Review

A Concise Review on Dysregulation of LINC00665 in Cancers

Soudeh Ghafouri-Fard 1, Tayyebeh Khoshbakht 2, Bashdar Mahmud Hussen 3,4, Aria Baniahmad 5, Mohammad Taheri 5,6,* and Mohammadreza Hajiesmaeili 7,*

1 Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran 19835-35511, Iran
2 Men’s Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran 16666-63111, Iran
3 Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Erbil 44001, Iraq
4 Center of Research and Strategic Studies, Lebanese French University, Erbil 44001, Iraq
5 Institute of Human Genetics, Jena University Hospital, 07743 Jena, Germany
6 Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran 16666-63111, Iran
7 Critical Care Quality Improvement Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran 16666-63111, Iran
* Correspondence: mohammad.taheri@uni-jena.de (M.T.); mrhajiesmaeili@sbmu.ac.ir (M.H.)

Abstract: Long Intergenic Non-Protein Coding RNA 665 (LINC00665) is an RNA gene located on the minus strand of chromosome 19. This IncRNA acts as a competing endogenous RNA for miR-4458, miR-379-5p, miR-551b-5p, miR-3619-5p, miR-424-5p, miR-9-5p, miR-126-5p, miR-149-3p, miR-379-5p, miR-665, miR-34a-5p, miR-186-5p, miR-138-5p, miR-181c-5p, miR-98, miR-195-5p, miR-224-5p, miR-3619, miR-708, miR-101, miR-1224-5p, miR-34a-5p, and miR-142-5p. Via influencing expression of these miRNAs, it can enhance expression of a number of oncogenes. Moreover, LINC00665 can influence activity of Wnt/β-Catenin, TGF-β, MAPK1, NF-κB, ERK, and PI3K/AKT signaling. Function of this lncRNA has been assessed through gain-of-function tests and/or loss-of-function studies. Furthermore, different research groups have evaluated its expression levels in tissue samples using microarray and RT-qPCR techniques. In this manuscript, we have summarized the results of these studies and categorized them in three sections, i.e., cell line studies, animal studies, and investigations in clinical samples.

Keywords: LINC00665; cancer; biomarker

1. Introduction

Long non-coding RNAs (IncRNAs) are a group of transcripts participating in the chromatin remodeling, transcriptional regulation of gene expression as well as post-transcriptional events, via different chromatin-associated routes and through interaction with other RNA molecules [1]. Their functions largely depend on their subcellular localization and interplays with DNA, RNA, and proteins [2]. In addition to their role in the modulation of chromatin function, they can influence the stability of mRNAs and their translation in the cytoplasm [2]. Their involvement in diverse biological and physiopathological functions has potentiated them as important participants in the pathoetiology of different disorders.

Long Intergenic Non-Protein Coding RNA 665 (LINC00665) is an RNA gene located on chr19:36,259,540-36,332,581. At least 33 splice variants have been identified for this gene (http://asia.ensembl.org/Homo_sapiens/Gene, accessed on 10 October 2022). This IncRNA has been shown to act as an oncogene in diverse malignancies. Function of this IncRNA has been assessed through gain-of-function tests and/or loss-of-function studies. Moreover, different groups have evaluated its expression levels in tissue samples using microarray and real time-quantitative polymerase chain reaction (RT-qPCR) techniques.
Similar to some other lncRNAs, LINC00665 has been shown to encode a micropeptide. This micropeptide is called CIP2A-BP. Experiments in breast cancer cells have revealed that translation of CIP2A-BP is decreased by TGF-β. This micropeptide has an inhibitory role in the development of triple negative breast cancer possibly through suppression of PI3K/AKT/NF-κB signals and the subsequent down-regulation of matrix metalloproteinase (MMP)-2, MMP-9, and Snail levels [3].

Since this lncRNA has been dysregulated in different malignancies, it represents a potential target for therapeutic interventions. Thus, it is necessary to identify the functionally related molecules and pathways with this lncRNA in different tissues. In this manuscript, we have summarized the results of these studies and categorized them in three sections, i.e., cell line studies, animal model investigations, and investigations in clinical samples.

2. Cell Line Studies

LINC00665 has been shown to be up-regulated in acute myeloid leukemia (AML) cells parallel with the increase in expression of Dedicator Of Cytokinesis 1 (DOCK1) and decrease in expression of miR-4458. Knock-down of LINC00665 or DOCK1 has resulted in a significant decrease in proliferation, migration, and adhesion of these cells. On the other hand, suppression of miR-4458 has led to enhancement of these features and inhibition of apoptosis of AML cells. Mechanistically, LINC00665 could sponge miR-4458 and increase expression of DOCK1 through this route [4].

In breast cancer cells, LINC00665 has been found to act as a sponge for miR-379-5p, reducing the capacity of miR-379-5p to suppress expression of Lin-28 Homolog B (LIN28B). The impact of LINC00665 in induction of expression of LIN28B is associated with induction of progression of breast cancer and activation of epithelial–mesenchymal transition (EMT) program in these cells [5]. Another study in breast cancer cells has revealed attenuation of migration and invasion aptitude of these cells following LINC00665 silencing. Moreover, downregulation of this lncRNA has inhibited expressions of EMT-associated proteins in these cells [6]. LINC00665 can also influence progression of breast cancer via sponging miR-551b-5p [7]. LINC00665 silencing has also suppressed proliferation, migration, and invasive features of breast cancer cells, while it enhanced apoptosis. The effects of LINC00665 on these features of breast cancer cells are possibly exerted through sponging miR-3619-5p. Up-regulation of miR-3619-5p has been shown to be similar to LINC00665 silencing at cellular level. Expression of β-catenin has been reduced following LINC00665 silencing and miR-3619-5p up-regulation, supporting the importance of LINC00665/miR-3619-5p/β-catenin axis in the progression of breast cancer [8].

