Taurine-upregulated gene 1: A vital long non-coding RNA associated with cancer in humans (Review)

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Abstract. It is widely reported that long non-coding RNAs (lncRNAs) are involved in regulating cell differentiation, proliferation, apoptosis and other biological processes. Certain lncRNAs have been found to be crucial in various types of tumor. Taurine-upregulated gene 1 (TUG1) has been shown to be expressed in a tissue-specific pattern and exert oncogenic or tumor suppressive functions in different types of cancer in humans. According to previous studies, TUG1 is predominantly located in the nucleus and may regulate gene expression at the transcriptional level. It mediates chromosomal remodeling and coordinates with polycomb repressive complex 2 (PRC2) to regulate gene expression. Although the mechanisms of how TUG1 affects the tumor genesis process remain to be fully elucidated, increasing studies have suggested that TUG1 offers potential as a diagnostic and prognostic biomarker, and as a therapeutic target in certain types of tumor. This review aims to summarize current evidence concerning the characteristics, mechanisms and associations with cancer of TUG1.

Contents

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1. Introduction

Long non-coding RNAs (lncRNAs) are characterized as a subgroup of RNAs>200 nucleotides in length without, or with limited, protein-coding potential (1-3). Previous studies have demonstrated that certain lncRNAs have regulatory roles in diverse biological processes at the epigenetic, transcriptional and post-transcriptional levels due to their various structural and biochemical characteristics (4-9). The aberrant expression of lncRNAs has been shown in various human diseases, including cancer (Table I).

Taurine-upregulated gene 1 (TUG1), a 7.1-kb lncRNA, was originally detected in a genomic screen for genes upregulated in response to taurine treatment in developing mouse retinal cells (10). It is located on chromosome 22q12.2 in the human genome, and has been reported to be expressed in a tissue-specific pattern and to exert oncogenic or tumor suppressive functions in different types of cancer in humans (11-14). The downregulation of TUG1 has been detected in glioma and non-small-cell lung cancer (NSCLC), with TUG1 shown to induce apoptosis as a tumor suppressor (15,16). By contrast, the overexpression of TUG1 has been reported in osteosarcoma (17), bladder cancer (18,19), colorectal cancer (CRC) (20), esophageal squamous cell carcinoma (ESCC) (21), gastric cancer (22) and hepatocellular cancer (HCC) (23). TUG1 was shown to function as an oncogene by promoting cell proliferation and was correlated with a poor prognosis (17-23).

Polycomb repressive complex 2 (PRC2) is a methyltransferase, which is composed of enhancer of zeste homolog 2 (EZH2), suppressor of zeste 12 (SUZ12) and embryonic ectoderm development, and is capable of catalyzing the di- and trimethylation of lysine residue 27 of histone 3 (H3K27me3), which regulates gene expression. Various lncRNAs, including TUG1, modulate specific genetic loci by recruiting and binding to PRC2 protein complexes, and PRC2-mediated epigenetic regulation is vital in tumorigenesis and development (24-27). The knockdown of TUG1 results in wide changes in gene expression, particularly the upregulation of cell-cycle genes, indicating that TUG1 is important in cell proliferation and apoptosis through effects on the cell cycle (22). However, the comprehensive mechanisms remain to be fully elucidated.

2. TUG1 in human cancer

Colorectal cancer (CRC). It was previously reported that the expression of TUG1 was significantly enhanced in CRC tumor tissues, compared with that in paratumor tissues. Further analysis showed that the expression of TUG1 was negatively correlated with overall survival rates in patients (20). The stable knockdown of histone deacetylase 1 (HDAC1) induced the expression of TUG1, indicating that the expression of TUG1 is regulated by histone modification (20,28). *In vitro* experiments have confirmed that the knockdown of TUG1 suppresses the colony formation, migration and invasion of CRC cells *in vitro*. In addition, an *in vivo* liver metastasis model revealed that the overexpression of TUG1 increased the number of metastatic tumor nodules in the liver, indicating that TUG1 promoted CRC metastasis (20). The molecular mechanism by which TUG1 promotes the invasion and metastasis of CRC has also been investigated. It was demonstrated that the overexpression of TUG1 reduced the expression of E-cadherin, and upregulated the expression levels of N-cadherin, vimentin and fibronectin, whereas knockdown of the expression of TUG1 showed the opposite effects. This suggested that TUG1 may affect CRC metastasis and invasion through mediating epithelial-mesenchymal transition (EMT)-associated gene expression (20,29). However, the mechanisms by which HDAC1 affects TUG1 and regulates EMT require further investigation.

Bladder cancer. The expression of TUG1 was also found to be upregulated in bladder cancer tissues and cell lines. A higher expression of TUG1 was found to be associated with poorer tumor-necrosis-metastasis (TNM) staging and shorter overall survival rates (18,19). Subsequent investigations revealed that TUG1 promoted bladder cancer cell invasion and radioresistance. The expression level of epithelial markers increased whereas those of mesenchymal markers decreased following the overexpression of TUG1, indicating that TUG1 was involved in bladder cancer through EMT (19,29). TUG1 acted as a microRNA (miRNA) sponge, as miRNA (miR)-145 was able to bind to TUG1 and exhibit reciprocal regulatory effects. In addition, Zinc finger E-box binding homeobox 2 (ZEB2), a transcription factor regulating the EMT marker E-cadherin (30), has been identified as a direct target of miR-145 (31). The evidence above indicates a possible mechanism by which TUG1 is involved in EMT and the radioresistance in bladder cancer through the miR-145/ZEB2 axis.

