Nakagawa et al., 2011). While paraspeckles were absent in examined knockout tissues, no differences in bodyweight and fertility were found in their initial study (Nakagawa et al., 2011). Further investigations revealed that NEAT1 is required for the development of the corpus luteum (Nakagawa et al., 2014), and *Neat1* knockout results in an approximately 50% decreased rate of pregnancy. This defect is related to low progesterone levels, implying that Neat1 plays a role in hormonal signaling necessary for pregnancy (Nakagawa et al., 2014). Furthermore, another study showed that *Neat1* knockout mice have defective mammary gland morphogenesis, resulting in lactation defects due to the inability of *Neat1* knockout luminal cells to proliferate during alveolar development (Standaert et al., 2014). Consistently, paraspeckles were preferentially detected in luminal epithelial cells (Standaert et al., 2014), suggesting that the *in vivo* function of paraspeckles is required for mammary gland development.

Pathological roles of NEAT1

Accumulating recent evidence has shown that NEAT1 expression is dysregulated in numerous types of cancer, including brain cancer, head and neck cancer, breast cancer, lung cancer, esophageal cancer, gastric cancer, liver cancer, leukemia, ovarian cancer, and prostate cancer. This section reviews and discusses the pathological roles of NEAT1 in a variety of cancers.

Brain cancer

NEAT1 has been found to be overexpressed in glioma tissues compared with noncancerous brain tissues. NEAT1 overexpression correlated with clinicopathological characteristics, such as larger tumor size, higher WHO grade, recurrence, and with a poor prognosis in glioma patients (He et al., 2016). In line with these clinical results, overexpression of NEAT1 conferred malignancies on glioma, and NEAT1 knockdown inhibited glioma cell proliferation, invasion, and migration (Zhen et al., 2016). The mechanistic study further identified that NEAT1 serves as a competitive endogenous lncRNA sponge for miR-449b-5p, suppressing the inhibitory effect of this microRNA on its target genes. This leads to induction of c-Met expression, a miR-449b-5p target gene, potentially contributing to the development of glioma (Zhen et al., 2016). Therefore, dysregulation of the NEAT1/miR-449b-5p/c-Met signaling axis is a mechanism that promotes glioma pathogenesis, and is a potential target for the prognosis and treatment of glioma.

Head and neck cancer

NEAT1 has been shown to be significantly upregulated in nasopharyngeal carcinoma (NPC), and its knockdown sensitized NPC cells to radiation *in vitro* (Lu et al., 2016). This NEAT1-mediated radioresistance was attributable to modulation of the epithelial-to-mesenchymal transition (EMT) phenotype (Lu et al., 2016). Further mechanistic investigations revealed that NEAT1 represses miR-204 expression to induce expression of the EMT-driving factor ZEB1, which is a miR-204 target (Lu et al., 2016). This indicates that NEAT1 regulates the EMT phenotype and radioresistance of NPC via modulating the miR-204/ZEB1 signaling axis.

In addition to NPC, NEAT1 levels were shown to be significantly higher in human laryngeal squamous cell cancer (LSCC) compared to corresponding adjacent non-neoplastic tissues. Moreover, LSCC patients with neck nodal metastasis or with an advanced clinical stage were diagnosed to have NEAT1 overexpression (Wang et al., 2016). Further functional analyses revealed that NEAT1 is required for cell proliferation and survival of LSCC cells. In line with *in vitro* results, NEAT1 knockdown impaired the *in vivo* growth of LSCC xenografts (Wang et al., 2016). This study unraveled a regulatory mechanism wherein NEAT1 positively regulates CDK6 expression (a miR-107 target) via downregulating miR-107 expression (Wang et al., 2016). CDK6 is a key regulator that drives the G1/S cell cycle transition. It has been shown that Cdk6 is overexpressed in head and neck squamous cell carcinoma and significantly correlates with tumor progression (Poomsawat et al., 2016). Therefore, this study suggests that dysregulation of NEAT1 contributes to the development of LSCC via modulating the miR-107/CDK6 axis.

