Recent comprehensive molecular profiling in many types of cancers has revealed oncogenic mutations and the aberrant expressions of protein-coding genes. However, because the coding genome accounts for <2% of all DNA sequences and many mutations were reported in non-coding sequences, the dysregulation of non-coding RNAs might affect tumor phenotypes. For example, significant numbers of non-coding RNAs such as microRNA (miRNA, miR), siRNA, piwi-interacting RNA, and long non-coding RNAs (lncRNAs), were recently discovered and identified as biologically functional non-coding RNAs, some of which had a significant impact on tumor biology. Among such non-coding RNAs, miRNAs are short non-coding RNAs (approximately 22 nt long) that bind to short regions of complementary sequences of target mRNAs to post-transcriptionally regulate the expression of target genes. MicroRNAs have important roles in a wide variety of pathological processes related to tumor formation. The aberrant expression of miRNA was shown to induce tumor suppression or induce oncogenic effects resulting in tumor formation. Extensively studied examples of tumor-suppressive miRNAs include the let-7, miR-15a/16-1, miR-26a, or miR-34 family members, which are associated with anti-proliferative, anti-tumorigenic, and pro-apoptotic activities and whose expressions are sometimes aberrantly suppressed in many types of cancers. Examples of oncogenic miRNAs include the miR-17-92 cluster, miR-155, and miR-21, the functions of which are associated with the repression of tumor-suppressor genes such as PTEN and CDKN1A, and whose expressions are sometimes aberrantly upregulated in cancers. In addition to miRNAs, lncRNAs, defined as transcripts >200 nt in length, are also functional. Although the precise roles of the vast majority of ~40 000 lncRNAs are still under investigation, some of these transcripts were shown to be potential key regulators of cellular differentiation and proliferation, as well as having oncogenic functions in many types of cancers. Furthermore, studies have shown that lncRNAs affect chromatin structure and RNA interactions, such as the miRNA sponge, which upregulates protein expression by inhibiting the binding of miRNAs to their targets. With regard to RNA interactions between lncRNAs and miRNA in cancers, Hox transcript antisense intergenic RNA (HOTAIR), an lncRNA, has an oncogenic role in tumor formation by upregulating fibroblast growth factor 1 by sponging miR-326, which activates the PI3K/AKT and MEK1/2 pathways. We also recently found that Notch1 activation in glioma cells specifically induced the expression of lncRNA for taurine upregulated gene 1 (TUG1), which coordinately promoted self-renewal by sponging miR-145. Thus, accumulating studies of cancer-associated lncRNAs have reported their roles in the multiple pathological steps of tumorigenesis, including cell proliferation, cellular signaling, angiogenesis, and metastasis, which may provide a strong rationale for the targeting of lncRNAs as a specific and potent...
therapeutic approach to eliminate cancer cells.\(^{(6)}\) In this review, we provide a summary of the current understanding of lncRNAs, including TUG1, which were recently reported to have pathological roles in cancer, and we discuss the future perspective of targeting lncRNAs as a new approach for cancer treatment.

**Roles of lncRNA in gene regulation**

Recent studies reported the regulatory mechanisms of gene expression by lncRNAs in at least seven pathways (Fig. 1).\(^{(10–13)}\) These functions are closely associated with the subcellular localization of lncRNAs, although the precise factors (e.g. binding proteins) and sequence elements in lncRNAs that determine their localization remain largely unknown.\(^{(14)}\) Generally, lncRNAs have a more nuclear-biased localization pattern when compared with mRNAs, although large amounts of lncRNAs are located in the cytoplasm.\(^{(14)}\) This localization bias may support the idea that lncRNAs function as essential molecules in the scaffolding and recruitment of multiple proteins to specific genomic loci to form 3-D nuclear structures, which affect gene expression (Fig. 1). Furthermore, nascent RNA transcripts in the nucleus are processed by different methods including splicing, polyadenylation, 5' capping, and methylation. During these processes, lncRNAs affect RNA splicing and mRNA stability. For example, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which is restricted to the nucleus, especially to nuclear speckles, affects alternative splicing through interactions with serine/arginine-rich splicing factors and pre-mRNA.\(^{(13,15)}\) In addition to their nuclear functions, cytoplasmic lncRNAs function as a modulator by interacting with other types of RNAs (e.g. competitive endogenous RNAs [ceRNAs]). These functions of lncRNAs are exemplified and explained in more detail below.

