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REVIEW ARTICLE

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TUG1: a pivotal oncogenic long non-coding RNA of human cancers

Zheng Li[1] | Jianxiong Shen[1] | Matthew T.V. Chan[2] | William Ka Kei Wu[2,3]

[1]Department of Orthopedics Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100042, China

[2]Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China

[3]State Key Laboratory of Digestive Disease, LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China

Correspondence
Jianxiong Shen, Department of Orthopedics Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100042, China.
Email: shenjianxiong@medmail.com.cn

Abstract

Long non-coding RNAs (lncRNAs) are a group greater than 200 nucleotides in length. An increasing number of studies has shown that lncRNAs play important roles in diverse cellular processes, including proliferation, differentiation, apoptosis, invasion and chromatin remodelling. In this regard, deregulation of lncRNAs has been documented in human cancers. TUG1 is a recently identified oncogenic lncRNA whose aberrant upregulation has been detected in different types of cancer, including B-cell malignancies, oesophageal squamous cell carcinoma, bladder cancer, hepatocellular carcinoma and osteosarcoma. In these malignancies, knock-down of TUG1 has been shown to suppress cell proliferation, invasion and/or colony formation. Interestingly, TUG1 has been found to be downregulated in non-small cell lung carcinoma, indicative of its tissue-specific function in tumourigenesis. Pertinent to clinical practice, TUG1 may act as a prognostic biomarker for tumours. In this review, we summarize current knowledge concerning the role of TUG1 in tumour progression and discuss mechanisms associated with it.

1 | INTRODUCTION

It has been estimated that approximately 2% of the human genome is transcribed into protein-coding RNAs, whereas the remaining transcribed regions give rise to non-coding RNAs (ncRNAs),[1–3] which can be separated into two major groups: small/short ncRNAs (<200 nucleotides) and long ncRNAs (>200 nucleotides; lncRNAs).[4–8] Initially regarded as a consequence of transcriptional noise or promiscuous RNA polymerase II activity, an increasing number of studies have now demonstrated that lncRNAs play important roles in a repertoire of biological processes, including development, cell differentiation, proliferation, apoptosis and invasion through controlling gene expression through different mechanisms, including (1) chromatin remodelling; (2) regulation of recruitment of transcription factors and co-activators (cis-acting); (3) negatively regulation of RNA polymerase II activity; (4) alternative splicing of pre-mRNAs; (5) regulation of mRNA stability; and (6) sequestration of microRNAs.[9–13] Pertinent to chromatin remodelling, lncRNAs could form extensive networks of ribonucleoprotein complexes with numerous chromatin regulators, such as Polycomb-group proteins and G9a, and then target these complexes to specific locations in the genome.[14] lncRNAs could also interact widely to regulate physiological processes (e.g. apoptosis) in an orchestrated manner.[15] The detailed mechanisms by which lncRNAs regulate gene expression at the transcriptional and post-transcriptional levels have been extensively reviewed by other investigators.[16–18]

The abnormal expression of lncRNAs has been documented in different cancer types, such as gastric cancer, osteosarcoma, hepatocellular carcinoma, nasopharyngeal carcinoma, colorectal cancer, oesophageal squamous cell carcinoma, prostate cancer and cervical cancer.[3, 19–27] The common deregulation of lncRNAs in human cancers is exemplified by a recent integrative analysis of ~7200 RNA-sequencing libraries from tumours, normal tissues and cell lines, which identified ~8000 lineage- or cancer-associated lncRNAs. Most of these lncRNAs were previously unannotated.[28] These deregulated lncRNAs could function as oncogenes (e.g. KRASP, HULC, HOTAIR, MALAT1/NEAT) or tumour-suppressor genes (e.g. MEG3, GAS5, LincRNA-p21, PTENP1).[29] Overexpression of such onco-lncRNAs or inactivation/downregulation of such tumour-suppressing lncRNAs contribute to acquisition of malignant phenotypes, including sustained proliferation, resistance to growth suppression and replicative

TABLE 1 Functional characterization of the TUG1 in tumours

Cancer types	Expression	Functional role	Related gene	Role	References
B-cell neoplasms	Up			Oncogene	(25)
Lung cancer	Down	Proliferation	p53 HOXB7	Tumour-suppressor gene	(28)
Oesophageal squamous cell carcinoma	Up	Migration proliferation		Oncogene	(46)
Glioma	Up			Oncogene	(31)
Bladder cancer	Up	Radioresistance EMT metastasis	miR-145 ZEB2	Oncogene	(48)
Hepatocellular carcinoma	Up	Colony formation proliferation tumourigenicity apoptosis	SP1 KLF2 PRC2	Oncogene	(29)
Osteosarcoma	Up		ALP	Oncogene	(30)

senescence, invasiveness and metastasis, angiogenesis, resistance to apoptosis and reprogrammed energy metabolism.[30] Furthermore, lncRNA may be used as biomarkers for diagnosis, prognostication or monitoring of human cancers due to their tissue-specific expression, efficient detection in body fluids and high stability,[30] providing clinicians with extra information for evidence-based judgment.[31–34] For instance, the lncRNA MALAT1 has been promulgated as a candidate circulating biomarker for the diagnosis of non-small cell lung cancer (NSCLC).[35]

