The pathogenic roles of IncRNA-Taurine upregulated 1 (TUG1) in colorectal cancer

Shirin Azizidoost¹, Ava Nasrolahi², Farhoodeh Ghaedrahmati³, Bartosz Kempisty⁴, Paul Mozdziak⁴, Klaudia Radoszkiewicz⁵ and Maryam Farzaneh⁶*

Abstract
Colorectal cancer (CRC) is a gastrointestinal tumor that develops from the colon, rectum, or appendix. The prognosis of CRC patients especially those with metastatic lesions remains unsatisfactory. Although various conventional methods have been used for the treatment of patients with CRC, the early detection and identification of molecular mechanisms associated with CRC is necessary. The scientific literature reports that altered expression of long non-coding RNAs (lncRNAs) contributed to the pathogenesis of CRC cells. LncRNA TUG1 was reported to target various miRNAs and signaling pathways to mediate CRC cell proliferation, migration, and metastasis. Therefore, TUG1 might be a potent predictive/prognostic biomarker for diagnosis of CRC.

Keywords Colorectal cancer, LncRNAs, TUG1, Tumorigenesis

Introduction
Colorectal cancer (CRC) is a gastrointestinal malignancy, ranked as the third most commonly diagnosed, and the second cause of cancer mortality worldwide [1]. This type of cancer originates from the colon, rectum, or appendix [2]. Pieces of evidence showed that the CRC incidence rate has risen during the past decades, specifically in developing countries [3]. Over 1.85 million new CRC cases are reported annually, with an increasing number of young people before the age of 50 [4]. Several factors such as genetics, epigenetics, and environment distributed across the CRC etiology and are responsible for disease heterogeneity [5, 6]. Etiologically, the three patterns of disease onset are sporadic, familial, and hereditary forms that affected 70%, 25%, and 5% of patients [7, 8]. It has been found that the age, environmental factors, dietary, lifestyle, gut microbiota, and genetic changes predispose persons to CRC [9]. Current treatment of CRC in primary and metastatic patients include laparoscopic surgery for primary disease, resection in case of metastatic tumors, radiotherapy for rectal neoplasm along with palliative, and neoadjuvant chemotherapies [10]. Besides, antibodies, probiotics, agarose tumor macrobeads, and gold-based drugs or their combinations are used for patients with CRC [11]. It has been found that the combination of chemotherapy and anti-EGFR (epidermal growth factor receptor) monoclonal antibodies cetuximab and panitumumab can prolong the median survival rate of these patients by 2 to 4 months compared with chemotherapy alone [12]. However, the impact of these therapies on the 5-year survival remains limited.

*Correspondence: Maryam Farzaneh maryamfarzaneh1394@gmail.com
1Atherosclerosis Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
2Infectious Ophthalmologic Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
3Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
4Graduate Physiology Program, North Carolina State University, 27695 Raleigh, NC, USA
5Translational Platform for Regenerative Medicine, Mossakowski Medical Research Institute, Polish Academy of Sciences, 02-106 Warsaw, Poland
6Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

© The Author(s) 2022. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
and very expensive [13, 14]. Several mutations in oncogenes, tumor suppressor genes, and genes associated with DNA repair have been identified as genetic risk factors for CRCs [15]. It has been reported that genetic mutations in SMAD4, BRAF, KRAS, PIK3CA, SMAD2, PTEN, and c-MYC play essential roles in patients with CRC [11]. Recent studies demonstrated that long non-coding RNAs (lncRNAs) as a subgroup of RNAs longer than 200 nucleotides presented important functions in the pathogenesis of CRC [16–18]. Aberrant expression of lncRNA is associated with several diseases, as well [17]. Previous investigations reported that lncRNA TUG1 showed tumor-suppressive or oncogenic functions in different types of cancers [19, 20]. Studies revealed that TUG1 expression was increased in CRC tumor tissues and promoted cell proliferation [21–23]. Further analysis revealed a significant negative correlation between the levels of TUG1 and the overall survival rate of patients with CRC [24]. In this review, we summarized functional roles of this IncRNA in the tumorigenesis of CRC cells.