**Interactions between chromatin regulatory proteins and lncRNAs.** Long non-coding RNAs regulate gene expression through their scaffolding activity for chromatin modifying proteins (e.g. methyltransferases, demethylases, acetyltransferases, and deacetylases), and recruiting these proteins to target loci through cis-regulation (regulation of the transcription of nearby genes) or trans-regulation (regulation of the transcription of genomically distant genes). These interactions occur by affecting the nuclear structure.\(^{(16)}\)

One of the most studied lncRNAs is X-inactive specific transcript (Xist), which is expressed from one of the two X chromosomes at the initial phase of X chromosome inactivation (XCI) in early female embryonic development. Xist binds to chromatin by scaffold attachment factor A (also known as hnRNPU) and recruits SMRT/histone deacetylase 1 (HDAC1)-associated repressor protein (SHARP), which interacts with HDAC3, polycomb repressive complex 1 (PRC1), and PRC2\(^{(17,18)}\). Intriguingly, although the induction of Xist expression and the recruitment of SHARP-HDAC3 are prerequisites for the initiation of XCI, Xist appears to be dispensable for the maintenance of transcriptional inactivation.\(^{(16,19)}\) Furthermore, it appears that the presence of PRC2 is not required for the initiation of XCI, because the genetic deletion of PRC2 had no effect on the initiation of transcriptional silencing,\(^{(20,21)}\) although it was required for the maintenance of transcriptional inactivation.\(^{(22)}\)

Similar to Xist, a set of lncRNAs are thought to interact with PRC2, resulting in gene inactivation of certain specific
genome loci. HOTAIR is transcribed in the Homeobox (HOX) C gene cluster region on chromosome 12 and is co-expressed with the HOXC genes. HOTAIR regulates the expression of HOXD genes in chromosome 2 through transregulation, whereas interactions between HOTAIR, lysine-specific demethylase 1, and PRC2 promotes coordinated H3K27 methylation and H3K4 demethylation. Many cancers, including breast cancer, pancreatic cancer, non-small-cell lung cancer (NSCLC), and gastrointestinal stromal tumor overexpress HOTAIR, which affects tumor behavior. For example, the overexpression of HOTAIR in breast cancer cells increased their invasive and metastatic abilities and reprogrammed PRC2 occupancy throughout the genome, which is similar to embryonic fibroblasts.

A recent study showed that although HOTAIR binds to PRC2 with a high affinity to silence target loci by H3K27me3 deposition, the genetic deletion of PRC2 components did not affect the silencing activity of HOTAIR, indicating that PRC2 is dispensable for the inhibition of HOTAIR-mediated silencing machinery. This is similar to Xist-mediated gene silencing, as mentioned above. These two examples of functional interactions between an lncRNA (Xist and HOTAIR) and PRC2 suggest interesting mechanistic consequences of lncRNA-guided gene regulation, in which many chromatin regulatory proteins are involved. Thus, in addition to the dysregulation of many chromatin modifiers such as histone modification enzymes and chromatin remodelers that have been comprehensively analyzed in many cancers, the dysregulation of lncRNAs may also play an important functional role in tumorigenesis.

Interactions between lncRNAs and other types of RNA. Long non-coding RNAs interact with other types of RNA molecules in cells, such as mRNA and miRNA, and modulate their stability, splicing, translation, and metabolism (Fig. 1). MALAT1, a highly abundant lncRNA, regulates alternative splicing through interactions with serine/arginine-rich splicing factors and pre-mRNA. Details of MALAT1 functions were well documented in a recent review. In cancer studies, the high expression of MALAT1 in NSCLC was associated with metastatic progression. The genetic loss or systemic knockdown of Malat1 in a mouse cancer model resulted in slower tumor growth and a reduction in the metastasis of lung cancer and breast cancer. Long non-coding RNAs also stabilize mRNA. Terminal tissue differentiation-inducing ncRNA (TINCR) is a characteristic lncRNA that binds to miRNAs with a 25-nT TINCR box motif. TINCR recruits Staufen-I protein, a regulator of tissue differentiation, to mRNA with a TINCR box motif, and stabilizes the target miRNAs to promote its translation.