Hepatocellular cancer (HCC). A previous study detected an upregulation in the expression of TUG1 in HCC tissues, which was confirmed to be associated with tumor size and Barcelona Clinic Liver Cancer stage (23).The transcription factor, stimulatory protein 1 (SP1) was later confirmed to directly bind to TUG1 promoter regions and positively regulate the expression of TUG1. In previous *in vitro* and xenograft model experiments, the functions of TUG1 in inhibiting cell proliferation and inducing cell apoptosis in HCC were demonstrated. Kruppel-like factor 2 (KLF2) was identified as a novel downstream gene of TUG1, which was found to be involved in HCC cell G0/G1 arrest, suppression of cell proliferation and the induction of apoptosis. TUG1 inhibited the transcription of KLF2 through binding to EZH2/SUZ12, the core subunits of PRC2, to the KLF2 gene promoter locus in HCC cells, thus acting as an oncogenic factor (32).

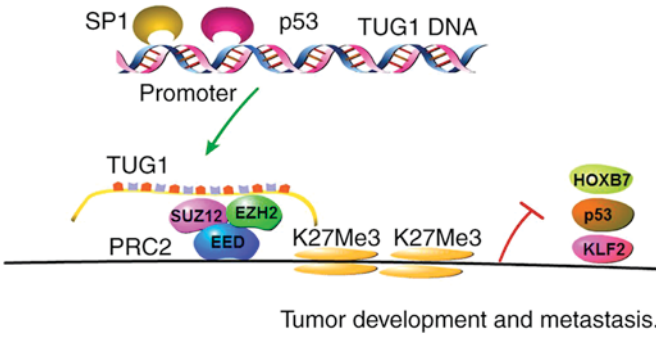

Figure 1. Schematic illustration of TUG1 binding to PRC2 in the regulation of tumor development and metastasis. TUG1, taurine-upregulated gene 1; PRC2, polycomb repressive complex 2; SP1, stimulatory protein 1; SUZ12, suppressor of zeste 12; EZH2, enhancer of zeste homolog 2; EED, embryonic ectoderm development; K27Me3, trimethylated histone H3 at lysine 27; HOXB7, homeobox B7; KLF2, Kruppel-like factor.

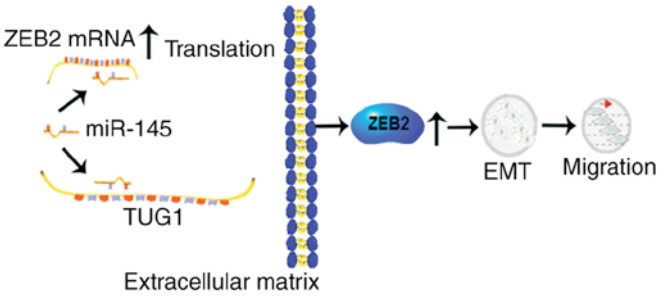

Figure 2. Schematic illustration of TUG1 altering EMT through miR-145 in the regulation of tumor development and metastasis. TUG1, taurine-upregulated gene 1; miR-145, microRNA-145; ZEB2, Zinc finger E-box binding homeobox 2; EMT, epithelial-mesenchymal transition.

Gastric cancer (GC). A previous study observed that TUG1 was overexpressed in GC cells, and was positively correlated with invasion depth and TNM stage, but negatively correlated with overall survival rates (22). *In vitro* and *in vivo* experiments confirmed that TUG1 suppressed GC cell proliferation through its effects on cell cycle progression in a pattern of G0/G1 arrest. Subsequent investigation of the mechanism demonstrated that TUG1 specifically targeted EZH2 and epigenetically regulated the expression of cyclin-dependent kinase inhibitor (CKI) family members, including p15, p16, p21, p27 and p57 (22,33,34). Analysis of the mechanism showed that TUG1 epigenetically repressed CKIs by binding to PRC2, and thereby regulated the cell cycle to promote GC cell proliferation.

ESCC. It was previously found that TUG1 was overexpressed in ESCC. Patients with a family history of esophageal cancer and upper segment ESCC were shown to express higher levels of TUG1. TUG1 also promoted the proliferation and migration of ESCC cell lines *in vitro* (21).

Osteosarcoma. TUG1 is upregulated in osteosarcoma tissues and cells (17). Experiments have demonstrated that

Table I. Effects of taurine-upregulated gene 1in various types of cancer.