**Biological properties of lncRNA TUG1**

An initial genomic screening for genes upregulated in response to taunine treatment in developing mouse retinal cells detected taunine-upregulated gene 1 (TUG1) (also known as TI-227 H, LINC00080, and NCRNA00080), a 7.1-kb IncRNA that in the human genome is located on chromosome 22q12.2 [25]. Functional studies revealed mice lacking TUG1 had impaired retinal development [26]. There is also evidence that TUG1 is transcriptionally regulated by p53 [27]. The polycomb-repressive complex 2 (PRC2) contains enhancer of zeste homologue 2 (EZH2), suppressor of zeste 12 (SUZ12), and embryonic ectoderm development (EED) [28] that catalyzes lysine residue 27 di- and trimethylation on histone 3 (H3K27me3) to repress gene expression [29]. TUG1 by recruiting and binding to the PRC2 complex functions as a dynamic scaffold [30, 31]. TUG1 knockdown induced an upregulation of the cell-cycle genes, suggesting that TUG1 is involved in both cell proliferation and apoptosis [22]. TUG1 as a potent epigenetic regulator can mediate histone modification and DNA methylation in target genes [24, 32]. Besides, TUG1 by acting as a competing endogenous RNA (ceRNA) could sponge and repress microRNA (miRNA) [33]. Figure 1 displays different functions of TUG1.

TUG1 has recently been proposed as an oncogene in several types of cancer [34–36]. TUG1 is associated with large tumor size, advanced pathological stages, and distant metastasis [37, 38]. Experimental studies have disclosed that TUG1 significantly stimulated tumor cell proliferation, invasion, colony formation, and drug resistance in CRC cells (Table 1). Overexpression of TUG1 via mediating epithelial-mesenchymal transition (EMT)-associated gene expression, reduction of E-cadherin expression, and boosted the vimentin, N cadherin, and fibronectin expression promoted the invasion and metastasis of CRC cells [24, 39, 40].

**The critical TUG1/miRNAs/transcription factors axes in colorectal cancer**

There is growing evidence that TUG1 by targeting several signaling pathways plays critical roles in the progression of CRC cells [24]. Here, we described multiple miRNAs/transcription factors axes (Fig. 2) that can be regulated via this lncRNA in CRC.

**TUG1/miR-145-5p/TRPC6**

High expression of TUG1 has been proved to be correlated with CRC pathogenesis including proliferative along with the migratory ability, cell viability, tumor growth, and subcutaneous tumor formation [41, 42]. TUG1 is known to interact with miR-145-5p and regulate CRC cellular processes. Moreover, miR-145-5p suppressed the expression transient receptor potential cation channel subfamily c member 6 (TRPC6) as its candidate target, which its overexpression brought back miR-145-5p function in CRC. Altogether, TUG1 induces progression of CRC through miR-145-5p/TRPC6 axis, thereby regarding as a possible diagnostic marker for CRC management [42].

**TUG1/miR-138-5p/ZEB2**

It has been shown that high expression of TUG1 is correlated with increased proliferation and invasion along with reduced apoptosis of CRC cells [43]. TUG1 overexpression was also closely associated with the overall survival of CRC patients, indicating TUG1 as poor
prognosis biomarker for CRC [44]. Zinc finger E-box binding homeobox 2 (ZEB2) is a binding protein that participated in CRC metastasis and associated with human CRC poor prognosis [45]. There was a positive and negative correlation between TUG1 with ZEB2 and miR-138-5p, respectively. Low expression of ZEB2 or overexpression of miR-138-5p reversed the induction of EMT which was caused by TUG1 overexpression. Therefore, TUG1 by suppressing the miR-138-5p/ZEB2 axis facilitated CRC occurrence and metastasis [3, 41, 43, 44].

TUG1/Wnt/β-catenin
High expression of TUG1 has been implicated in clinico-pathological features of CRC including advanced tumor stage along with reduced overall survival and disease-free survival [24, 44, 46]. The Wnt/β-catenin signaling was found to transcriptionally regulate CRC proliferation [47]. TUG1 silencing resulted in low activity of Wnt/β-catenin and suppression of proliferation. In the CRC xenograft model, low expression of TUG1 inhibited both tumorigenicity and β-catenin nuclear localization. TUG1 through changing the nuclear localization of β-catenin reduced the Wnt/β-catenin signaling activity and subsequent induced CRC proliferation. Therefore, TUG1/Wnt/β-catenin could exert promising advancement for CRC prevention [44, 46].