Among all cancer-related lncRNAs, the taurine upregulated gene 1 (TUG1) is a rising star.[36–38] Increasing evidences have shown that TUG1 plays important roles in a number of human cancers, such as hepatocellular carcinoma, osteosarcoma, glioma and bladder cancer.[39–42] In this review, we summarize current evidences concerning the role of TUG1 in the development and progression of cancers (Table 1).

2 | STRUCTURAL CHARACTERIZATION OF TUG1

TUG1 is a 7.1-kb lncRNA and was first identified in a genomic scan for genes upregulated in response to taurine treatment in developing mouse retinal cells.[43] Functional studies further revealed that knock-down of TUG1 inhibited mouse retinal development. Khalil et al. demonstrated that about 20% of all lncRNAs including TUG1 are bound to the polycomb repressive complex 2 through genome-wide RNA immunoprecipitation analysis.[44] PRC2 harbours methyltransferase activity and is composed of enhancer of zeste homologue 2 (EZH2), suppressor of zeste 12 (SUZ12) and embryonic ectoderm development (EED).[45–48] PRC2 catalyses the di- and trimethylation of lysine residue 27 of histone 3 (H3K27me3) to repress gene expression.[49–51] Deregulated PRC2-related lncRNAs expression is involved in tumour initiation and development.[52–55] Yang et al.[56] further demonstrated that binding of methylated polycomb 2 protein to TUG1 controls the relocation of growth-control genes between Polycomb bodies and interchromatin granules in response to growth signals, linking TUG1 to relocation of transcription units in the three-dimensional space of the nucleus for coordinated gene expression.

3 | TUG1 IN HUMAN CANCERS

3.1 | B-cell malignancies

Isin et al.[37] measured the levels of five selected lncRNAs (LincRNA-p21, TUG1, HOTAIR, MALAT1 and GAS5) by real-time PCR using cDNA synthesized from plasma RNAs isolated from chronic lymphocytic leukaemia and multiple myeloma patients. The investigators showed that LincRNA-p21 was the only lncRNA displaying significant upregulation in chronic lymphocytic leukaemia patients, while other four lncRNAs, including TUG1, showed significant downregulation in multiple myeloma patients as compared with healthy subjects.

3.2 | Non-small cell lung cancer

Zhang et al.[38] demonstrated that TUG1 was downregulated in NSCLC tissues as compared with non-tumour tissues. The lower TUG1 expression was correlated with poorer overall survival, larger tumour size and higher tumour-node-metastasis (TNM) staging. Moreover, TUG1 expression could act as an independent predictor for overall survival of NSCLC patients. Mechanistically, TUG1 was directly induced by p53. Knock-down of TUG1 increased NSCLC cell proliferation in vitro and in vivo and promoted the expression of homeobox B7 (HOXB7), an oncogenic homeo domain protein. These data suggested that TUG1 is a tumour-suppressive lncRNA in NSCLC.

3.3 | Oesophageal squamous cell carcinoma

Xu et al.[57] showed that TUG1 was upregulated in the oesophageal squamous cell carcinoma (ESCC) tissues compared to adjacent non-tumour tissues. Higher expression of TUG1 was also correlated with upper segment and family history of oesophageal cancer. Moreover, knock-down of TUG1 suppressed ESCC cell migration

and proliferation, accompanied by inhibition of cell cycle progression. These results suggested that TUG1 is a potential oncogenic lncRNA in ESCC.

3.4 | Glioma

Liu et al.[41] measured the expression of nine lncRNAs (neat1, TUG1, GAS5, Malat1, BC200, MIR155HG, MEG3, ST7OT1 and PAR5) during DNA damage-induced apoptosis in glioma cell lines U87 and U251 upon treatment with resveratrol and doxorubicin. The investigators also measured the expression levels of these lncRNAs in U87 and U251 upon necrosis induction with a higher dose of doxorubicin. It was demonstrated that the expression of TUG1 and two other lncRNAs BC200 and MIR155HG were downregulated upon necrosis induction in both cell lines but unchanged during apoptosis.