Author, year	Cancer	Expression	Clinical significance	Function	Associated factors	(Refs.)
Zhang *et al*, 2014	Non-small cell lung cancer	Downregulated	Prognosis	Proliferation; cell cycle	P53; PRC2; HOXB7	(15)
Li *et al*, 2016	Glioma	Downregulated	Pathological stage; tumor size	Not reported	Not reported	(16)
Zhang *et al*, 2013	Osteosarcoma	Upregulated	Not reported	Not reported	Not reported	(17)
Han *et al*, 2013; Tan *et al*, 2015	Bladder cancer	Upregulated	TNM stage; overall survival	Invasion; radioresistance	miR145; ZEB2	(18,19)
Sun *et al*, 2016	Colorectal cancer	Upregulated	Prognosis	Proliferation; invasion; metastasis	HDAC1	(20)
Xu *et al*, 2015	Esophageal squamous cell carcinoma	Upregulated	Family history; tumor location	Proliferation; migration	Not reported	(21)
Zhang *et al*, 2016	Gastric	Upregulated	Invasion depth; TNM stage; overall survival	Proliferation; apoptosis; cell cycle	EZH2; p57	(22)
Huang *et al*, 2015	Hepatocellular carcinoma	Upregulated	Tumor size; BCLC stage	Proliferation; apoptosis; cell cycle	SP1; KLF2	(23)
Isin *et al*, 2014	Malignant melanoma	Upregulated	Stage	Not reported	Not reported	(35)

PRC2, polycomb repressive complex 2; HOXB7, homeobox B7; miR, microRNA; ZEB2, Zinc finger E-box binding homeobox 2; HDAC1, histone deacetylase 1; EZH2, enhancer of zeste homolog 2; SP1, stimulatory protein 1; KLF2, Kruppel-like factor 2; BCLC, Barcelona Clinic Liver Cancer.

TUG1 acts as an oncogenic gene via increasing osteosarcoma cell proliferation and affecting apoptosis. However, the detailed mechanisms require further investigation.

Multiple myeloma (MM). It has been reported that, in the plasma of patients with MM, the expression of TUG1 was upregulated and showed marked association with clinical stages (35).

Glioma. Unlike the overexpression of TUG1 found in the types of cancer described above, TUG1 was downregulated in human glioma tissues and cells, and negatively associated with advanced pathological progression, serving as an indicator of poor prognosis (16). TUG1 exerts its antitumor function in glioma through promoting cell apoptosis via intrinsic pathways mediated by caspase-3 together with caspase-9, and simultaneously suppressing anti-apoptotic pathways mediated by B-cell lymphoma 2 (36-39).

Non-small-cell lung cancer (NSCLC). The expression of TUG1 was also shown to be downregulated in human NSCLC tissues and correlated with poor prognosis of patients (15). TUG1 has been shown to modulate NSCLC cell proliferation *in vitro* and *in vivo* through alterations in cell cycle progression. Further analysis demonstrated that p53 was able to directly bind to the promoter region of TUG1 and regulate the expression of TUG1. In addition, investigations have suggested that homeobox B7 (HOXB7), a known oncogene, is a downstream gene of TUG1, and it was suggested that TUG1 targets PRC2 to regulate HOXB7 at the transcriptional level (40,41). The role of HOXB7 has also been investigated, which showed that HOXB7 promoted NSCLC cell proliferation via activating the AKT and mitogen-activated protein kinase pathways (15,38,39,42,43). Therefore, the p53/TUG1/PRC2/HOXB7 axis was found to be vital in the tumorigenesis and progression of NSCLC, which may be a target for future therapy.

3. Conclusions and perspectives

In previous years, widespread investigations have been performed on the biological roles and clinical significance of lncRNAs. The deregulation of lncRNAs is capable of affecting tumor development, functioning as tumor inducers or suppressors. One of the most comprehensively investigated lncRNAs is the hox transcript antisense intergenic RNA (HOTAIR). HOTAIR has been identified as an oncogenic gene, recruiting PRC2 and interacting with lysine-specific demethylase1 (LSD1), regulating the expression of its downstream targets (8,11,42).

This review discusses TUG1 and its association with cancer in humans. TUG1 is expressed in a tissue-specific pattern, showing oncogenic or tumor inhibiting capacities in different types of cancer in humans (Table I). The downregulation of TUG1 is observed in glioma and NSCLC, showing that TUG1 serves as a tumor suppressor. By contrast, the overexpression of TUG1 has been reported in ESCC, CRC, HCC, bladder cancer and osteosarcoma, indicating that TUG1 functions as an oncogene. The mechanisms underlying the biological functions of TUG1 are shown in Figs. 1 and 2. These findings indicate that the expression of TUG1 can be enhanced or weakened by upstream or downstream interference to slow down or alter tumor progression. The level of TUG1 in tumor tissues correlates with tumor stage and prognosis, which may be utilized as a diagnostic and prognostic biomarker clinically. In a previous study, TUG1 was moderately elevated in secreted exosomes (44), and this may enable the isolation of exosomes from blood plasma or serum to assist in monitoring the state of disease dynamically (45). However, further investigations are required in order to fully elucidate the mechanisms underlying TUG1 and cancer development. TUG1 may offer potential as a novel diagnostic biomarker and therapeutic approach for clinical utilization.

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