An in vitro experiment in cervical cancer cells has revealed that short hairpin RNA (shRNA)-mediated knock down of LINC00665 can lead to reduction of cell viability, up-regulation of E-cadherin level, down-regulation of N-cadherin, Vimentin and CTNNB1 levels, and suppression of migration and invasiveness of HeLa cells. The impact of LINC00665 on enhancement of EMT is possibly mediated via activation of WNT-CTNNB1/β-catenin signals [9].

A microarray-based assay in gemcitabine resistant cholangiocarcinoma cell lines has led to identification of LINC00665 among the top 10 over-expressed. Knock down of this lncRNA in chemoresistant cells has led to enhancement of gemcitabine effects, whereas up-regulation of LINC00665 has augmented gemcitabine resistance in chemosensitive cholangiocarcinoma cells. Chemoresistant cholangiocarcinoma cells have exhibited higher EMT and stemness features, and LINC00665 knock-down has inhibited sphere formation, migratory potential, invasiveness, and levels of EMT and stemness marker proteins. While Wnt/β-Catenin signals have been activated in chemoresistant cholangiocarcinoma cells, LINC00665 silencing has inhibited activity of this pathway. Mechanistically, LINC00665 can regulate expression of the nuclear transcriptional regulator of this pathway, i.e., BCL9L through sponging miR-424-5p. BCL9L down-regulation or miR-424-5p up-regulation has reduced resistance to gemcitabine, and decreased EMT, stemness, and Wnt/β-Catenin activity in chemoresistant cholangiocarcinoma cells [9].
In vitro experiments in colorectal cancer cells have shown the sponging role of LINC00665 on miR-9-5p and subsequent regulation of ATF1 as an important mechanism of carcinogenesis [10]. Moreover, LINC00665-mediated up-regulation of CTNNB1 has been demonstrated to result in activation of Wnt/β-catenin signals in colorectal cancer cells [11]. Finally, LINC00665 could stimulate proliferation and impede apoptosis of colorectal cancer cells through regulation of miR-126-5p expression [12].

Figure 1. Oncogenic role of LINC00665 in prostate cancer, colorectal cancer, breast cancer, and osteosarcoma. Detailed information about the assays is shown in Table 1.

Table 1. LINC00665 expression in cell lines (A: knock-down or deletion, CRC: colorectal cancer, DDP: cisplatin, AML: acute myeloid leukemia).

| Tumor Type            | Interactions                  | Cell Line                                      | Function                                      | Reference |
|-----------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|-----------|
| Acute myeloid leukemia| miR-4458/DOCK1 axis           | KG1, U937, NB4 and HL60 and HS-5              | ∆ LINC00665: ↓ proliferation, migration and adhesion and ↑ apoptosis | [4]       |
| Breast cancer         | miR-379-5p/LIN28B axis        | MCF10A, 293FT, MCF7, BT474, BT549, MDA-MB-231, MDA-MB-468, and T47D | ∆ LINC00665: ↓ proliferation, migration, and invasion | [5]       |
|                       |                               | MCF-10A, MCF-7, MDA-MB-231, ZR-75-30, and MDA-MB-415 | ↑↑ LINC00665: ↑ proliferation, migration, and invasion, EMT process | [6]       |
|                       | miR-551b-5p                   | MCF10A and HCC-1937, MDA-MB-231, and MCF-7    | ∆ LINC00665: ↓ cell growth and ↑ apoptosis    | [7]       |
|                       | miR-3619-5p/β-catenin axis    | MDA-MB-231 and MCF-7 and MCF-10A              | ∆ LINC00665: ↓ cell proliferation, migration, and invasion | [8]       |
| Tumor Type | Interactions | Cell Line | Function | Reference |
|------------|--------------|-----------|----------|-----------|
| Cervical cancer | WNT-CTNNB1/β-catenin signaling pathway | HeLa and HEK293T cells | ∆ LINC00665: ↓ cell viability, migration, invasion and EMT process | [9] |
| Cholangiocarcinoma | miR-424-5p/BCL9L axis, Wnt/β-Catenin signaling | HuCCT1, HuH28, SNU-1196, SNU-1079, SNU-308, SNU-245, SNU-478 and SNU-869 | ∆ LINC00665: ↓ sphere formation, migration, invasion, EMT process, gemcitabine resistance, and sternness ↑↑ LINC00665: ↑ gemcitabine resistance | [9] |
| Colorectal cancer | miR-9-5p/ATF1 axis | DLD-1, SW480, KM12, SW116, SW620 and NCM460 | ∆ LINC00665: ↓ cell proliferation, migration, invasion and ↑ apoptosis ↑↑ LINC00665: ↑ cell proliferation, migration, invasion and ↓ apoptosis | [10] |
| Glioma | HMGA1 | RL-95-2, Ishikawa, HEC-1B, KLE and HBGA | ∆ LINC00665: ↓ viability, migration and invasion, ↑ apoptosis and G1 phase arrest | [11] |
| Gastric cancer | miR-379-5p/GRP78 axis | GES-1, SGC-7901, AGS, HCT-27 and GES-1 | ∆ LINC00665: ↓ DDP-resistant GC cell proliferation, Endoplasmic reticulum (ER) stress, and ↑ apoptosis | [12] |
| Endometrial carcinoma | Wnt signaling | MNK28, BGC-823, SGC-7901, AGS, HCT-27 and GES-1 | ∆ LINC00665: ↓ proliferation, migration, invasion, and ↑ apoptosis and cell cycle arrest | [13] |
| Hepatocellular carcinoma | miR-149-3p/RNF2 axis | AGS, SGC-7901, HGC-22, MGC-803, MKN-45, BGC-823 and GES-1 | ∆ LINC00665: ↓ cell viability and invasion | [14] |
| Lung cancer | YB-1-ANGPT4/ANGPTL3/VEGFA axis | HUVECs, A549 and H1299 | LINC00665 was found to interact with YB-1 and induce angiogenesis in lung adenocarcinoma by activating YB-1-ANGPT4/ANGPTL3/VEGFA axis. | [15] |
| Melanoma | miR-224-5p/VMAT2 axis | A375, M21, A2058, A-875 and HEMa-LP | ∆ LINC00665: ↓ proliferation and migration | [16] |
In glioma cells, in vitro experiments have indicated down-regulation of TAF15 and LINC00665. Forced up-regulation of TAF15 has increased stability of LINC00665, suppressing malignant features in these cells. Moreover, MTF1 and YY2 transcription factor have been shown to be over-expressed in glioma cells, and their silencing has suppressed malignant behaviors of these cells. Up-regulation of LINC00665 could decrease stability of MTF1 and YY2 transcripts through interplay with STAUI, and STAUI silencing has reversed LINC00665-mediated down-regulation of MTF1 and YY2. Finally, MTF1 or YY2 silencing has reduced expression of GTSE1 oncogene in glioma. Taken together, the TAF15/LINC00665/MTF1(YY2)/GTSE1 axis has been acknowledged as an important axis in the modulation of the malignant features of glioma cells [18]. Contrary to this study, another study has shown an oncogenic role for this lncRNA in glioma. This study has indicated that LINC00665 sponges miR-34a-5p to influence expression of AGTR1 [19].