Breast cancer

As aforementioned, the NEAT1 lncRNA has been shown to be a direct transcriptional target of HIF-2 in many breast cancer cell lines and in solid tumors (Choudhry et al., 2015). Given that NEAT1 functions as an architectural lncRNA required for paraspeckle formation, upregulation of NEAT1 expression by activated HIF-2 upon hypoxia triggers the nuclear retention of A-I edited mRNAs (e.g. F11R) in paraspeckles, and in turn inhibits their translation in the cytoplasm (Choudhry et al., 2015). This new mode of gene expression regulation potentially contributes to the responses of breast cancer cells to hypoxic stress. The outcomes of hypoxia-triggered NEAT1 induction in breast cancer cells exhibit hallmarks of promoted tumorigenesis, including enhanced cellular proliferation, increased clonogenic survival and reduced apoptosis. Moreover, the NEAT1 expression status correlates with poor survival of breast cancer patients (Choudhry et al., 2015). These findings suggest a novel role of HIF-dependent transcriptional pathways in regulating biogenesis of nuclear bodies, which contributes to the hypoxia-induced tumorigenic phenotype in breast cancer.

NEAT1 knockdown has also been shown to impair proliferation and survival of breast cancer cells via induction

of apoptosis (Ke et al., 2016), suggesting NEAT1 is required for breast cancer cell survival even under normoxic conditions. This function likely involves the interaction between NEAT1 and the RNA binding protein FUS/TLS (fused in sarcoma/translocated in liposarcoma). Consistently, knockdown of FUS/TLS also induced apoptosis in breast cancer cells (Ke et al., 2016). miR-548ar-3p was further identified as an upstream regulator that suppressed NEAT1 expression, and its overexpression triggered apoptosis (Ke et al., 2016). These findings reveal a novel interaction between NEAT1, miR-548ar-3p, and FUS and their roles in the regulation of breast cancer cell survival.

Germline mutations of breast cancer susceptibility gene 1 (*BRCA1*) are one of the leading causes of hereditary breast cancer. BRCA1 has been shown to be functionally required for morphogenesis of mammary glands (Foulkes, 2004; Buckley and Mullan, 2012). We recently identified NEAT1 as a potential transcriptional target of BRCA1. BRCA1 downregulates NEAT1 expression potentially through its genomic binding site upstream of the *NEAT1* gene (Lo et al., 2016). In contrast, inactivation of BRCA1 in human normal/cancerous breast cells and mouse mammary glands led to NEAT1 overexpression (Lo et al., 2016). We showed that NEAT1 upregulation resulting from BRCA1 deficiency enhanced *in vitro* and *in vivo* breast tumorigenicity (Lo et al., 2016). We further found that NEAT1 negatively regulates miR-129-5p expression via promoting the DNA methylation of the CpG island in the *miR-129* gene. Downregulation of miR-129-5p results in increased expression of its target WNT4, subsequently leading to activation of oncogenic WNT signaling (Lo et al., 2016). Our data reveal that this NEAT1/miR-129-5p/WNT4 axis contributes to the tumorigenic effects of BRCA1 deficiency. Therefore, our studies suggest that the dysregulation of the BRCA1/NEAT1/miR-129-5p/WNT4 signaling axis is involved in promoting breast tumorigenesis.

Lung cancer

In a lung cancer study, NEAT1 was identified to be a target of the tumor-suppressive microRNA miR-449a, which is found to be downregulated in lung cancer tissues (You et al., 2014). Gain- and loss-of-function studies of miR-449a in lung cancer cells confirmed that miR-449a negatively regulates NEAT1 expression (You et al., 2014). As the role of NEAT1 in lung cancer cells was not addressed in the study, further investigations are needed to reveal the exact role of the miR-449a/NEAT1 axis in lung tumorigenesis. Nevertheless, based on the tumor-suppressive role of miR-449a, it is likely that NEAT1 is an oncogenic factor in lung cancer.

In a therapeutic study of non-small cell lung cancer (NSCLC), NEAT1 was revealed as a crucial lncRNA that determines the sensitivity of NSCLC cells to platinum-based anti-cancer drugs (e.g. cisplatin) (Jiang et al., 2016). In the study, the green tea polyphenol, EGCG, was shown to increase cisplatin sensitivity in NSCLC cells by inducing expression of cisplatin transporter CTR1 (Jiang et al., 2016). Further investigations revealed that CTR1 expression is negatively and positively regulated by miR-98-5p and NEAT1, respectively. Of interest, NEAT1 was revealed to contain two miR-98-5p targeting sites and serve as a sponge lncRNA for miR-98-5p. Given that EGCG treatment reciprocally affected expression of these two non-coding RNAs, upregulation of NEAT1 and downregulation of miR-98-5p by EGCG led to the competitive suppression of miR-98-5p by NEAT1, resulting in elevated expression of CTR1 and increased cisplatin sensitivity in NSCLC cells (Jiang et al., 2016). This is the first report demonstrating that NEAT1 is involved in regulation of drug sensitivity.