Recently, a model of ceRNA was proposed, where abundant cytoplasmic IncRNAs containing miRNA-binding sites interacted with miRNAs through their seed sequences (i.e. sequence-specific sequesterer) to reduce their regulatory effect on target mRNA, the so-called miRNA sponge. Phosphatase and tensin homolog (PTEN) is a well-known tumor-suppressor gene. Studies have shown that PTEN pseudogene 1 (PTENP1) increased PTEN protein levels by competing for a set of PTEN-targeting miRNAs, which downregulate PTEN independent of its protein-coding function. In colon cancer, the loss of focal copy number at the PTENP1 locus was associated with the downregulation of PTEN expression in colon cancer patients. A similar relationship was shown between the oncogene KRAS and its pseudogene KRASIP in colon cancer.

These lncRNA contributions to tumorigenesis through mechanisms including ceRNA have generated substantial interest and have been reported in many cancers. However, the ceRNA hypothesis should consider the physiological stoichiometry of miRNAs and ceRNAs in cells because the suppressive activity of ceRNAs might be closely associated with miRNA cellular abundance. Generally, high amounts of miRNAs are unlikely to be susceptible to ceRNA competition. Therefore, a similar abundance of ceRNAs is thought to be required for efficient competition with target miRNAs. Although further studies are required to clarify more precisely the regulatory cross-talk between transcripts, including...

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**Fig. 2.** Aberrant signal transduction induces long non-coding RNA (IncRNA) dysregulation in cancer cells. (a) Notch triggers oncogenic activity by the activation of two different IncRNAs (leukemia-induced non-coding activator RNA [LUNAR1] and taurine upregulated gene 1 [TUG1]) in cancers. LUNAR1 enhances insulin-like growth factor 1 receptor (IGF1R) expression through a cis-activation mechanism in leukemia (left). TUG1 coordinately promotes self-renewal by sponging microRNA-145 (miR-145) in the cytoplasm and recruiting polycomb repressive complex 2 (PRC2) to repress differentiation genes by the locus-specific methylation of histone H3K27 by YY1 binding activity in glioma stem cells. Me, methylation; Pol II, RNA polymerase II. (b) IncRNA activated by transforming growth factor-β (TGF-β) (IncRNA-ATB) is upregulated by TGF-β signaling in hepatocellular carcinoma. IncRNA-ATB upregulates Zinc finger E-box-binding homeobox (ZEB1) and ZEB2 by sequestering miR-200 family members (miR-200s) and inducing epithelial mesenchymal transition and invasion. In addition, IncRNA-ATB promotes the organ colonization of tumor cells by binding to interleukin (IL)-11 mRNA.
mRNAs, miRNAs, and lncRNAs, the ceRNA mechanism might explain the complexity of the dysregulation of mRNA through its 3′-UTR in cancers.

**Mechanisms of dysregulated IncRNA expression in cancer**

Increasing evidence has shown that the dysregulation of lncRNAs is associated with cancer pathogenesis and that lncRNAs function as regulators of cancer-related genes. Several lines of evidence showed that aberrant signal transduction induces IncRNA dysregulation (Fig. 2). The Notch signaling pathway plays a dominant role in inhibiting neural stem cell differentiation through the activities of its downstream effectors, such as Hairy and enhancer of split 1/Spl. A recent study showed that Notch triggered oncogenic activity through IncRNA activation in leukemia (Fig. 2a). In human T-cell acute lymphoblastic leukemia, a set of lncRNAs, including leukemia-induced non-coding activator RNA (LUNAR1), are directly controlled by the Notch1 signaling. LUNAR1 is required for T-cell acute lymphoblastic leukemia growth through the enhancement of insulin-like growth factor 1 receptor expression and sustained insulin-like growth factor 1 signaling. Notch1 signaling also induces another IncRNA, TUG1, which is a cancer-related IncRNA that binds to PRC2 or PRC1 and also represses gene expression in glioma cells.

Long non-coding RNA activated by TGF-β (lncRNA-ATB) was upregulated by transforming growth factor-β signaling in hepatocellular carcinoma metastases. This lncRNA upregulates Zinc finger E-box-binding homeobox 1 and 2 by competitively binding to miR-200 family members to induce epithelial–mesenchymal transition and invasion. Furthermore, lncRNA-ATB promoted the organ colonization of tumor cells by binding to interleukin-11 mRNA and triggering signal transducer and activator of transcription 3 signaling (Fig. 2b).