In hepatocellular carcinoma, LINC00665 has been found to sponge miR-214-3p and increase expression of MAPK1, thus accelerating cell proliferation and Warburg effect [20]. Moreover, it can regulate the viability, apoptotic pathways, and autophagy of these cells through modulation of miR-186-5p/MAP4K3 [21] and Double-Stranded RNA–Activated Protein Kinase/NF-κB [22] axes. Another study in hepatocellular carcinoma cells has shown that LINC00665 silencing could decrease proliferation, migration, and invasion, whereas up-regulation the CIP2A-BP micropeptide enhances these features [36].

Figure 2. Role of LINC00665 in hepatocellular carcinoma, glioma, melanoma, gastric cancer, and lung cancer. Detailed information about the assays is shown in Table 1.

Table 1. Cont.

| Tumor Type            | Interactions                                      | Cell Line                                      | Function                                      | Reference |
|-----------------------|---------------------------------------------------|-----------------------------------------------|------------------------------------------------|-----------|
| Osteosarcoma          | miR-3619                                          | 143B, U2OS, MG63 and Saos-2, hFOB1.19 and 293T cells | ∆ LINC00665: ↓ viability, invasion, and migration | [30]      |
| Osteosarcoma          | miR-708 and miR-142-5p, RAP1B                    | MG63, U2OS, 143B and Saos-2 and hFOB         | ∆ LINC00665: ↓ proliferation, migration, and invasion | [31]      |
| Ovarian cancer        | miR-34a-5p/E2F3 axis                              | A2780, OVCAR3, CAOV3, SKOV3 and IOSE80       | ∆ LINC00665: ↓ proliferation, migration, and invasion | [32]      |
| Prostate cancer       | miR-1224-5p/SND1 axis                             | LNCaP, PC-3, DU-145, 22RV1 and RWPE-1        | ∆ LINC00665: ↓ growth and metastasis           | [33]      |
| T cell acute lymphoblastic leukemia | miR-101 and PI3K/Akt pathway                 | T-ALL cells                                   | ∆ LINC00665: ↓ viability, migration and invasion | [35]      |

↑ upregulation; ↓ Downregulation; ↑↑ significantly higher.
TAF15/LINC00665/MTF1(YY2)/GTSE1 axis has been acknowledged as an important axis in the modulation of the malignant features of glioma cells [18]. Contrary to this study, another study has shown an oncogenic role for this lncRNA in glioma. This study has indicated that LINC00665 sponges miR-34a-5p to influence expression of AGTR1 [19].

In hepatocellular carcinoma, LINC00665 has been found to sponge miR-214-3p and increase expression of MAPK1, thus accelerating cell proliferation and Warburg effect [20]. More over, it can regulate the viability, apoptotic pathways, and autophagy of these cells through modulation of miR-186-5p/MAP4K3 [21] and Double-Stranded RNA–Activated Protein Kinase/NF-κB [22] axes. Another study in hepatocellular carcinoma cells has shown that LINC00665 silencing could decrease proliferation, migration, and invasion, whereas up-regulation the CIP2A-BP micropeptide enhances these features [36].

Figure 2. Shows the role of LINC00665 in liver cancer, glioma, melanoma, gastric cancer, and lung cancer.

3. Animal Studies

Experiment in xenograft models of breast, colorectal, gastric, liver, lung, and prostate cancers as well as cholangiocarcinoma, endometrial carcinoma, and melanoma have confirmed that up-regulation of LINC00665 increases tumor burden, while its silencing decreases tumor weight (Table 2). Thus, these studies consistently point to the oncogenic effects of LINC00665.

