

Review Article

Role of long non-coding RNA TP73-AS1 in cancer

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Cancer incidence rate has increased so much that it is the second leading cause of deaths worldwide after cardiovascular diseases. Sensitive and specific biomarkers are needed for an early diagnosis of cancer and in-time treatment. Recent studies have found that long non-coding RNAs (lncRNAs) participate in cancer tumorigenesis. LncRNA P73 antisense RNA 1T (TP73-AS1), also known as KIAA0495 and p53-dependent apoptosis modulator (PDAM), is located in human chromosomal band 1p36.32 and plays a crucial role in many different carcinomas. This review summarizes current findings on the role of TP73-AS1 and its signaling pathways in various cancers, including glioma, esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma (HCC), colorectal cancer (CRC), osteosarcoma, gastric cancer (GC), clear cell renal cell carcinoma (ccRCC), breast cancer (BC), bladder cancer, ovarian cancer, cholangiocarcinoma (CCA), lung cancer, and pancreatic cancer. Its aberrant expression generally correlates with clinicopathological characterization of patients. Moreover, TP73-AS1 regulates proliferation, migration, invasion, apoptosis, and chemoresistance cancer mechanisms, both *in vivo* and *in vitro*, through different signaling pathways. Therefore, TP73-AS1 may be considered as a marker for diagnosis and prognosis, also as a target for cancer treatment.

Introduction

Cancer incidence rate has increased so much that it is the second leading cause of deaths around the world after angiocardopathy [1]. In 2015, it was estimated that there would be approximately 4292000 new cancer cases and 2814000 cancer deaths in China [2]. Whereas, approximately 18.1 million new cancer cases and 9.6 million cancer deaths due to 36 different cancers occurred in 185 countries around the world in 2018 [3]. Moreover, 1762450 new cancer cases and 606880 cancer deaths are expected in 2019 in the United States [4]. With the increasing burden of cancer, sensitive biomarkers are needed to detect and diagnose cancer at an early stage, to reduce both morbidity and mortality during treatment. Long non-coding RNA (lncRNAs) are among the most sensitive and specific cancer biomarkers known.

lncRNAs are transcripts longer than 200 nucleotides transcribed by RNA polymerase II (RNA Pol II), but not translated into proteins [5]. In the past, they were considered as transcriptional noise; only 2% of the human genome is formed by protein-coding genes [6]. However, in recent years, an increasing number of studies have found that lncRNAs are involved in the regulation of the development of various diseases, especially cancer. The results indicated that lncRNAs implicated in epigenetic regulation, genomic instability, tumor progression, drug resistance, and gene therapy in cancer. Moreover, lncRNAs could be used as the diagnostic and prognostic biomarkers in human malignancies [7].

lncRNAs may work in different ways within the cell: (1) as scaffolds to collect and activate protein complexes [8]; (2) as enhancers for the recruitment of protein complexes, inducing chromosomal cyclization and the transcription of target genes [9]; (3) as decoys, capturing inhibitory complexes, thus preventing inhibition of gene expression [10]; (4) as guides for transcriptional repressors toward targeting genes, leading to transcriptional repression [11]; (5) as a competitive endogenous RNA (ceRNA) that functions as a microRNA (miRNA) sponge to avoid the degeneration of mRNA, thereby increasing the expression