Esophageal cancer

From a study of esophageal squamous cell carcinoma (ESCC), NEAT1 was identified to be overexpressed in ESCC tissues and cells compared with the normal counterparts (Chen et al., 2015). Clinical association analyses showed that elevated NEAT1 levels significantly correlated with clinicopathological features of ESCC, such as tumor size, lymph node metastasis and tumor stage. Moreover, higher expression of NEAT1 was significantly associated with poor survival of ESCC patients (Chen et al., 2015). *In vitro* gain-/loss-of-function analyses revealed that dysregulation of NEAT1 promotes malignancies of ESCC cells (Chen et al., 2015). The overall results suggest an oncogenic role of NEAT1 in esophageal tumorigenesis and its potential as a therapeutic/prognostic target in ESCC.

Gastric cancer

In two studies the NEAT1 lncRNA was detected to be overexpressed in gastric cancer tissues and cell lines (Fu et al., 2016; Ma et al., 2016). NEAT1 overexpression is positively associated with clinical stage, histological type, lymph node metastasis, and distant metastasis (Fu et al., 2016; Ma et al., 2016). Using univariate and multivariate Cox regression analyses, NEAT1 overexpression was shown to be a poor independent prognostic indicator for gastric cancer patients (Fu et al., 2016). *In vitro* studies showed that NEAT1 knockdown significantly attenuated proliferation, migration and invasion of gastric cancer cells (Fu et al., 2016; Ma et al., 2016). These findings together suggest that NEAT1 is clinically relevant in gastric cancer and may functionally contribute to gastric tumorigenesis.

Liver cancer

In line with other studies of solid tumors, NEAT1 was detected to have higher expression in the hepatocellular carcinoma (HCC) tissues compared with the adjacent noncancerous liver tissues (Guo et al., 2015). NEAT1 overexpression positively correlated with malignant features of

HCC, including increased tumor nodes, metastasis, TNM stage, the status of portal vein tumor embolus, vaso-invasion and the infiltration of tumor cells (Guo et al., 2015). This study suggests an oncogenic role of NEAT1 in tumorigenesis and metastasis of hepatocellular carcinoma, and implicates this lncRNA as a therapeutic target and/or a prognostic biomarker for HCC.

Leukemia

The reciprocal translocation t(15;17) that fuses *PML* with retinoic acid receptor alpha (*RARα*) is known to be a main factor leading to the development of acute promyelocytic leukemia (APL). This genetic translocation generates the fused PML-RARα protein that is crucially responsible for tumorigenesis and responsiveness to retinoic acid-based treatment (Zhu et al., 1999; Nasr et al., 2008). NEAT1 was found to be significantly underexpressed in *de novo* APL samples compared with those of healthy donors (Zeng et al., 2014). Downregulation of NEAT1 expression in APL is mediated by PML-RARα. In contrast, NEAT1 expression was significantly increased during the differentiation of an APL cell model induced by all-trans retinoic acid (ATRA) treatment. Reduction of NEAT1 expression by small interfering RNA (siRNA) blocked ATRA-induced differentiation (Zeng et al., 2014). These results suggest that reduced expression of the NEAT1 lncRNA may play a role in suppressing the myeloid differentiation of APL cells. This finding highlights a possible tumor-suppressive role of NEAT1 in some specific types of cancer in addition to its oncogenic role in solid tumors.

Ovarian cancer

In an ovarian cancer (OC) study, NEAT1 levels were found to be upregulated in OC tissue specimens and cell lines, and its overexpression correlated with the FIGO stage and lymph node metastasis (Chai et al., 2016). Results from gain-/loss-of-function assays indicate that NEAT1 upregulation promotes the malignancy of OC cells. Furthermore, RNA binding protein HuR and miR-124-3p were identified to positively and negatively regulate NEAT1_1 expression in OC cells, respectively. Consistently, the upregulated HuR mRNA and downregulated miR-124-3p levels were observed in OC patients (Chai et al., 2016). These findings, taken together, suggest that dysregulation of the regulatory interaction between NEAT1, HuR and miR-124-3p contributes to ovarian carcinogenesis.