Table 2. LINC00665 function in the carcinogenesis based on studies in animal models (Δ: knock-down or deletion).

| Tumor Type             | Animal Models                  | Results                                                                 | Reference |
|------------------------|--------------------------------|-------------------------------------------------------------------------|-----------|
| Breast cancer          | 5-week-old female SCID mice    | Δ LINC00665: ↓ tumor volume †† LINC00665: ↑ tumor volume                | [5]       |
|                        | 4-week-old BALB/c nude mice    | Δ LINC00665: ↓ tumor growth                                             | [7]       |
| Cholangiocarcinoma     | nude mice                      | Δ LINC00665: ↓ Tumor growth, and tumor weight                          | [9]       |
| Colorectal cancer      | Female nude mice               | Δ LINC00665: ↓ Tumor growth, tumor volumes and tumor weights           | [11]      |
| Endometrial carcinoma  | 12 8-week-old female mice      | Δ LINC00665: ↓ tumor growth and tumor volume                           | [13]      |
| Gastric cancer         | 6-week-old male nude mice      | Δ LINC00665: ↓ tumor weights and tumor development                     | [14]      |
|                        | 6-week-old BALB/c nude mice    | Δ LINC00665: ↓ tumor growth                                             | [17]      |
| Glioma                 | 4-week-old nude mice           | †† LINC00665: ↑ tumor growth and tumor weights                         | [19]      |
| Hepatocellular carcinoma | 6-week-old male BALB/c nude mice | Δ LINC00665: ↓ tumor volumes and weights                              | [20]      |
|                        | female BALB/c nude mice        | Δ LINC00665: ↓ tumor growth and tumor volume                           | [21]      |
Table 2. Cont.

| Tumor Type | Animal Models                  | Results                                                                 | Reference |
|------------|--------------------------------|-------------------------------------------------------------------------|-----------|
| Lung cancer| BALB/c nude mice               | Δ LINC00665: ↓ tumor volumes, tumor weights and proliferation          | [23]      |
|            | 6–8-week-old BALB/c nude male mice | Δ LINC00665: ↓ tumor formation                                          | [24]      |
|            | 4-week-old female BALB/c athymic nude mice | Δ LINC00665: ↓ tumor size, tumor growth, tumor weight and metastasis | [26]      |
|            | male BALB/c nude mice          | Δ LINC00665: ↓ tumor growth and metastasis                              | [27]      |
|            | 5-week-old male athymic BALB/c nude mice | Δ LINC00665: ↓ tumor growth and ↑ gefitinib sensitivity               | [28]      |
|            | 4–5-week-old male BALB/c nude mice | Δ LINC00665: ↓ tumor size and tumor weight                             | [27]      |
| Melanoma   | 6-week-old male BALB/C nude mice | Δ LINC00665: ↓ tumor volumes and weights                               | [29]      |
| Prostate cancer | 4-week-old female Balb/c nude mice | Δ LINC00665: ↓ tumor volumes and tumor weights             | [33]      |
|            | 8-week-old male nude mice      | Δ LINC00665: ↓ tumor growth and tumor weights                          | [34]      |

↑ upregulation; ↓ Downregulation; † † significantly higher.

4. Studies in Clinical Samples

LINC00665 has been shown to be over-expressed in breast cancer tissue samples in association with poor prognosis of breast cancer patients [6]. Similarly, up-regulation of LINC00665 in breast cancer samples has been correlated with tumor size and TNM stages in another cohort of breast cancer patients [8]. Over-expression of LINC00665 has also been associated with poor prognosis and resistance of cholangiocarcinoma patients to chemotherapy [9]. In liver cancer, expression of LINC00665 has also been elevated, which noticeably designated poor prognosis. Moreover, up-regulation of LINC00665 has been associated with further development of the tumors, which has been closely correlated with clinical diagnosis. Accuracy of LINC00665 levels in prediction of overall survival has also been verified by ROC curve analyses [36].

The association between over-expression of LINC00665 and poor survival of patients has been verified in breast cancer [6], cholangiocarcinoma [9], gastric cancer [15], glioma [19], hepatocellular carcinoma [20], lung cancer [24], osteosarcoma [30], ovarian cancer [33], and prostate cancer [34] (Table 3).

Table 3. Dysregulation of LINC00665 in clinical samples (ANCTs: adjacent non-cancerous tissues, OS: overall survival, DFS: disease-free survival, BC: Breast cancer, pCR: pathological complete response, GC: Gastric cancer, PFS: progression-free survival, TNM: tumor node metastasis).

| Tumor Type           | Samples            | Expression (Tumor vs. Normal) | Kaplan—Meier Analysis (Impact of LINC00665 Up-Regulation) | Uniivariate Multivariate Cox Regression | Association of LINC00665 Expression with Clinicopathologic Characteristics | Reference |
|----------------------|--------------------|-------------------------------|----------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------|-----------|
| Acute myeloid leukemia| 36 patients and 36 healthy controls | Up-regulated                  | --                                                      | --                                    | --                                                                              | [4]        |
### Table 3. Cont.