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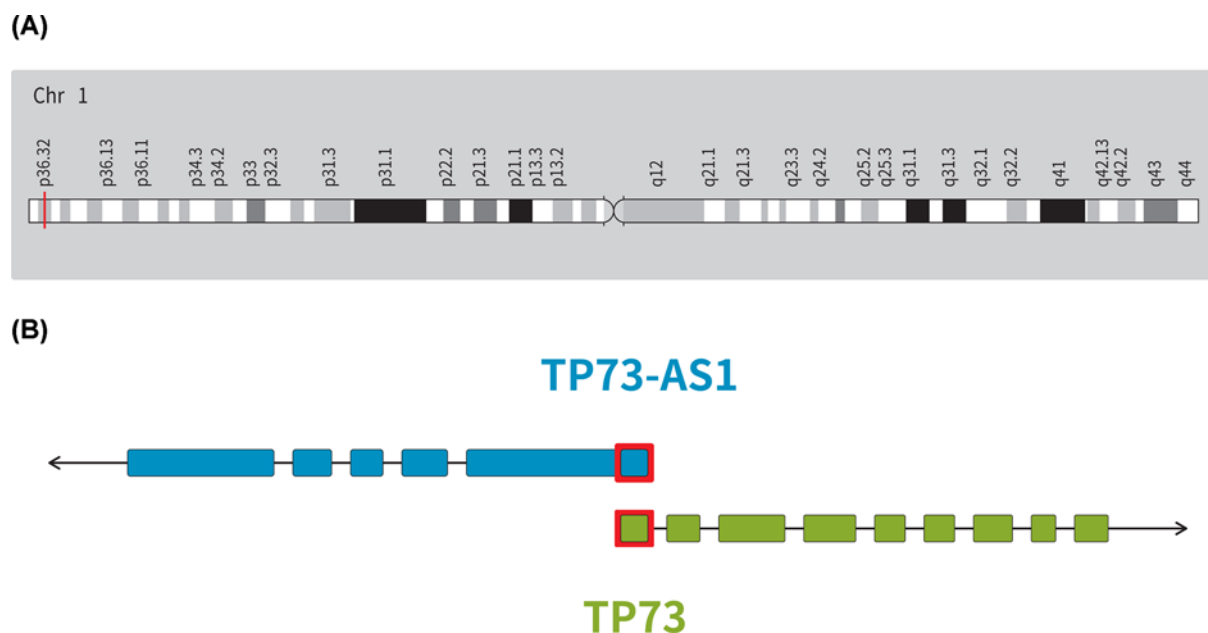


Figure 1. The location of TP73-AS1 on the chromosomal band and its relationship with TP73

(A) TP73-AS1 location and (B) schematic diagram of the sequence relationship between TP73-AS1 and *TP73* gene (black arrow for transcription direction, red border for overlapping region).

of specific transcripts [12]; (6) as transcription inhibitors through lncRNA–DNA binding, thus inducing the stalling of RNA Pol II [13].

LncRNA P73 antisense RNA 1T (TP73-AS1), also known as KIAA0495 or p53-dependent apoptosis modulator (PDAM), is located on the human chromosomal band 1p36.32 and has an approximately 216-bp overlap with the untranslated region of an adjacent gene, *TP73* (p73), that is transcribed from the opposite strand starting from its own promoter (Figure 1A). Genomic structure analysis has showed that TP73-AS1 contains six exons with a length of 4690 bp. TP73 is a member of the tumor protein 53 (TP53) family of transcription factors, it contains nine exons and 636 amino acids (Figure 1B) [14]. TP73-AS1 covers substantial portions of TP73, suggesting that TP73-AS1 may function by post-transcriptional regulation of TP73 gene expression [15]. Many years of research has shown that TP73-AS1 plays a key role in the development of cancer. For this review, we searched Pubmed and Web of Science databases using ‘TP73-AS1’, ‘KIAA0495’, and ‘PDAM’ as key words and then selected those articles associated with cancer. Based on selected articles, we summarize the role of TP73-AS1 in different cancers, including dysregulated expression, biological functions, related molecules, and associated clinical characteristics (Table 1).