These studies indicate that a set of lncRNAs may act as key regulators of signaling pathways. Downstream of the cancer-promoting signals, lncRNAs may sustain cancer cell proliferation and enhance viability and motility, which are linked to the clinically relevant cancer subtypes that predict tumor behavior and prognosis.

**Taurine upregulated gene 1 plays important roles in tumorigenesis**

We recently identified the Notch-regulated IncRNA, TUG1, in glioma cells by whole-genome RNA sequencing and comprehensively characterized its function in relation to gliomagenesis. Taurine upregulated gene 1 is a cancer-related IncRNA that plays important roles in tumorigenesis. We have demonstrated that TUG1 is a key regulator of Notch signaling in glioma cells.

**Table 1. Function of taurine upregulated gene 1 (TUG1) in human cancers**

| Cancer type                               | Molecular function                  |
|-------------------------------------------|-------------------------------------|
| **Oncogenic function**                    |                                     |
| Glioma(53)                                | miRNA sponge (miR-144)              |
| Glioma(59)                                | Recruitment of PRC2, miRNA sponge (miR-145) |
| Glioma(54)                                | miRNA sponge (miR-26a)              |
| Glioma(55)                                | miRNA sponge (miR-299)              |
| Oral squamous cell carcinoma(56)          | Unknown                             |
| Esophageal squamous cell carcinoma(57,58) | Unknown                             |
| Cervical cancer(59)                       | Unknown                             |
| Small cell lung cancer(60)                | Unknown                             |
| Gastric cancer(61)                        | Unknown                             |
| Hepatocellular carcinoma(63)              | Unknown                             |
| Hepatoblastoma(64)                        | Unknown                             |
| Gallbladder carcinoma(65)                 | Unknown                             |
| Breast cancer(66)                         | Unknown                             |
| Breast cancer(67)                         | Unknown                             |
| Colorectal cancer(68–70)                  | Unknown                             |
| Ovarian cancer(71)                        | Unknown                             |
| Renal cell carcinoma(72)                  | Unknown                             |
| Bladder cancer(73)                        | Unknown                             |
| Bladder cancer(74)                        | Unknown                             |
| Osteosarcoma(75)                          | Unknown                             |
| Osteosarcoma(76)                          | Unknown                             |
| **Tumor-suppressive function**            |                                     |
| Cervical cancer(46)                       | Recruitment of PRC1 and PRC2        |
| Non-small-cell lung carcinoma(51,76)      | Recruitment of PRC2                 |
| Prostate cancer(77)                       | miRNA sponge (unknown)              |

Text in parentheses shows target microRNA (miRNA, miR) of TUG1 in each cancer type. PRC, polycomb repressive complex.

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**Fig. 3.** Inhibition of taurine upregulated gene 1 (TUG1) by an antiTUG1 drug delivery system (DDS) in a mouse xenograft model. Mice bearing brain tumors were given i.v. antisense oligonucleotide (ASO) targeting TUG1 coupled with a potent DDS using cyclic Arg-Gly-Asp peptide-conjugated polymeric micelle (antiTUG1-DDS). AntiTUG1-DDS was specifically accumulated and retained in the tumors and markedly reduced tumor growth. Tumor areas are surrounded by red dotted line.
that binds to PRC2 or PRC1.\(^{(45,46)}\) This lncRNA was originally identified as a transcript upregulated by taurine, whose function is associated with retinal development.\(^{(47)}\) It is overexpressed in bladder cancer, gastric cancer, and osteosarcoma;\(^{(48–50)}\) in contrast, it is downregulated in NSCLC,\(^{(51)}\) suggesting context-dependent roles in different types of cancers (Table 1). Because the length of TUG1 lncRNA is long (approximately 7.1 kb), it is plausible that TUG1 has multiple functions.