TUG1/TGF-β/TWIST1
Transforming growth factor-beta (TGF-β) is involved in CRC tumorigenesis [48]. A recent study reported that TGF-β induced migration of CRC and overexpressed TUG1 as its downstream molecule. Recent findings demonstrated that TUG1 blockade suppressed migration, invasion, in vitro EMT along with in vivo lung metastasis. Hence, TUG1 is necessary for TGF-β-promoted pathophysiological features of CRC [49]. Twist family BHLH transcription factor 1 (TWIST1) stands as a kind of transcriptional modulator which is activated by TGF-β, resulting in low expression of E-cadherin [50]. TWIST1 silencing using siRNA resulted in significant reduction of CRC migration and EMT. It can be concluded that TGF-β-induced metastasis of CRC is regulated through the TUG1/TWIST1/EMT network, highlighting TUG1 as a novel target to inactivate the TGF-β signaling [49].

TUG1/miR-421/KDM2A/ERK/SP1
Specificity protein 1 (SP1) has a positive-regulated manner with TUG1 in CRC cells [51]. SP1 as an oncogene was found to promote CRC progression and metastasis [51, 52]. TUG1 loss of function inhibited cell growth and induced apoptosis of CRC cells [51]. Growing evidence revealed a negative correlation between TUG1 and miR-421 as a CRC tumor suppressor factor [53, 54]. Lysine demethylase 2 A (KDM2A) is a CRC oncogenic...
gene and a target for miR-421. TUG1 by sponging miR-421 induced KDM2A expression [51, 55]. Moreover, TUG1 has been found to intensify in vitro progression of CRC through the ERK signaling. Also, SP1 promoted in vivo CRC tumorigenesis by miR-421 suppression and KDM2A induction through TUG1 overexpression. Altogether, TUG1 as an oncogene can interact with SP1 and the miR-421/ KDM2A/ERK axis to facilitate CRC progression [51].

**TUG1/miR-542-3p/TRIB2/Wnt/β-catenin**

Tribbles homolog 2 (TRIB2) is an atypical protein kinase that has been dramatically upregulated with TUG1 in CRC tissues and cells [56, 57]. High expression of TUG1 by suppressing miR-542-3p was associated with tumor stage, lymph node metastasis, and histological differentiation of CRC patients. TUG1 or TRIB2 loss of function prohibited proliferation, migration, invasion along with in vivo tumor growth but facilitated CRC apoptosis. Besides, upregulation of TRIB2 as a miR-542-3p target reversed the impact of TUG1 silencing on CRC progression [58]. Considering the role of the Wnt/β-catenin signaling in CRC development, miR-542-3p suppression or TRIB2 upregulation has been reported to partly bring back the inhibitory function of TUG1 knockdown on the Wnt/β-catenin signaling. Therefore TUG1 is regarded as a tumor promoter that stimulated CRC pathogenesis and drug resistance through the miR-542-3p/TRIB2 axis [58, 59].

**TUG1/miR-153-1/KLF4**

In contrast to highly-expressed TUG1 in CRC, miR-153-1 was under expressed. Depletion of TUG1 using si-TUG1 as well as ectopic expression of miR-153-1 repressed proliferation, migration, invasion, and in vivo tumor growth but facilitated CRC apoptosis. Kruppel-like factor 4 (KLF4) is a zinc finger transcription factor that plays as a tumor suppressive gene in CRC [61]. Recent findings identified KLF4 as a direct transcription factor for miR-153-1 that can suppress CRC pathogenesis but its expression negatively modulated by TUG1. Interestingly, TUG1-deficient mice demonstrated high and low expressions of E-cadherin along with N-cadherin as tumor metastasis-correlated EMT markers exerting the TUG1/miR-153-1/KLF4 axis in vivo EMT of CRC cells. Such regulatory axis might provide great insights for either diagnostic or treatment possibility of CRC [60].