TP73-AS1 in cancer

Glioma

TP73-AS1 was found to be down-regulated in oligodendroglioma; its low levels were related to an 1p/19q co-deletion and to tumor location. This implies that both the loss of chromosome 1p and epigenetic modifications were the main mechanisms leading to TP73-AS1 down-regulation. Moreover, it was confirmed that a knockdown of PDAM in glioma cells induced cisplatin resistance mainly because of the up-regulation of the anti-apoptotic gene, *BCL2-like 1* (*BCL2L1*) [16]. In contrast, a study by Xiao et al. [17] showed that the expression of TP73-AS1 was up-regulated in glioma tissue samples and that knocking down TP73-AS1 could suppress glioma cell proliferation and invasion. Mechanistically, TP73-AS1 might be acting as a ceRNA to regulate inhibitor of apoptosis stimulating protein of p53 (iASPP) expression through sponging miR-124. Furthermore, Zhang et al. [18] found that TP73-AS1 was significantly up-regulated in brain glioma clinical tissue specimens and cells, which was linked to tumor size, WHO stage, overall survival (OS), and poor prognosis. Silencing of TP73-AS1 inhibited glioma cell proliferation, invasion and high mobility group box 1 protein (HMGB1) protein expression. Further investigation revealed that TP73-AS1 competed with HMGB1 for miR-142 binding to modulate HMGB1 expression via an miR-142 sponge, which participated in the modulation of glioma cell proliferation and invasion. In summary, TP73-AS1 may be regarded as a novel therapeutic biomarker for glioma treatment, but further studies are needed to confirm this conclusion.

Table 1 The role of TP73-AS1 in human cancers/tumors

Cancer/tumor	Source of samples	Aberrant expression	Associated clinical features	Biological functions	Target molecules of TP73 AS1	REF
Glioma	Human patient/tumor samples and <i>in vitro</i> assays	Down-regulated	1p/19q co-deletion, tumor location in frontal lobe	Promote chemoresistance to cisplatin	BCL2, BCL2L1	[16]
		Up-regulated		Promote cell proliferation and invasion	miR-124/p53 (iASPP)	[17]
		Up-regulated	WHO stage, OS and tumor size	Promote cell proliferation and invasion	miR-142/HMGB1/RAGE	[18]
ESCC	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	TNM stage and tumor location	Promote proliferation and chemoresistance to 5-FU, cisplatin, inhibit apoptosis	BDH2	[19]
Hepatocellular carcinoma	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	TNM stage, tumor size, tumor nodule number and poor prognosis	Promote cell proliferation	miR-200a/HMGB1/RAGE	[20]
Colorectal cancer	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	Metastasis and clinical stage	Promote cell growth, proliferation, migration, and invasion	miR-194/TGF- α	[21]
		Down-regulated	Clinical stage, OS and DFS	Promote cell proliferation, inhibit apoptosis	miR-103/PTEM	[22]
Osteosarcoma	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	Clinical stage, tumor size, metastasis, OS, histological grade	Promote cell proliferation, migration and invasion		[23]
Gastric cancer	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	TNM stage, LNM, DM, OS, depth of invasion, and differentiation	Promoted cell proliferation, invasion, metastasis and inhibited apoptosis, decreased chemosensitivity to cisplatin	miR-142/Rac1	[24]
					miR-194-5p/SDAD1	[25]
					HMGB1/RAGE	[26]
Clear cell renal cell carcinoma	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	Tumor metastasis, tumor size, TNM stage and poor prognosis	Promote cell proliferation, invasion, inhibit apoptosis	EMT/Bcl-2/caspase-3	[27]
					KISS/EZH2, PI3K/Akt/mTOR	[28]
Breast cancer	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	Tumor size, LNM, TNM stage, and OS	Promote vasculogenic mimicry, cell proliferation, invasion and migration	miR-490-3p/TWIST1	[29]
					miR-200a/TFAM	[30]
					miR-200a/ZEB1	[31]
Bladder cancer	Human patient/tumor samples and <i>in vitro</i> assays	Down-regulated	Tumor stage, TNM stage, OS and DFS	Promote cell growth, cell cycle, migration and invasion, inhibit apoptosis	EMT	[32]
Ovarian cancer	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	Tumor size, FIGO stage and LNM	Promote cell proliferation, invasion and migration	MMP2, MMP9	[33]
Cholangiocarcinoma	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	Tumor size and TNM stage	Promote cell proliferation, migration and invasion, inhibit apoptosis		[34]
Non-small cell lung cancer	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	Tumor size, TNM stage, LNM and poor prognosis	Promote cell proliferation, tumor growth and cycle progression	miR-449a/EZH2	[35]
Lung adenocarcinoma	human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	TNM stage, tumor size, LNM and OS	Promote cell proliferation, migration, and invasion, repress apoptosis	PI3K/AKT	[36]
Pancreatic cancer	Human patient/tumor samples and <i>in vitro</i> assays	Up-regulated	TNM stage, LNM, OS	Promote migration and invasion	miR-141-3p/BDH2	[37]