| Tumor Type         | Samples                          | Expression (Tumor vs. Normal) | Kaplan—Meier Analysis (Impact of LINC00665 Up-Regulation) | Univariate/ Multivariate Cox Regression | Association of LINC00665 Expression with Clinicopathologic Characteristics | Reference |
|--------------------|----------------------------------|-------------------------------|----------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------|-----------|
| Breast cancer      | TCGA database                    | Up-regulated                  | –                                                        | –                                      | –                                                                                | [5]       |
|                    | GEPIA database, 60 pairs of tumors and ANCTs | Up-regulated                  | Shorter OS and DFS                                        | –                                      | tumor stage and tumor metastasis                                                 | [6]       |
|                    | 36 pairs of tumors and ANCTs     | Up-regulated                  | Shorter OS                                                | LINC00665 was found to be a possible biomarker to predict OS of BC patients.     | TNM stage and lymph node metastasis                                             | [7]       |
|                    | SHPD002 study, 102 advanced breast cancer patients | Up-regulated                  | –                                                        | Linco0665 expression was found to be an independent predictor of pCR, especially in HR-positive/HER2-negative subtype patients. | lymph node metastasis                                                           | [37]      |
|                    | 106 pairs of tumors and ANCTs    | Up-regulated                  | –                                                        | –                                      | tumor size and tumor, node, and metastasis stages                              | [8]       |
| Cholangiocarcinoma | 100 pairs of tumors and ANCTs    | Up-regulated                  | Shorter OS and recurrence-free survival time              | –                                      | higher TNM stage, lymph node involvement, and distant metastasis                | [9]       |
| Colorectal cancer  | 46 pairs of tumors and ANCTs     | Up-regulated                  | –                                                        | –                                      | local lymph node metastasis and poor differentiation                           | [10]      |
|                    | 67 pairs of tumors and ANCTs     | Up-regulated                  | –                                                        | –                                      | –                                                                                | [12]      |
| Endometrial carcinoma | 10 pairs of tumors and ANCTs   | Up-regulated                  | –                                                        | –                                      | TNM stage, histological grade, and poor prognosis of GC patients               | [13]      |
|                    | 49 pairs of tumors and ANCTs     | Up-regulated                  | Shorter OS                                                | LINC00665 was found to be an independent prognostic biomarker in GC patients.   | tumor depth, lymph node metastasis, and TNM stage                               | [15]      |
| Gastric cancer     | GEO and TCGA databases           | Up-regulated                  | Shorter OS and DFS                                        | –                                      | –                                                                                | [17]      |
|                    | GEPIA database, and GEO datasets (GSE109476 and GSE93415) | Up-regulated                  | –                                                        | –                                      | –                                                                                | [16]      |
| Glioma             | 48 pairs of tumors and ANCTs     | Up-regulated                  | Shorter OS                                                | –                                      | –                                                                                | [19]      |
|                    | 50 pairs of tumors and ANCTs     | Up-regulated                  | Shorter OS                                                | –                                      | –                                                                                | [20]      |
|                    | 76 pairs of tumors and ANCTs     | Up-regulated                  | Shorter OS                                                | –                                      | tumor size and Edmondson grade                                                  | [21]      |
| Hepatocellular carcinoma | 50 pairs of tumors and ANCTs | Up-regulated                  | –                                                        | –                                      | –                                                                                | [22]      |
|                    | TCGA, GEPIA and GEO databases   | Up-regulated                  | Shorter OS                                                | –                                      | gender, histological grade, stage, and vascular invasion                       | [38]      |
### Table 3. Cont.

| Tumor Type       | Samples                                      | Expression (Tumor vs. Normal) | Kaplan—Meier Analysis (Impact of LINC00665 Up-Regulation) | Univariate/ Multivariate Cox Regression | Association of LINC00665 Expression with Clinicopathologic Characteristics | Reference |
|------------------|----------------------------------------------|------------------------------|---------------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------|-----------|
| Lung cancer      | 37 pairs of tumors and ANCTs                 | Up-regulated                 | –                                                       | –                                       | TNM stage                                                                        | [23]      |
|                  | GEPIA and starBase databases                 | Up-regulated                 | Shorter OS                                             | –                                       | differential, tumor size, lymph node metastasis, TNM stage, and lymphovascular invasion | [24]      |
|                  | 60 pairs of tumors and ANCTs                 | Up-regulated                 | –                                                       | –                                       | High levels of linc00665, positive lymph node metastasis, high TNM stage, were found to be independent prognostic factors for predicting poor recurrence-free survival in LUAD patients. | [25]      |
| Lung cancer      | 80 pairs of tumors and ANCTs GEO database    | Up-regulated                 | Shorter OS and recurrence-free survival time           |                                         | larger tumor size, advanced TNM stage, and lymph node metastasis                  | [26]      |
|                  | (GSE27262)                                   |                              |                                                         |                                         |                                                                                   |           |
| TCGA database    | 52 pairs of tumors and ANCTs                 | Up-regulated                 | Shorter OS                                             | –                                       | poor prognosis and advanced T stage                                               | [27]      |
| GEO database     | (GSE18842, GSE19184, and GSE33532)           | Up-regulated                 | –                                                       | –                                       |                                                                                  | [39]      |
| 20 patients      | Up-regulated gfeitinib-resistance            | –                            | –                                                       | –                                       |                                                                                  | [28]      |
| TCGA database    | 60 pairs of tumors and ANCTs                 | Up-regulated                 | Shorter OS and PFS                                     | –                                       | advanced TNM stage, lymph node metastasis, and tumor size                         | [27]      |
| Osteosarcoma     | 33 pairs of tumors and ANCTs                 | Up-regulated                 | Shorter OS                                             | –                                       |                                                                                  | [30]      |
|                  | 42 pairs of tumors and ANCTs                 | Up-regulated                 | Shorter OS                                             | –                                       | larger tumor size and later clinical stages                                       | [31]      |
| Ovarian cancer   | 56 pairs of tumors and ANCTs GEO database    | Up-regulated                 | Shorter OS and PFS                                     | –                                       | tumor size, FIGO stage, and lymph node metastasis                                 | [32]      |
|                  | (GSE45238, GSE40595, GSE38666 and GSE26712) | Up-regulated                 | Shorter OS                                             | –                                       |                                                                                  | [40]      |
| Prostate cancer  | 41 pairs of tumors and ANCTs                 | Up-regulated                 | Shorter OS                                             | –                                       |                                                                                  | [33]      |
|                  | 50 pairs of tumors and ANCTs                 | Up-regulated                 | Shorter OS                                             | –                                       | higher T stage and lymph node metastasis                                          | [34]      |