In the aforementioned study of NEAT1 and p53, the association between NEAT1 expression status and chemotherapeutic response was studied in the two cohorts of ovarian cancer patients (Adriaens et al., 2016). The result indicated that the high expression levels of NEAT1_2 significantly correlated with the worst progression-free survival (PFS) of ovarian cancer patients who had been treated with chemotherapy. In contrast, NEAT1_1 expression levels had no significant correlation with the PFS (Adriaens et al., 2016). This clinical analysis suggests that NEAT1 is involved in modulating the response of ovarian cancer patients to chemotherapy via regulating p53 signaling activity.

Prostate cancer

Aberrant activation of the androgen receptor (AR) is known to be a main pathological mechanism leading to prostate tumorigenesis. However, some prostate cancers escape AR dependence and become more aggressive. Since estrogen receptor (ER), another steroid hormone receptor, was found to be expressed in prostate cancers regardless of AR status, the role of ER in AR-independent prostate cancers has been studied (Ricke et al., 2008; Setlur et al., 2008). Estrogen receptor signaling activity via ER is increased with prostate cancer progression (Ricke et al., 2008), and drives important oncogenic events (Arredouani et al., 2009). Furthermore, studies of mouse prostate cancer models suggest that antagonism of ER can be a potential strategy for inhibiting prostate carcinogenesis (Ricke et al., 2008). Therefore, the elucidation of the oncogenic mechanism underlying ER signaling can provide new insights into how prostate cancer becomes AR-independent and what dysregulated genes can be targeted for therapy of AR-independent prostate cancers.

In the aforementioned study by Chakravarty et al. (2014), NEAT1 was identified as a potential target of ERα. Their study revealed an oncogenic role for NEAT1 in an experimental animal model of prostate cancer and in cell culture models, suggesting that NEAT1 is an important mediator for maintenance of prostate cancer. Analysis of two large clinical prostate cancer cohorts also revealed that NEAT1 expression correlated with prostate cancer progression (Chakravarty et al., 2014). The further mechanistic studies showed that NEAT1 functions as a transcriptional modulator and its aberrant recruitment to the chromatin contributes to a cancer-favorable transcriptome potentially via altering the epigenomic landscape (Chakravarty et al., 2014). Interestingly, the ERα/NEAT1 signaling axis was recalcitrant to AR inhibitors and AR deficiency, thus suggesting a mechanism whereby prostate cancer cells may develop therapeutic resistance through positive selection of the alternate ERα/NEAT1 signaling pathway in the absence of AR or during androgen ablation therapy (Chakravarty et al., 2014). These findings suggest that targeting of NEAT1 in conjunction with AR antagonism therapy might be a potential strategy for the treatment of prostate cancer.

Concluding remarks

NEAT1 was initially identified as an architectural lncRNA essential for paraspeckle formation and to have paraspeckle-related functions. However, growing evidence implies that

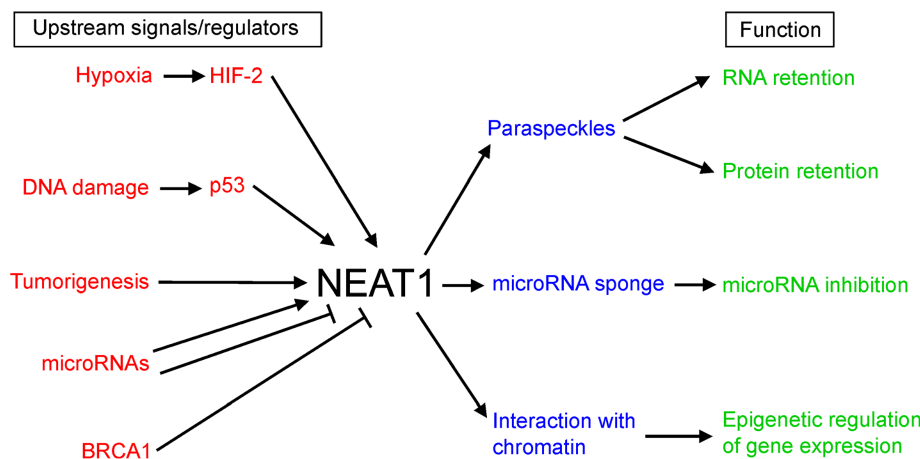

Figure 2 The regulation and function of NEAT1 in the cell. NEAT1 expression is upregulated by hypoxia and DNA damage stress via activation of upstream transcription factors HIF-2 and p53, respectively. microRNAs (listed in Table 1) are involved in positively and negatively regulating NEAT1 expression. BRCA1 is also found to negatively regulate NEAT1 expression. NEAT1 is overexpressed during tumorigenesis of various types of tissue through dysregulation of the aforementioned signaling pathways, microRNA expression and other unknown mechanisms. NEAT1 executes its functions through acting as an architectural RNA for paraspeckle assembly and as a sponge RNA for inhibiting microRNAs, and through interacting with chromatin for epigenetic regulation of gene expression.