Abbreviations: BCL2L1, BCL2-like 1; BDH2, butyrate dehydrogenase 2; DFS, disease-free survival; DM, distant metastasis; EMT, epithelial-to-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; EZH2, enhancer of zeste homolog 2; FIGO, Federation of Gynecology and Obstetrics; HMGB1, high mobility group box 1 protein; iASPP, inhibitor of apoptosis stimulating protein of p53; LNM, lymph node metastasis; MMP, matrix metalloproteinase; OS, overall survival; Rac1, Ras-related C3 toxin substrate 1; RAGE, receptor for advanced glycation end product; REF, reference; TFAM, mitochondrial transcription factor A; TNM, tumor lymph node metastasis; ZEB1, zinc finger E-box binding homeobox 1.

Esophageal squamous cell carcinoma

TP73-AS1 and butyrate dehydrogenase 2 (BDH2) were both up-regulated in esophageal squamous cell carcinoma (ESCC) tissue samples, while the expression of TP73-AS1 was obviously correlated both with tumor lymph node metastasis (TNM) stage and tumor location, BDH2 expression was only statistically associated with TNM stage. Silencing of TP73-AS1 induced ESCC apoptosis and inhibited proliferation, whereas overexpression of BDH2 could reverse this process via the caspase-3 pathway. Moreover, it was confirmed that silencing of TP73-AS1 reduced the average tumor size in mice. In addition, knocking down TP73-AS1 or BDH2 increased the chemosensitivity of ESCC to cisplatin and 5-FU [19]. These results indicate that lncRNA TP73-AS1 could be used as a novel target for ESCC treatments.

Hepatocellular carcinoma

TP73-AS1 was dramatically up-regulated in hepatocellular carcinoma (HCC) cell lines and tissues; up-regulation correlated with TNM stage, tumor size, tumor nodule number, OS, and poor prognosis. Additionally, silencing of TP73-AS1 inhibited HCC cell proliferation. It has also been demonstrated that TP73-AS1 suppresses miR-200a to facilitate HCC cell proliferation via the HMGB1/receptor for advanced glycation end product (RAGE) signaling pathway [20]. Thus, TP73-AS1 may be playing an important role as a modulator of tumor growth in HCC and could be regarded as a potential biomarker for HCC treatment.

Colorectal cancer

As expected, TP73-AS1 was found to be up-regulated in colorectal cancer (CRC) cell lines as well as in CRC tissue samples; its overexpression was linked to advanced clinical stages and metastasis. Furthermore, knocking down TP73-AS1 markedly depresses CRC cell proliferation, migration, and invasion *in vitro* as well as tumor growth *in vivo*. Mechanistically, TP73-AS1 modulated CRC tumorigenesis by regulating the expression of transforming growth factor α (TGF α), acting as a ceRNA to sponge miR-194 [21]. However, other studies showed that TP73-AS1 was down-regulated in CRC tissue samples and cell lines; here, low expression levels were correlated to TNM stage, prognosis, OS, and disease-free survival (DFS) of patients with CRC. Additionally, TP73-AS1 overexpression significantly promoted CRC apoptosis and inhibited cell growth. Functionally, TP73-AS1 facilitated CRC cell proliferation by inducing phosphate and tension homology deleted on chromosome ten (PTEN) expression by binding to miR-103 [22]. All these results have provided a foresight into the potential role of a TP73-AS1 signaling pathway mediating CRC.