Expression of TUG1 is regulated by the Notch signaling pathway, and TUG1 was highly expressed in glioma stem cell populations and downregulated during its differentiation. Intriguingly, in cell nuclei, TUG1 physically interacts with PRC2, which might direct it to modify histone H3K27me3 levels in neuronal differentiation-associated genes. In the cytoplasm, TUG1 shares miR-145-response elements with the mRNAs of several stemness markers (MYC and SOX2) and prevents them from miR-145-mediated degradation (Fig. 2). Importantly, the inhibition of TUG1 expression impaired stemness and tumorigenesis in gliomas both in vitro and in vivo, indicating that targeting TUG1 is a potent therapeutic approach to eliminate glioma stem cell populations.\(^{9)}\) Indeed, antisense oligonucleotide (ASO) targeting TUG1, especially coupled with a potent drug delivery system, is an effective novel strategy for glioblastoma (GBM) treatment\(^{(9)}\) (Fig. 3). Cyclic Arg-Gly-Asp (cRGD) peptides are promising ligands for targeting αvβ3 and αvβ5 integrins, which are frequently overexpressed in GBM cells. We used cRGD ligand-conjugated polymeric micelles for delivery. These targetable polymeric micelles retained ASO accumulation within tumors. Although further investigations are required, cRGD-mediated drug delivery is a powerful strategy for targeting GBMs through facilitated ASO delivery beyond the blood–brain tumor barrier.\(^{(52)}\)

Similar to miR-145, TUG1 interacts with other miRNAs such as miR-144, miR-26a, miR-299, miR-34a, miR-300, miR-9, and miR-335, in different types of cancers (Table 1). Although further experimental validation is required to clarify the impact of ceRNA mechanisms on tumorigenesis, TUG1 functions through a ceRNA mechanism that can dynamically change the transcriptome. Therefore, it will be particularly interesting to understand the pathologies of plastic cancer cells.

Concluding remarks

In this review, we exemplified and explained the functional roles of lncRNAs (Table 2) and discussed the future clinical implications of lncRNAs in cancers. Recent comprehensive studies have shown that, in addition to genetic alterations, the spatial and temporal epigenetic regulation of gene functions in pre-cancer and cancer cells is particularly important in tumorigenesis. In particular, given that cancer cells are dynamic in response to extracellular signals, the plastic epigenetic control of gene expression plays a central role in cancer cell adaptation to new microenvironments. A better understanding of lncRNA pathways and other epigenetic mechanisms in cancer cells will hopefully provide multiple novel therapeutic strategies for devastating cancers in the near future.

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Disclosure Statement

The authors have no conflict of interest.

References

1 Fujimoto A, Furuta M, Totoki Y et al. Whole-genome mutation landscape and characterization of noncoding and structural mutations in liver cancer. Nat Genet 2016; 48: 500–9.
2 Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev 2014; 15: 459–69.
3 Lujambio A, Lowe SW. The microcossomas of cancer. Nature 2012; 482: 347–55.
4 Schlosser K, Hanson J, Villeneuve PJ et al. Assessment of Circulating LncRNAs Under Physiologic and Pathologic Conditions in Humans Reveals Potential Limitations as Biomarkers. Sci Rep 2016; 6: 36596.
5 Wahlestedt C. Targeting long non-coding RNA to therapeutically upregulate gene expression. Nat Rev Drug Discov 2013; 12: 433–46.
6 Schmitt AM, Chang HY. Long Noncoding RNAs in Cancer Pathways. Cancer Cell 2016; 29: 452–63.
7 Gutmann D, Donaghey J, Carey BW et al. lncRNAs act in the circuitry controlling pluripotency and differentiation. Nature 2011; 477: 295–300.
8 Ke J, Yao YL, Zheng J et al. Knockdown of long non-coding RNA HOTAIR inhibits malignant biological behaviors of human glioma cells via modulation of miR-326. Oncotarget 2015; 6: 21934–49.
9 Katsushima K, Natsume A, Ohka F et al. Targeting the Notch-regulated non-coding RNA TUG1 for glioma treatment. Nat Commun 2016; 7: 13616.
10 Yuan JH, Yang F, Wang F et al. A long non-coding RNA activated by TGF-beta promotes the invasion-metastasis cascade in hepatocellular carcinoma. Cancer Cell 2015; 28: 666–81.
11 B早くまと Wolf A, Stottmeister C, Glazar P et al. Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. Mol Cell 2015; 58: 870–85.
12 Carriere C, Cimatti L, Biagioli M et al. Long non-coding antisense RNA controls Uchl1 translation through an embedded SINEB2 repeat. Nature 2012; 491: 454–7.
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13 Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet* 2016; 17: 47–62.