### 5. Conclusions

LINC00665 has been regarded as an oncogenic lncRNA in diverse tissues. In fact, apart from a single study on glioma [18], other studies have consistently demonstrated that LINC00665 facilitates proliferation and malignant behaviors of cancer cells. It is not clear whether LINC00665 has a tissue-dependent function in the carcinogenesis or if the finding on glioma is an exception to the oncogenic role of this lncRNA. The main way of contribution of this lncRNA in the carcinogenesis is its sponging impact on tumor suppressor miRNAs. miR-4458, miR-379-5p, miR-551b-5p, miR-3619-5p, miR-424-5p, miR-9-5p, miR-214-3p, miR-126-5p, miR-149-3p, miR-379-5p, miR-665, miR-34a-5p, miR-186-5p, miR-138-5p, miR-181c-5p, miR-98, miR-195-5p, miR-224-5p, miR-3619, miR-708, miR-101, miR-1224-5p, miR-34a-5p, and miR-142-5p are among the miRNAs that are sponged by
LINC00665. Through modulating expression of these miRNAs, it can enhance expression of a number of oncogenes. Moreover, LINC00665 can influence activity of Wnt/β-Catenin, TGF-β, MAPK1, NF-κB, ERK and PI3K/AKT signaling. This lncRNA can also enhance tumor metastasis through activation of EMT program.

LINC00665 can also affect response to a number of anticancer drugs including gemcitabine, apatinib, and gefitinib. Thus, therapies targeted against LINC00665 are expected to decrease tumor volume, reduce malignant features, and improve the response of cancer cells to both chemotherapeutic drugs and targeted therapies. Although the results of investigations in animal models of diverse kinds of cancers have been promising, these results have not been validated in clinical settings due to several obstructions, particularly regarding safety and bioavailability issues. Moreover, LINC00665 has interactions with a wide range of biomolecules including miRNAs. Identification of other LINC00665 targets, particularly possible tissue-specific targets, is a prerequisite for the design of more specific therapeutic modalities.

An important note about this lncRNA is its ability in the production of a functional micropeptide. The encoded micropeptide by this lncRNA can promote progression of breast cancer and hepatocellular carcinoma. Future studies should assess the impact of this micropeptide in other types of cancers and find the possible functional relationship between lncRNA and micropeptide. Notably, expression of this micropeptide is regulated by TGF-β [3].

Finally, in spite of adequate data about the prognostic impact of LINC00665, there is no data about its role in diagnostic approaches. Thus, future studies should evaluate whether LINC00665 levels can separate patients with malignancies from normal subjects.

In conclusion, LINC00665 is an lncRNA that affects several aspects of carcinogenesis, particularly in response to both chemotherapeutic agents and small molecules that are used in targeted cancer therapy. Therefore, this lncRNA is a candidate for designing novel drugs for the treatment of cancer.

Author Contributions: S.G.-F.: wrote the manuscript and revised it. M.T.: supervised and designed the study. A.B., B.M.H., M.H. and T.K. collected the data and designed the figures and tables. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Acknowledgments: The authors would like to thank the clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Fang, Y.; Fullwood, M.J. Roles, functions, and mechanisms of long non-coding RNAs in cancer. Genom. Proteom. Bioinform. 2016, 14, 42–54.
2. Statello, L.; Guo, C.-J.; Chen, L.-L.; Huarte, M. Gene regulation by long non-coding RNAs and its biological functions. Nat. Rev. Mol. Cell Biol. 2021, 22, 96–118. [CrossRef] [PubMed]
3. Guo, B.; Wu, S.; Zhu, X.; Zhang, L.; Deng, J.; Li, F.; Wang, Y.; Zhang, S.; Wu, R.; Lu, J. Micropeptide CIP 2A-BP encoded by LINC00665 inhibits triple-negative breast cancer progression. EMBO J. 2020, 39, e102190. [CrossRef] [PubMed]
4. Yang, X.; Wang, Y.; Pang, S.; Li, X.; Wang, P.; Ma, R.; Ma, Y.; Song, C. LINC00665 promotes the progression of acute myeloid leukemia by regulating the miR-4458/DOCK1 pathway. Sci. Rep. 2021, 11, 5009. [CrossRef]
5. Ji, W.; Diao, Y.-L.; Qiu, Y.-R.; Ge, J.; Cao, X.-C.; Yu, Y. LINC00665 promotes breast cancer progression through regulation of the miR-379-5p/LIN28B axis. Cell Death Dis. 2020, 11, 1–11.
6. Zhou, J.; Zou, L.; Zhu, T. Long non-coding RNA LINC00665 promotes metastasis of breast cancer cells by triggering EMT. *Eur. Rev. Med. Pharm. Sci.* 2020, 24, 3097–3104.

7. Qi, L.; Sun, B.; Yang, B.; Lu, S. LINC00665 Stimulates Breast Cancer Progression via Regulating miR-551b-5p. *Cancer Manag. Res.* 2021, 13, 1113. [CrossRef]

8. Lv, M.; Mao, Q.; Li, J.; Qiao, J.; Chen, X.; Luo, S. Knockdown of LINC00665 inhibits proliferation and invasion of breast cancer via competitive binding of miR-3619-5p and inhibition of catenin beta 1. *Cell. Mol. Biol. Lett.* 2020, 25, 1–13.