Osteosarcoma

TP73-AS1 was found to be up-regulated in osteosarcoma cell lines and tissue samples; its overexpression was significantly linked to clinical stage, tumor size, metastasis, histological grade, OS, and poor prognosis. Moreover, a knockdown mutation of TP73-AS1 suppressed cell survival, migration, and invasion, inducing cell cycle arrest in osteosarcoma *in vitro* [23]. Mechanistically, TP73-AS1 silencing depressed osteosarcoma tumor growth *in vivo* as well as cell proliferation and invasion *in vitro* via regulating the miR-142/Ras-related C3 toxin substrate 1 (Rac1) pathway [24]. In conclusion, TP73-AS1 might be regarded as a carcinogenic lncRNA involved in the development of osteosarcoma, offering a novel therapeutic insight for osteosarcoma treatment.

Gastric cancer

Several studies have shown that TP73-AS1 is up-regulated in gastric cancer (GC) cell lines as well as in tissue samples; expression clearly correlated with TNM stages, lymph node metastasis, distant metastasis, depth of invasion, differentiation, and OS. Moreover, TP73-AS1 facilitated cell proliferation, invasion, and metastasis, while inhibited apoptosis and provoked a decreased chemosensitivity of GC cells to cisplatin. Mechanistically, TP73-AS1 modulated the tumor progression of GC cells through several signaling pathways, involving targeting miR-194-5p/SDAD1, down-regulation of HMGB1/RAGE, and regulating Bcl-2/caspase-3 or reversing epithelial-to-mesenchymal transition (EMT) [25–27]. Therefore, TP73-AS1 might function as a GC oncogenic factor and provide an effective prognostic/therapeutic target for patients with GC.

Clear cell renal cell carcinoma

TP73-AS1 was up-regulated in clear cell renal cell carcinoma (ccRCC) tumor cells compared with adjacent normal tissues. High expression levels were associated with TNM stage, tumor size, metastasis, and poor prognosis. Moreover, a TP73-AS1 knockdown suppressed cell proliferation and invasion, and facilitated apoptosis, whereas overexpression of TP73-AS1 reversed this progression. Furthermore, It has been shown that TP73-AS1 regulates cell proliferation

and apoptosis via the down-regulation of KISS1 expression and the PI3K/Akt/mTOR pathway, respectively [28]. Thus, TP73-AS1 plays a crucial role in the tumorigenesis of ccRCC and may offer a novel therapeutic biomarker for this disease.

Breast cancer

Both in breast cancer (BC) tissue samples and cell lines, TP73-AS1 has been found to be up-regulated and this overexpression has been related to several BC clinicopathologic characterizations, such as TNM stage, tumor size, lymph node metastasis, and oOS. In contrast, TP73-AS1 silencing suppressed vasculogenic mimicry, invasion, migration, and inhibited BC cell proliferation. Mechanistically, it was shown that several pathways participate in those biological functions altered after the knockdown of TP73-AS1. Targeting the miR490-3p/TWIST1 axis, regulating the expression of mitochondrial transcription factor A (TFAM) by depressing miR-200a, and forming the TP73-AS1/miR-200a/zinc finger E-box binding homeobox 1 (ZEB1) modulating loop in BC cells [29–31], are among these mechanisms. All these findings suggest that TP73-AS1 might provide an insight into BC management.

Bladder cancer

Studies have shown that TP73-AS1 is down-regulated in bladder cancer tissues and cell lines, which is significantly linked to tumor stage, TNM stage, OS, and progression-free survival (PFS). Mechanistically, the overexpression of TP73-AS1 could stimulate cell apoptosis and depress tumor growth, arrest cell cycle, and weaken cell invasion and migration *in vitro* by the suppression of EMT [32]. These results indicate that lncRNA TP73-AS1 might serve as a tumor suppressor since a low expression level contributes to the progression of bladder cancer, offering a prospective therapeutic target for the treatment of this disease.