**Chemoresistance features of TUG1**

Chemotherapy in combination with targeted therapy has been found to impair tumor recurrence and increase
survival rate of CRC patients, but chemotherapeutic resistance is considered as the leading cause of CRC therapy failure. Therefore, molecular knowledge of chemotherapeutic resistance is required for CRC tumor biology [62, 63]. 5-fluorouracil (5-FU) is regarded as an effective first-line drug for CRC patients, but unknown molecular approaches are still complicated its recovery features [17, 64]. Accumulating data demonstrated that TUG1 is over-expressed in 5-FU resistant CRC tissue and cells, which were associated with poor prognosis. TUG1 blockade was implicated to dramatically promote CRC cells sensitive to 5-FU through suppressing CRC cell apoptosis which is regulated by miR-197-3p and TYMS as a direct target of miR-197-3p. Such findings highlighted the possible significance of TUG1 as a predictive marker for exerting CRC response to 5-FU therapy and indicated TUG1 silencing as a novel therapeutic approach to reverse 5-FU resistance [65]. Besides, cancer stem cells are shown to be involved in CRC chemoresistance [66]. It has been found that TUG1 silencing inhibited CRC stem cell resistant to oxaliplatin through reducing GATA6 and targeting the BMP pathway. Altogether, TUG1 promoted CRC stem cell features and chemotherapeutic resistance via inducing the stability of the GATA6 protein, providing promising insights for CRC clinical therapy [67]. Improvement of drug resistant sensitivity remains an immediate necessity for CRC chemotherapies. CRC resistance to methotrexate (MTX) as the earliest cytotoxic drugs is still a main challenge to the physicians [62, 68]. A recent study indicated that TUG1 repressed CRC cell sensitivity to MTX through targeting its interaction with miR-186. TUG1 blockade re-sensitized CRC cell resistant to MTX. Indeed, a negative correlation between miR-186 and the cytoplasmic polyadenylation element binding protein 2 (CPEB2) protein has been shown in MTX resistant tumors. Therefore, TUG1 regulated CRC resistant to MTX through targeting miR-186 and consequent induction of CPEB2 expression, thereby holding TUG1 as a possible target for CRC management [69].

Insulin-like growth factor-2 mRNA–binding protein (IGF2BP) family members as a kind of RNA-binding proteins participated in tumorigenesis as well as chemoresistance via influencing either stability, translatability, or localization of lncRNA [70–72]. It has been found that TUG1 and IGF2BP2 were both high-expressed in CRC cell resistant to cisplatin through autophagy activation. Low TUG1 expression decreased CRC chemoresistance to cisplatin and facilitated miR-195-5p expression. Therefore, the TUG1/IGF2BP2/miR-195-5p axis intensify CRC cell growth and induce such malignant cell resistance to cisplatin, regarding as underlying target for CRC therapy [73].

**Prognostic significance of TUG1 in colorectal cancer**

Along with the biological behaviors of TUG1 in regulating CRC pathogenesis, it is also emerging as a crucial substrate for the progress of CRC biomarkers for early detection, prognosis prediction, and anticipating therapy response to diverse chemotherapies and developing therapies [74]. Currently, a study proposed that TUG1 could play a vital function in CRC metastasis. Following investigation of the TUG1 expression levels in 120 CRC patients, high TUG1 expression was observed in tumor tissue which was closely associated with the poor survival time of the CRC patients [24, 75, 76]. Further in vitro experiments revealed the oncogenic impact of TUG1 upregulation in CRC cell lines. In the xenograft animal model, increased expression of TUG1 stimulated colony formation, migratory ability, and metastatic potential. Indeed, the researchers observed that TUG1 activated EMT-correlated gene expression [24, 77]. Another study proposed that the highly-expression of TUG1 was a CRC convinced unfavorable prognosis marker [78]. Cumulatively, TUG1 may act as a prognostic biomarker and a curative target. With more attempts affirm to the study of IncRNA particularly TUG1, it is optimistic that TUG1 will finally attain clinical utility [79]. In contrast, a recent study on 47 CRC patients indicated that there were no remarkable correlations between TUG1 expression and clinicopathological features of CRC. Besides, TUG1 expression could not forecast the overall survival and progression-free survival in CRC patients [80].