9. Xia, L.; Chen, Y.-X.; Lian, J.-B. LINC00665 promotes HeLa cell proliferation, migration, invasion and epithelial-mesenchymal transition by activating the WNT-CTNNB1/β-catenin signaling pathway. *Sheng Li Xue Bao Acta Physiol. Sin.* 2021, 73, 233–243.

10. Zhao, X.; Weng, W.; Long, Y.; Pan, W.; Li, Z.; Sun, F. LINC00665/miR-9-5p/ATF1 is a novel axis involved in the progression of colorectal cancer. *Hum. Cell* 2020, 33, 1142–1154. [CrossRef]

11. Han, T.; Gao, M.; Wang, X.; Li, W.; Zhou, J.; Qu, Z.; Chen, Y. LINC00665 stabilized by TAF15 promotes cell proliferation, invasion, and metastasis by activating the TGF-β pathway in gastric cancer. *Cancer Cell Int.* 2021, 1113. [CrossRef][PubMed]

12. Wu, C.-L.; Shan, T.-D.; Han, Y.; Kong, Y.; Li, Y.-B.; Peng, X.-G.; Shang, L.; Wang, P.-G.; Li, L.-P. Long intergenic noncoding RNA 00665 promotes proliferation and inhibits apoptosis in colorectal cancer by regulating miR-126-5p. *Aging* 2021, 13, 13571. [CrossRef][PubMed]

13. Cai, Y.; Hao, M.; Chang, Y.; Liu, Y. LINC00665 enhances tumorigenicity of endometrial carcinoma by interacting with high mobility group AT-hook 1. *Cancer Cell Int.* 2021, 21, 1–10. [CrossRef][PubMed]

14. Yang, B.; Bai, Q.; Chen, H.; Su, K.; Gao, C. LINC00665 induces gastric cancer progression through activating Wnt signaling pathway. *J. Cell. Biochem.* 2020, 121, 2268–2276. [CrossRef][PubMed]

15. Qi, H.; Xiao, Z.; Wang, Y. Long non-coding RNA LINC00665 gastric cancer tumorigenesis by regulation miR-149-3p/RNF2 axis. *OncoTargets Ther.* 2019, 12, 6981. [CrossRef][PubMed]

16. Yue, C.; Yu, C.; Peng, R.; Wang, J.; Li, G.; Xu, L. LINC00665/miR-379-5p/GRP78 regulates cisplatin sensitivity in gastric cancer by modulating endoplasmic reticulum stress. *Cytotechnology 2021*, 1–10. [CrossRef]

17. Zhang, X.; Wu, J. LINC00665 promotes cell proliferation, invasion, and metastasis by activating the TGF-β pathway in gastric cancer. *Pathol.-Res. Pract.* 2021, 224, 153492. [CrossRef]

18. Ruan, X.; Zheng, J.; Liu, X.; Liu, Y.; Liu, M.; Ma, J.; He, Q.; Yang, C.; Wang, D.; Cai, H. IncRNA LINC00665 stabilized by TAF15 impeded the malignant biological behaviors of glioma cells via STA1-mediated mRNA degradation. *Mol. Ther.-Nucleic Acids* 2020, 20, 823–840. [CrossRef][PubMed]

19. Dai, Y.; Zhang, Y.; Hao, M.; Zhu, R. LINC00665 functions as a competitive endogenous RNA to regulate AGTR1 expression by sponging miR-34a-5p in glioma. *Onco. Rep.* 2021, 45, 1202–1212. [CrossRef]

20. Han, H.; Tian, Y.; Zhao, J.; Su, X. LINC00665 Targets miR-214-3p/MAPK1 Axis to Accelerate Hepatocellular Carcinoma Growth and Warburg Effect. *J. Oncol.* 2021, 2021. [CrossRef]

21. Shan, Y.; Li, P. Long intergenic non-protein coding RNA 665 regulates viability, apoptosis, and autophagy via the MiR-186-5p/MAP4K3 axis in hepatocellular carcinoma. *Yonsei Med. J.* 2019, 60, 842–853. [CrossRef][PubMed]

22. Ding, J.; Zhao, J.; Huan, L.; Liu, Y.; Qiao, Y.; Wang, Z.; Chen, Z.; Huang, S.; Zhao, Y.; He, X. Inflammation-Induced Long Intergenic Noncoding RNA (LINC00665) Increases Malignancy Through Activating the Double-Stranded RNA–Activated Protein Kinase/Nuclear Factor Kappa B Pathway in Hepatocellular Carcinoma. *Hepatology 2020*, 72, 1666–1681. [CrossRef][PubMed]

23. Wang, H.; Wang, L.; Zhang, S.; Xu, Z.; Zhang, G. Downregulation of LINC00665 confers decreased cell proliferation and invasion via the miR-138-5p/E2F3 signaling pathway in NSCLC. *Mol. Ther.-Nucleic Acids* 2020, 127, 110214. [CrossRef]

24. Wei, W.; Zhao, X.; Liu, J.; Zhang, Z. Downregulation of LINC00665 suppresses the progression of lung adenocarcinoma via regulating miR-181c-5p/ZIC2 axis. *Aging 2021*, 13, 17499. [CrossRef][PubMed]

25. Cong, Z.; Diao, Y.; Li, X.; Jiang, Z.; Xu, Y.; Zhou, H.; Qiang, Y.; Wu, H.; Shen, Y. Long non-coding RNA linc00665 interacts with YB-1 and promotes angiogenesis in lung adenocarcinoma. *Biochem. Biophys. Res. Commun.* 2020, 527, 545–552. [CrossRef][PubMed]

26. Cong, Z.; Diao, Y.; Xu, Y.; Li, X.; Jiang, Z.; Shao, C.; Ji, S.; Shen, Y.; De, W.; Qiang, Y. Long non-coding RNA linc00665 promotes lung adenocarcinoma progression and functions as ceRNA to regulate AKR1B10-ERK signaling by sponging miR-9. *Cell Death Dis.* 2019, 10, 1–15.