Ovarian cancer

Expression studies have shown that TP73-AS1 is markedly up-regulated in tissue samples and cell lines of ovarian cancer. High expression levels have also been correlated with FIGO stage, tumor size, and lymph node metastasis. Silencing of TP73-AS1 inhibited cell proliferation, migration, and invasion, while overexpression stimulated progression *in vitro*. Furthermore, the knockdown of the TP73-AS1 gene depressed tumor growth in mice. Mechanistically, down-regulation of matrix metalloproteinase (MMP) 2 (*MMP2*) and 9 (*MMP9*) genes reduced the influence of TP73-AS1 overexpression in cell migration and invasion, but further investigation is still needed to unveil the mechanism of action of these genes in ovarian cancer progression [33]. Nevertheless, these results acknowledge the carcinogenic role of TP73-AS1 in ovarian cancer; TP73-AS1 might be a target in the search for new ways to fight against this disease.

Cholangiocarcinoma

When studying cholangiocarcinoma (CCA) tissue samples and cell lines, it was found that TP73-AS1 was up-regulated; this overexpression was markedly correlated both with TNM stage and tumor size. Meanwhile, a knockdown mutation of the TP73-AS1 gene inhibited tumor growth both *in vitro* and *in vivo*. In addition, knocking down TP73-AS1 promoted apoptosis through the activation of the caspase-3 and caspase-9 pathways. Furthermore, TP73-AS1 could potentially stimulate invasion and migration capacities of CCA cells [34]. In summary, the study concluded that TP73-AS1 might be a novel therapeutic biomarker for CCA treatment.

Lung cancer

TP73-AS1 was up-regulated in both cell lines and tissue samples of non-small cell lung cancer (NSCLC) and lung adenocarcinoma (LAD). Overexpression was linked to TNM stage, tumor size, lymph node metastasis, and poor prognosis. Additionally, a knockdown mutation of TP73-AS1 inhibited NSCLC cell proliferation *in vitro* and inhibited tumor growth and cycle development *in vivo* as well as *in vitro*. In LAD, TP73-AS1 facilitates cell proliferation, promotes cell migration and invasion, but represses apoptosis *in vitro*. Moreover, silencing TP73-AS1 depressed LAD tumor growth and metastasis *in vivo*. Mechanistically, the molecular pathway TP73-AS1/miR-449a/enhancer of zeste homolog 2 (*EZH2*) promotes NSCLC tumorigenesis via epigenetic modulation, whereas TP73-AS1 promotes the progression of LAD through the activation of the PI3K/AKT signaling pathway [35,36]. Collectively, TP73-AS1 might be a promising therapeutic and prognostic indicator both for LAD and NSCLC.