**Conclusion**

IncRNAs can be used as biomarkers for the diagnosis, prognosis, and monitoring of the progression of the disease because of their tissue-specific expression and high stability [81]. Several studies reported that IncRNAs are closely linked to a variety of cancer types and might function as oncogenes or oncogene suppressors depending on the type of cancer [82, 83]. Although the role of TUG1 in the characteristics and chemoresistance of CRC stem cells is still not well-defined, it has been already presented as an attractive potential biomarker because of its tumor-promotive function via diverse mechanisms, such as RNA-RNA and RNA/transcription factors interactions [46, 84]. It was investigated by the same group that TUG1 increased the characteristics and oxaliplatin resistance of CRC stem cells by enhancing GATA6 stability [14]. TUG1 is suggested to solve the problem of fluoropyrimidine (Fu)-based chemotherapy. TUG1 appears to mediate 5-Fu resistance in CRC through the miR-197-3p/TYMS axis [9]. Knockdown of TUG1 re-sensitized resistant cells to the exposure of 5-Fu and induced cell apoptosis. This IncRNA by targeting miR-186 stimulated CPEB2 to mediate methotrexate resistance in CRC [15]. Taken together, the role of IncRNA TUG1 in CRC drug...
resistance seems to be crucial and holds great promise as a potential therapeutic target. Current findings regarding TUG1 not only promote a better understanding of CRC pathogenesis and development but also facilitated the progress of cancer IncRNA therapy. However, many mechanisms remain poorly described suggesting a great need for further study.

Acknowledgements
Not applicable.

Authors’ contributions
SH. A., A. N., F. GH., K. R., B. K., P. M., and M. F., have made contributions to the writing of the manuscript. All authors have approved the submitted version of the article and have agreed to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. All authors read and approved the final manuscript.

Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that there is no competing interests.

Received: 28 June 2022 / Accepted: 7 October 2022
Published online: 04 November 2022

References
1. Sharma A, Yadav D, Rao P, Sinha S, Goswami D, Rawal RM, Shrivastava N. Identification of potential therapeutic targets associated with diagnosis and prognosis of colorectal cancer patients based on integrated bioinformatics analysis. Computers in Biology and Medicine 2022:105688.
2. Ottiaiano A, Santorosina M, Perini F, Pace U, Manna B, Corera M, Sabatino F, Cascella M, Pettrillo N, Ianniello M. Clinical and molecular characteristics of rare malignant tumors of colon and rectum. Biology. 2022;11:267.
3. Wang L, Zhao Z, Feng W, Ye Z, Dai W, Zhang C, Peng J, Wu K. Long non-coding RNA TUG1 promotes colorectal cancer metastasis via EM7 pathway. Oncotarget. 2016;7:51713.
4. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal Cancer (CRC) treatment and future perspectives. Curr Oncol. 2016;23:8211–8.
5. Wang X, Li X, Huang H, Liu X, Wang Y, et al. Increased expression of lncRNA NEAT1 in colorectal cancer. Cancer Cell Int. 2022;22:1–10.

Downloaded by [Health Science Library - Queen's University] at 01:48 10 October 2022
33. Wang H, Liao S, Li H, Chen Y, Yu J. Long Non-coding RNA TUG1 Sponges Mr-145a-5p to Regulate Microglial Polarization After Oxygen-Glucose Deprivation. Front Mol Neurosci. 2019;12:215–5.

34. Wang X, Chen X, Zhang D, Yang G, Yang Z, Yin Z, Zhao S. Prognostic and clinico-pathological role of long non-coding RNA taurine upregulated 1 in various human malignancies: a systematic review and meta-analysis. Tumor Biology. 2017;39:1014361717714361.

35. Jing B, Wang X, Sun Z, Sun D, Wei X, Ding Y. TUG1 promotes prostate cancer progression by acting as a ceRNA of miR-26a. Biosci Rep. 2018;38. Xie C, Chen B, Wu B, Guo L, Cao J. LncRNA TUG1 promotes cell proliferation and suppresses apoptosis in osteosarcoma by regulating miR-212-3p/FOXA1 axis. Biomed Pharmacother. 2018;97:1645–53.

36. Zhou Y, Li Y, Li R, Yan N, Li X, Dai T. Prognostic role of long non-coding RNA TUG1 expression in various cancers: a meta-analysis. Oncotarget. 2017;8:100499.

37. Tang Q, Li X, Chen Y, Long S, Yu Y, Sheng H, Wang S, Han L, Wu W. Solamargine enhances the growth of hepatocellular carcinoma and enhances the anticancer effect of sorafenib by regulating HOTTIP-TUG1/miR-4726 - Sp/MUC1 pathway. Mol Carcinog. 2022;61:417–32.