14 Ulitsky I, Bartel DP. lncRNAs: genomics, evolution, and mechanisms. *Cell* 2013; 154: 26–46.

15 Tripathy V, Ellis JD, Shen Z et al. The nuclear-detained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. *Mol Cell* 2010; 39: 925–38.

16 Engreitz JM, Ollikainen N, Guttman M. Long non-coding RNAs: spatial amplifiers that control nuclear structure and gene expression. *Nat Rev Genet* 2016; 17: 756–70.

17 McHugh CA, Chen CK, Chow A et al. The Xist long non-coding RNA interacts directly with SHARP to silence transcription through HDAC3. *Nature* 2015; 521: 232–6.

18 Chu C, Zhang QC, da Rocha ST et al. Systematic discovery of Xist RNA binding proteins. *Cell* 2015; 161: 404–16.

19 Splinter E, de Wit E, Nora EP. The inactive X chromosome adopts a unique three-dimensional conformation that is dependent on Xist RNA. *Genes Dev* 2011; 25: 1371–83.

20 Schoeftner S, Sengupta AK, Kubicek S et al. Notch signalling of Notch-regulated long noncoding RNAs in acute leukemia. *Cell* 2014; 158: 593–606.

21 McHugh CA, Lin C, Liu W et al. LincRNA-p21 methylation-dependence gene relocation between nuclear structures mediates gene activation programs. *Cell* 2011; 147: 733–88.

22 Young TL, Matsuda T, Cepko CL. The noncoding RNA taurine upregulated gene 1 is required for differentiation of the murine retina. *Curr Biol* 2005; 15: 501–12.

23 Tan J, Qu K, Li M, Liang Y. Double-negative feedback loop between long non-coding RNA TUG1 and miR-145 promotes epithelial to mesenchymal transition and radiosensitivity in human bladder cancer cells. *FEBS Lett* 2015; 589: 3175–81.

24 Han Y, Liu Y, Gui Y, Cai Z. Long intergenic non-coding RNA TUG1 is overexpressed in uterine carcinoma of the bladder. *J Surg Oncol* 2013; 107: 555–9.

25 Zhang Q, Geng PL, Yin P, Wang XL, Jia JP, Yao J. Down-regulation of long non-coding RNA TUG1 inhibits osteosarcoma cell proliferation and chemoresistance. *Oncotarget* 2013; 4: 2311–15.

26 Zhang EB, Yin DD, Sun M et al. P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. *Cell Death Dis* 2014; 5: e1243.

27 Mumra Y, Takekana T, Toh K et al. Cyclic RGD-linked polymeric micelles for targeted delivery of platinum anticancer drugs to glioblastoma through the blood-brain tumor barrier. *ACS Nano* 2013; 7: 8583–92.

28 Cai H, Xue Y, Wang P et al. The long non-coding RNA TUG1 regulates blood-tumor barrier permeability by targeting miR-144. *Oncotarget* 2015; 6: 28489–97.

29 Li J, An G, Zhang M, Ma Q. Long non-coding RNA TUG1 acts as a miR-26a sponge in human glioma cells. *Biochem Biophys Res Commun* 2016; 477: 743–8.

30 Cai H, Liu X, Zheng J et al. Long non-coding RNA taurine upregulated 1 enhances tumor-induced angiogenesis through inhibiting miR-299 in human glioblastoma. *Oncogene* 2017; 36: 318–31.

31 Liang S, Zhang S, Wang P et al. LncRNA TUG1 regulates the oral squamous cell carcinoma progression possibly via interacting with Wnt/beta-catenin signaling. *Gene* 2017; 608: 49–57.

32 Xu Y, Wang J, Qin M et al. Upregulation of the long non-coding RNA TUG1 promotes proliferation and migration of esophageal squamous cell carcinoma. *Tumour Biol* 2015; 36: 1643–51.

33 Jiang L, Wang W, Li G et al. High TUG1 expression is associated with chemotherapy resistance and poor prognosis in esophageal squamous cell carcinoma. *Cancer Chemother Pharmacol* 2016; 78: 333–9.

34 Hu Y, Sun X, Mao C et al. Upregulation of long non-coding RNA TUG1 promotes cervical cancer cell proliferation and migration. *Cancer Med* 2017; 6: 471–82.