NEAT1 may have functions beyond these roles (Fig. 2). NEAT1 has been shown to interact with histone H3 and with the active, modified forms of histone H3, suggesting NEAT1 may have a regulatory role in the epigenomic landscape (Chakravarty et al., 2014). We also discovered that NEAT1 can modulate microRNA expression via regulating DNA methylation of microRNA gene loci (Lo et al., 2016). It is conceivable that investigating the epigenetic role of NEAT1 will become an exciting research topic in lncRNA studies.

Numerous studies have revealed the interactions between the NEAT1 lncRNA and various microRNAs, and their effects on gene expression regulation (summarized in Table 1). These findings suggest that the NEAT1-microRNA-regulatory network plays significant cellular and physiological roles and its dysregulation contributes to pathogenesis, in particular tumorigenesis. Further investigations will be necessary to elucidate molecular mechanisms underlying these interactions and what their biological functions are.

According to literature, it is preferentially observed that NEAT1 plays an oncogenic role in multiple types of cancer.

Table 1 The regulatory interactions between the lncRNA NEAT1 and microRNAs

Regulatory mechanism	microRNA	microRNA target	Interaction mechanism	Dysregulation in cancer	Reference
As a sponge for microRNAs	miR-98-5p	CTR1	NEAT1 inhibits miR-98-5p to induce CTR1 expression, resulting in increased chemosensitivity.	NSCLC (Lung cancer)	Jiang et al., 2016
	miR-107	CDK6	NEAT1 inhibits miR-107 to induce CDK6 expression, which promotes cell growth.	LSCC (Head and neck cancer)	Wang et al., 2016
	miR-204	ZEB1	NEAT1 inhibits miR-204 to induce ZEB1 expression, leading to EMT activation.	NPC (Head and neck cancer)	Lu, et al., 2016
	miR-449b-5p	c-Met	NEAT1 inhibits miR-449b-5p to induce c-Met expression.	Brain cancer	Zhen et al., 2016
Epigenetic regulation of microRNAs	miR-129-5p	WNT4	NEAT1 silences miR-129-5p expression via increasing DNA methylation of *miR-129* gene.	Breast cancer	Lo et al., 2016
Regulated by microRNAs	miR-124-3p	NEAT1	miR-124-3p inhibits NEAT1 expression.	Ovarian cancer	Chai et al., 2016
	miR-140	NEAT1	miR-140 stabilizes NEAT1 and increase its expression.	This regulation is required for adipogenesis	Gernapudi et al., 2016
	miR-449a	NEAT1	miR-449a suppresses NEAT1 expression.	Lung cancer	You et al., 2014
	miR-548ar-3p	NEAT1	miR-548ar-3p decreases NEAT1 expression.	Breast cancer	Ke et al., 2016

However, it is uncertain whether these observed oncogenic effects are NEAT1 isoform-specific as most studies do not address the role of each NEAT1 lncRNA isoform individually in their investigated cancers. It is reasonable to predict that these two NEAT1 isoforms have redundant and differential functions in cells. For instance, NEAT1_2, but not NEAT1_1, has been found to be a promising predictor of chemotherapeutic response in ovarian cancer patients (Adriaens et al., 2016). In some studies, overexpression of NEAT1_1 has been shown to promote the tumorigenicity of cancer cells (Chen et al., 2015; Adriaens et al., 2016; Chai et al., 2016; Lo et al., 2016). Therefore, it will be important in the future that NEAT1 lncRNA isoforms are studied individually in cancer to completely understand the role of NEAT1 in tumorigenesis. Moreover, whether the paraspeckle-dependent function of NEAT1 contributes to tumorigenesis remains an unanswered question. More creative ideas and investigations will be needed to answer this question. Overall, recent advances in the role of NEAT1 in cancer have revealed that this lncRNA is a potential biomarker for cancer diagnosis and prognosis, and a promising therapeutic target for cancer treatment.

Acknowledgements

This work was supported by National Institutes of Health (NIH) R01 grants [grant numbers 5R01CA157779-03, 5R01CA163820-04] to Q.Z.

Compliance with ethics guidelines

Pang-Kuo Lo, Benjamin Wolfson, Qun Zhou declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

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