38. Tan J, Qiu K, Li M, Liang Y. Double-negative feedback loop between long non-coding RNA TUG1 and miR-145 suppresses colorectal epithelial to mesenchymal transition and radioresistance in human bladder cancer cell. FEBS Lett. 2015;589:3175–81.

39. Thiery JP, Acloque H, Huang RF, Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell. 2009;139:879–90.

40. Zhai H, Hui F, Sun J, Li M, Qiu Z, Wu J, Xiong Z, Zhou T, Zhang J. Ovarian cancer: Overexpression of long non-coding RNA TUG1 promotes cancer cell progression. Med Sci monotor. Int Med J experimental Clin Res. 2016;22:3281.

41. Wang X, Bai X, Yuan G, Guo Z, Zhang Y. The IncRNA TUG1 promotes cell growth and migration via the TUG1/miR-145-3p/TRPC6 pathway in colorectal cancer. 2020.

42. Yan Z, Bi M, Zhang Q, Song Y, Hong S. LncRNA TUG1 promotes the progression of colorectal cancer via the miR-138-3p/SPZB2 axis. Bioscience Reports 2020, 40.

43. Sun J, Deng C, Yang Z, Liu T, Zhang X, Zhao C, Wang J. Correction to: The long non-coding RNA TUG1 indicates a poor prognosis for colorectal cancer and promotes metastasis by affecting epithelial-mesenchymal transition. J Translational Med. 2020;18:1–6.

44. Liu Q, Zhang W, Luo L, Han K, Liu R, Wei S, Guo X. Long non-coding RNA TUG1 regulates the progression of colorectal cancer through miR-542-3p/TR Ras2 axis and Wnt/β-catenin pathway. Diag Pathol. 2021;16:1–12.

45. Zhu G-X, Gao D, Shao Z-Y, Chen L, Ding W-J, Yu Q-F. Wnt/β-catenin signaling: ‘Causes- and treatment targets of drug resistance in colorectal cancer. Mol Med Rep. 2021;23:1–1.

46. Shao H, Dong D, Shao F. Long non-coding RNA TUG1-mediated down-regulation of KLF4 contributes to metastasis and the epithelial-to-mesenchymal transition of colorectal cancer by miR-153-1. Cancer Manage Res. 2019;11:8699.

47. Ma Y, Wu L, Liu X, Yu Y, Shi W, Liang Y, Yao L, Zheng J. TUG1 inhibits colorectal cancer cell proliferation dependent on NOD2 signaling. Oncol Rep. 2017;38:975–84.

48. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med. 2005;353:452–576. 

49. Zhu Y, Hu H, Yuan Z, Zhang Q, Xiong H, Hu Z, Wu H, Huang R, Wang G, Tang Q. LncRNA NEAT1 remodels chromatin to promote the FGF-5 resistance by acting as a ceRNA of miR-197-3p in colorectal cancer. J Cancer. 2019;10:4603.

50. Joag MG, Sise A, Murillo JC, Saided-Ahmed IO, Wong JR, Mercado C, Galor A, Karp CL. Topical S-fluorouracil 1% as primary treatment for ocular squamous neoplasia. Ophthalmology. 2016;123:1442–8.

51. Wang M, Hu H, Wang Y, Huang Q, Huang R, Chen Y, Ma T, Qiao Z, Zhang Q, Wu H. Long non-coding RNA TUG1 mediates S-fluorouracil resistance by acting as a ceRNA of miR-197-3p in colorectal cancer. Cancer Cell. 2020;21:15–11.

52. Tarazona N, Gimeno-Valente F, Gambardella V, Huerta M, Rosello S, Zuniga S, Calon A, Carbonell-Assins JA, Fontana E, Martinez-Carpaglin C. Detection of postoperative plasma circulating tumour DNA and lack of CDX2 expression as markers of recurrence in patients with localised colon cancer. ESMO open. 2020;5:e000847.

53. Sun J, Zhou H, Bao X, Wu Y, Jia H, Zhao H, Liu G. IncRNA TUG1 Facilitates Colorectal Cancer Stem Cell Characteristics and Chemoresistance by Enhancing GATA6 Protein Stability. Stem Cells International 2021, 2021.

54. Tol J, Koopman M, Cats A, Redenborg CJ, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, van Groeningen CJ, Sinnige HA. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563–72.