27. Wang, A.; Zhang, T.; Wei, W.; Wang, H.; Zhang, Z.; Yang, W.; Xia, W.; Mao, Q.; Xu, L.; Jiang, F. The Long Noncoding RNA LINC00665 facilitates c-myc transcriptional activity via the miR-195-5p MYCBP axis to promote progression of lung adenocarcinoma. *Front. Oncol.* 2021, 11, 2530. [CrossRef]

28. Liu, X.; Lu, X.; Zhen, F.; Jin, S.; Yu, T.; Zhu, Q.; Wang, W.; Xu, K.; Yao, J.; Guo, R. LINC00665 induces acquired resistance to gefitinib through recruiting EZH2 and activating PI3K/AKT pathway in NSCLC. *Mol. Ther.-Nucleic Acids* 2019, 16, 155–161. [CrossRef][PubMed]

29. Wang, X.; Wang, Y.; Lin, F.; Xu, M.; Zhao, X. Long non-coding RNA LINC00665 promotes melanoma cell growth and migration via regulating the miR-224-5p/VMA21 axis. *Exp. Dermatol.* 2020. [CrossRef]

30. Zhang, D.; Gu, G.; Chen, X.; Zha, G.; Yuan, Z.; Wu, Y. LINC00665 facilitates the progression of osteosarcoma via splicing miR-3619-5p. *Eur. Rev. Med. Pharmacol. Sci.* 2020, 24, 9852–9859. [CrossRef][PubMed]

31. Wang, L.; Song, X.; Yu, L.; Liu, B.; Ma, J.; Yang, W. LINC00665 Facilitates the Malignant Processes of Osteosarcoma by Increasing the RAP1B Expression via Sponging miR-708 and miR-142-5p. *Anal. Cell. Pathol.* 2021. [CrossRef][PubMed]
32. Xu, D.; Song, Q.; Liu, Y.; Chen, W.; Lu, L.; Xu, M.; Fang, X.; Zhao, W.; Zhou, H. LINC00665 promotes Ovarian Cancer progression through regulating the miRNA-34a-5p/E2F3 axis. *J. Cancer* 2021, 12, 1755. [CrossRef] [PubMed]
33. Chen, W.; Yu, Z.; Huang, W.; Yang, Y.; Wang, F.; Huang, H. LncRNA LINC00665 promotes prostate cancer progression via miR-1224-5p/SND1 axis. *OncoTargets Ther.* 2020, 13, 2527. [CrossRef] [PubMed]
34. Xue, P.; Yan, M.; Wang, K.; Gu, J.; Zhong, B.; Tu, C. Up-Regulation of LINC00665 Facilitates the Malignant Progression of Prostate Cancer by Epigenetically Silencing KLF2 Through EZH2 and LSD1. *Front. Oncol.* 2021, 11, 1165. [CrossRef] [PubMed]
35. Abuduer, M.; EZG, A. LINC00665 promotes the viability, migration and invasion of T cell acute lymphoblastic leukemia cells by targeting miR-101 via modulating PI3K/Akt pathway. *Tissue Cell* 2021, 71, 101579.
36. Li, Y.; Zong, R.; Zhang, H.-Y.; Meng, X.; Wu, F. Mechanism Analysis of LINC00665 and Its Peptides CIP2A-BP in Hepatocellular Carcinoma. *Front. Genet.* 2022, 13. [CrossRef]
37. Dai, H.; Sheng, X.; Sha, R.; Peng, J.; Yang, F.; Zhou, L.; Lin, Y.; Xu, Y.; Zhang, S.; Yin, W. Linc00665 can predict the response to cisplatin-paclitaxel neoadjuvant chemotherapy for breast cancer patients. *Front. Oncol.* 2021, 11. [CrossRef]
38. Wen, D.-Y.; Lin, P.; Pang, Y.-Y.; Chen, G.; He, Y.; Dang, Y.-W.; Yang, H. Expression of the long intergenic non-protein coding RNA 665 (LINC00665) gene and the cell cycle in hepatocellular carcinoma using the cancer genome atlas, the gene expression omnibus, and quantitative real-time polymerase chain reaction. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* 2018, 24, 2786. [CrossRef]
39. Huang, Y.; Zhong, L.; Nie, K.; Li, L.; Song, S.; Liu, F.; Li, P.; Cao, D.; Liu, Y. Identification of LINC00665-miR-let-7b-CCNA2 competing endogenous RNA network associated with prognosis of lung adenocarcinoma. *Sci. Rep.* 2021, 11, 4434. [CrossRef]
40. Gao, L.; Li, X.; Nie, X.; Guo, Q.; Liu, Q.; Qi, Y.; Liu, J.; Lin, B. Construction of novel mRNA-miRNA-lncRNA regulatory networks associated with prognosis of ovarian cancer. *J. Cancer* 2020, 11, 7057. [CrossRef]