35 Niu Y, Ma F, Huang W et al. Long non-coding RNA TUG1 is involved in cell growth and chemoresistance of small cell lung cancer by regulating LIMK2 via EZH2. * Mol Cancer* 2017; 16: 5.

36 Ji TT, Huang X, Jin J, Pan SH, Zhang XJ. Inhibition of long non-coding RNA TUG1 on gastric cancer cell transference and invasion through regulating and controlling the expression of miR-144/c-Met axis. *Asian Pac J Trop Med* 2016; 9: S40–6.

37 Zhang E, He X, Yin D et al. Increased expression of long non-coding RNA TUG1 predicts a poor prognosis of gastric cancer and regulates cell proliferation by epigenetically silencing of p57. *Cell Death Dis* 2016; 7: e2109.

38 Huang MD, Chen WM, Qi FZ et al. Long non-coding RNA TUG1 is up-regulated in hepatocellular carcinoma and promotes cell growth and apoptosis by epigenetically silencing of KLFC2. *Mol Cancer* 2015; 14: 165.

39 Dong R, Liu GB, Liu BH et al. Targeting long non-coding RNA-TUG1 inhibits tumor growth and angiogenesis in hepatoblastoma. *Cell Death Dis* 2016; 7: e2278.

40 Ma F, Wang SH, Cai Q et al. Long non-coding RNA TUG1 promotes cell proliferation and metastasis by negatively regulating miR-300 in gallbladder carcinoma. *Biomed Pharmacother* 2017; 88: 863–9.

41 Zhao XB, Ren GS. LncRNA Taurine-Upregulated Gene 1 Promotes Cell Proliferation by Inhibiting MicroRNA-9 in MCP-7 Cells. *J Breast Cancer* 2016; 19: 349–57.

42 Li T, Liu Y, Xiao H, Xu G. Long non-coding RNA TUG1 promotes cell proliferation and metastasis in human breast cancer. *Breast Cancer (Tokyo, Japan)* 2017; 24: 535–45.
68 Sun J, Ding C, Yang Z et al. The long non-coding RNA TUG1 indicates a poor prognosis for colorectal cancer and promotes metastasis by affecting epithelial-mesenchymal transition. *J Transl Med* 2016; 14: 42.

69 Zhai HY, Sui MH, Yu X et al. Overexpression of Long Non-Coding RNA TUG1 Promotes Colon Cancer Progression. *Med Sci Monit* 2016; 22: 3281–7.

70 Wang L, Zhao Z, Feng W et al. Long non-coding RNA TUG1 promotes colorectal cancer metastasis via EMT pathway. *Oncotarget* 2016; 7: 51713–19.

71 Kuang D, Zhang X, Hua S, Dong W, Li Z. Long non-coding RNA TUG1 regulates ovarian cancer proliferation and metastasis via affecting epithelial-mesenchymal transition. *Exp Mol Pathol* 2016; 101: 267–73.

72 Zhang M, Lu W, Huang Y et al. Downregulation of the long noncoding RNA TUG1 inhibits the proliferation, migration, invasion and promotes apoptosis of renal cell carcinoma. *J Mol Histol* 2016; 47: 421–8.

73 Iliev R, Kleinova R, Juracek J et al. Overexpression of long non-coding RNA TUG1 predicts poor prognosis and promotes cancer cell proliferation and migration in high-grade muscle-invasive bladder cancer. *Tumour Biol* 2016; 37: 13385–90.

74 Xie CH, Cao YM, Huang Y et al. Long non-coding RNA TUG1 contributes to tumorigenesis of human osteosarcoma by sponging miR-9-5p and regulating POU2F1 expression. *Tumour Biol* 2016; 37: 15031–41.

75 Wang Y, Yang T, Zhang Z et al. Long non-coding RNA TUG1 promotes migration and invasion by acting as a ceRNA of miR-335-5p in osteosarcoma cells. *Cancer Sci* 2017; 108: 859–67.

76 Lin PC, Huang HD, Chang CC et al. Long noncoding RNA TUG1 is downregulated in non-small cell lung cancer and can regulate CELF1 on binding to PRC2. *BMC Cancer* 2016; 16: 583.

77 Du Z, Sun T, Hacisuleyman E et al. Integrative analyses reveal a long non-coding RNA-mediated sponge regulatory network in prostate cancer. *Nat Commun* 2016; 7: 10982.