Blood-tumour barrier inhibits the delivery of chemotherapeutic drugs to brain tumour tissues. Cai et al.[58] demonstrated that TUG1 was upregulated in the glioma vascular endothelial cells from glioma tissues. The expression level of TUG1 was also increased in glioma co-cultured endothelial cells from model of blood-tumour barrier in vitro, in which inhibition of TUG1 promoted barrier permeability and repressed the expression of three junction proteins, namely occludin, ZO-1 and claudin-5. Moreover, TUG1 was shown to regulate blood-tumour barrier permeability through binding to miR-144. Inhibition of TUG1 suppressed the expression of heat shock transcription factor 2 (HSF2), which is a direct target of miR-144. These results suggested that inhibition of TUG1 might be a promising therapeutic strategy to promote the delivery of chemotherapeutic drugs to glioma *via* increasing blood-tumour barrier permeability.

3.5 | Bladder cancer

Tan et al.[59] demonstrated that TUG1 was upregulated in bladder cancer cell lines and tissues. Inhibition of TUG1 suppressed the bladder cancer cell metastasis both in vitro and in vivo. Overexpression of TUG1 increased the cellular radioresistance and invasion by inducing EMT (epithelial-to-mesenchymal transition). Upregulation of TUG1 suppressed miR-145 expression and there was a negative correlation between the expression of TUG1 and miR-145 in bladder cancer tissues. ZEB2 is a direct target of miR-145 and the authors' data supported that TUG1 could regulate EMT through the miR-145/ZEB2 axis.

3.6 | Hepatocellular carcinoma

Huang et al.[39] demonstrated that TUG1 was upregulated in hepatocellular carcinoma (HCC) tissues, in which TUG1 expression was positively associated with the Barcelona Clinic Liver Cancer (BCLC) stage and tumour size. Knock-down of TUG1 suppressed HCC cell colony formation, proliferation, tumourigenicity and promoted apoptosis. The expression of TUG1 was promoted by the nuclear transcription factor SP1, while overexpression of TUG1 downregulated the tumour-suppressor gene KLF2 (Kruppel-like factor 2) through binding to and recruiting PRC2 to KLF2 promoter region.

3.7 | Osteosarcoma

Ma et al.[40] showed that TUG1 was upregulated in osteosarcoma tissues compared to adjacent non-tumour tissues. TUG1 expression was also associated with the need of post-operative chemotherapy, tumour size and Enneking surgical stage. The higher level of TUG1 was correlated with poorer prognosis, including shortened overall and progression-free survival, independent of other clinicopathological parameters. The expression of TUG1 in plasma was decreased post-operation and the resurgence of TUG1 expression signalled disease recurrence. As a biomarker, TUG1 was superior to ALP (alkaline phosphatase) in distinguishing cases with osteosarcoma from healthy controls.

3.8 | Colorectal cancer

Sun et al.[60] demonstrated TUG1 levels were higher in colorectal cancer (CRC) cell lines and primary CRC clinical samples as compared with their normal counterparts. CRC patients with higher expression of TUG1 also showed shorter overall survival. Functionally, enforced expression of TUG1 increased the colony-forming ability, migration, and invasiveness of cultured CRC cells, whereas knock-down of TUG1 exerted opposite effects. TUG1-overexpressiong SW480 CRC cells also formed more metastatic nodules after injection into the spleens of nude mice. In this connection, overexpression of TUG1 induced EMT characterized by reduced expression of the epithelial marker E-cadherin and increased expression of mesenchymal markers N-cadherin, vimentin and fibronectin. These data suggest that TUG1 overexpression is an oncogenic event in CRC, in which TUG1 might serve as a prognostic biomarker and a therapeutic target.

4 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

TUG1, upregulated in multiply human cancers (except NSCLC and multiple myeloma), is a newly characterized oncogene. TUG1 can promote cancer cell proliferation, migration and invasion, and suppress apoptosis. TUG1 mediates its biological functions at least in part through chromatin remodelling and sequestration of microRNAs. However, the detailed downstream molecular mechanisms remain to be elucidated. Emerging technologies, such as high-throughput identification of binding partners and integrative analysis of omics data, will help delineate the downstream pathways mediated by TUG1. The upstream event underlying TUG1 deregulation in each cancer type may also be different and needs further characterization. As a potential prognostic marker, higher TUG1 levels are associated with poorer clinicopathological parameters, such as survival, in HCC, osteosarcoma and CRC. However, validating the prognostic significance of TUG1 in larger cohort is mandatory. TUG1 is also a viable drug target but the effect of systemic inhibition of TUG1 remains unknown. With more efforts put forth to the study of lncRNAs, especially TUG1, it is hopeful that TUG1 will eventually achieve clinical utility.

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