55. Li C, Gao Y, Li Y, Ding D. TUG1 mediates methotrexate resistance in colorectal cancer via miR-186/CPEB2 axis. Biochem Biophys Res Commun. 2017;491:552–7.

56. Huang X, Zhang H, Guo X, Zhu Z, Cai H, Kong X. Insulin-like growth factor 2 mRNA-binding protein 1 (IGFBP1) in cancer. J Hematol Oncol. 2016;11:8–15.

57. Zhai H, Liu J, Kong X, Xie J, Zhang Q, Pang G. Insulin-like growth factor-2 mRNA binding protein 2 regulates proliferation, migration, and angiogenesis of keratinocytes by regulating heparanase stability. Bioengineering. 2012;11:8697–67.

58. Fakhraldeen SA, Clark RJ, Roopra A, Chui EN, Huang W, Castorino J, Wessberg KB, Kim T, Spiegelman VS, Alexander CM. Two isoforms of the RNA binding protein, coding region determinant-binding protein (CRD-BP/IGF2BP1), are expressed in breast epithelium and support clonogenic growth of breast tumour cells. J Biol Chem. 2015;290:13386–400.

59. Xia C, Li Q, Cheng X, Wu T, Gao Q, Gu Y. Insulin-like growth factor 2 mRNA-binding protein 2-stabilized long non-coding RNA Taurine up-regulated gene 1 (TUG1) promotes cisplatin-resistance of colorectal cancer via modulating autophagy. Bioengineering. 2022;9:1050–69.

60. Wang Y, Yang J, Li X, Ma Y, Qiao J, Wang H, Long RNAs in colorectal cancer: Novel oncogenic mechanisms and promising clinical applications. Cancer Lett. 2021;504:67–80.

61. Talebi A, Azzizpour M, Agah S, Masoudi M, Mobini GR, Akbari A. The relevance of long noncoding RNAs in colorectal cancer biology and clinical settings. J Cancer Res Ther. 2020;16:622–3.

62. Li N, Shi K, Kang X, Li W. Prognostic value of long non-coding RNA TUG1 in various tumors. Oncotarget. 2017;8:65659.

63. Saus E, Brunet-Vega A, Iaola-Guzman S, Pequeiros C, Gabaldon T, Pericay C. Long non-coding RNAs as potential novel prognostic biomarkers in colorectal cancer. Front Genet. 2016;7:54.

64. Liu J, Lin J, Liu Y, Zhang Y, Chen X. Prognostic role of IncRNA TUG1 for cancer outcome: evidence from 840 cancer patients. Oncotarget. 2017;8:5055.

65. Li Z, Shen J, Chan JT, Wu WK. TUG 1: a pivotal oncogenic long non-coding RNA of human cancers. Cell Proif. 2016;49:471–5.
80. Abushouk AI, Kattan SW, Ahmedah HT, Baothman E, Shaheen S, Toraih EA, Fawzy MS. Expression of oncolong noncoding RNA taurine-upregulated gene-1 in colon cancer: A clinical study supported by in silico analysis. J Can Res Ther 2021.

81. Kunej T, Obsteter J, Pogacar Z, Horvat S, Calin GA. The decalog of long non-coding RNA involvement in cancer diagnosis and monitoring. Crit Rev Clin Lab Sci. 2014;51:344–57.

82. Wei S, Sun S, Zhou X, Zhang C, Li X, Dai S, Wang Y, Zhao L, Shan B. SNHG5 inhibits the progression of EMT through the ubiquitin-degradation of MTA2 in oesophageal cancer. Carcinogenesis. 2021;42:315–26.

83. Gong M, Wang X, Mu L, Wang Y, Pan J, Yuan X, Zhou H, Xing J, Wang R, Sun J. Steroid receptor coactivator-1 enhances the stemness of glioblastoma by activating long noncoding RNA XIST/miR-152/KLF4 pathway. Cancer Sci. 2021;112:604–18.

84. Sun J, Zhou H, Bao X, Wu Y, Jia H, Zhao H, Liu G. IncRNA TUG1 Facilitates Colorectal Cancer Stem Cell Characteristics and Chemoresistance by Enhancing GATA6 Protein Stability. Stem cells international 2021, 2021:1075481–1075481.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.