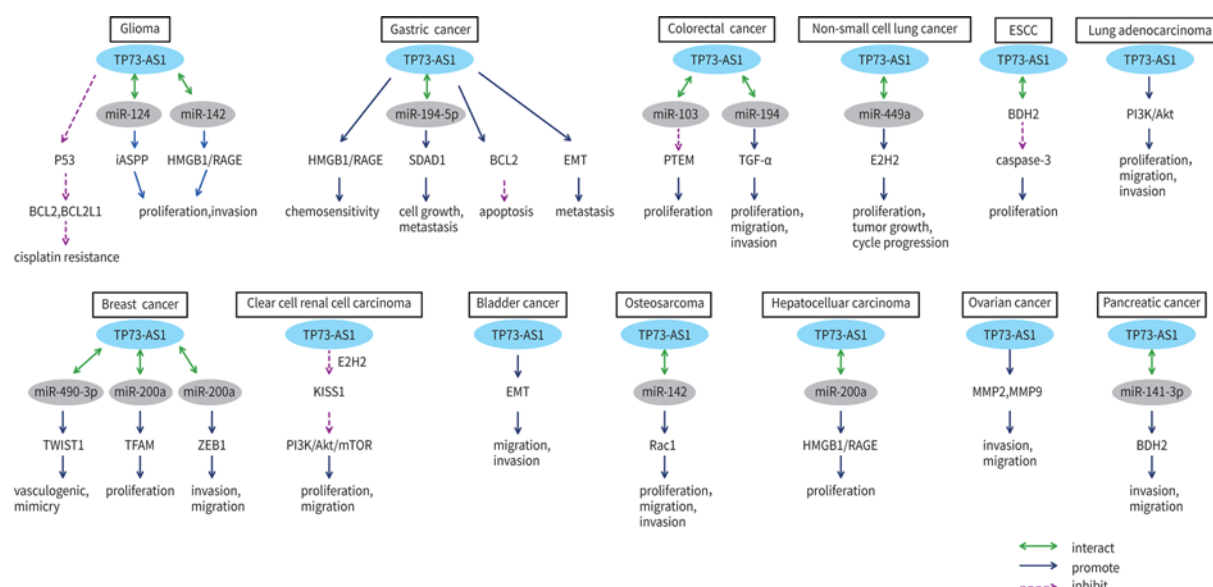


Figure 2. The molecular mechanisms of TP73-AS1 in various human cancers

Pancreatic cancer

Studies have demonstrated that TP73-AS1 is up-regulated in pancreatic cancer tissue and cells and that high expression levels are markedly related to the TNM stage and lymph node metastasis, as well as to OS. Silencing of TP73-AS1 suppresses pancreatic cancer migration and invasion. Furthermore, TP73-AS1 actively regulates BDH2 by modulating miR-141, which participates in pancreatic cancer progression [37]. In conclusion, TP73-AS1 could be regarded as a predictor and a novel target for the therapy and prognosis of pancreatic cancer.

Conclusions and future perspectives

LncRNAs play a crucial role in the progression of tumors. The recently discovered lncRNA TP73-AS1 is highly expressed in most tumor tissues and cell lines studied, except bladder cancer. Its abnormal expression is statistically correlated with clinicopathological characteristics of cancer, such as TNM stage, tumor size, lymph node metastasis, and prognosis. As a tumor promoter, lncRNA TP73-AS1 also participates in the regulation of a variety of cellular biological behaviors; it promotes cell proliferation, invasion, metastasis, chemotherapy sensitivity, and inhibition of apoptosis. In terms of the mechanisms involved in all these processes, it is known that TP73-AS1 often competes with miRNAs to regulate downstream signaling molecules, redirecting the cell metabolism to a completely different signaling pathway or directly acting on downstream targets leading to an abnormal expression of the *TP73-AS1* gene, activating a series of biological functions (Figures 2 and 3). Consequently, TP73-AS1 may be considered as a marker of both cancer diagnosis and prognosis, and as a target for the treatment of several cancers.

The function and molecular signaling pathways involving TP73-AS1 in various cancers have been studied thoroughly. In addition, methylated TP73-AS1 is frequently detected in cancer cell lines of multiple myeloma, but this methylation does not have a significant correlation with tumor pathogenesis and progression [38]. In retinoblastoma (Rb) tumor tissues, it was seen that TP73-AS1 was up-regulated while miR-139-3p was down-regulated; it is believed that lncRNA TP73-AS1 might down-regulate miR-139-3p directly to facilitate Rb cell proliferation [39]. In glioblastoma, TP73-AS1 was up-regulated in tumor tissues and its concentration was associated with a poor prognosis of patients. Furthermore, lncRNA TP73-AS1 facilitates tumor aggressiveness and temozolomide resistance in glioblastoma multiform cancer stem cell (gCSC) [40]. Moreover, Hu et al. [41] analyzed the expression of miR-194 and TP73-AS1 in a great number of healthy tissue samples and cancer cell lines and concluded that the TP73-AS1 and miR-941 duo represent an abnormal case of the exceedingly rapid progression of noncoding modulators managing cell proliferation, migration, and tumorigenesis.

However, there are still some existing problems among the previous studies. First, the function of TP73-AS1 has been well studied in many cancers, but studies on the function of this lncRNA in many common tumors, such as cervical cancer and prostate cancer, are still lacking. Second, the mechanism of the molecular signaling pathways in CCA are not clear. Third, the evaluation of TP73-AS1 in human cancers is very limited. Additionally, the precise

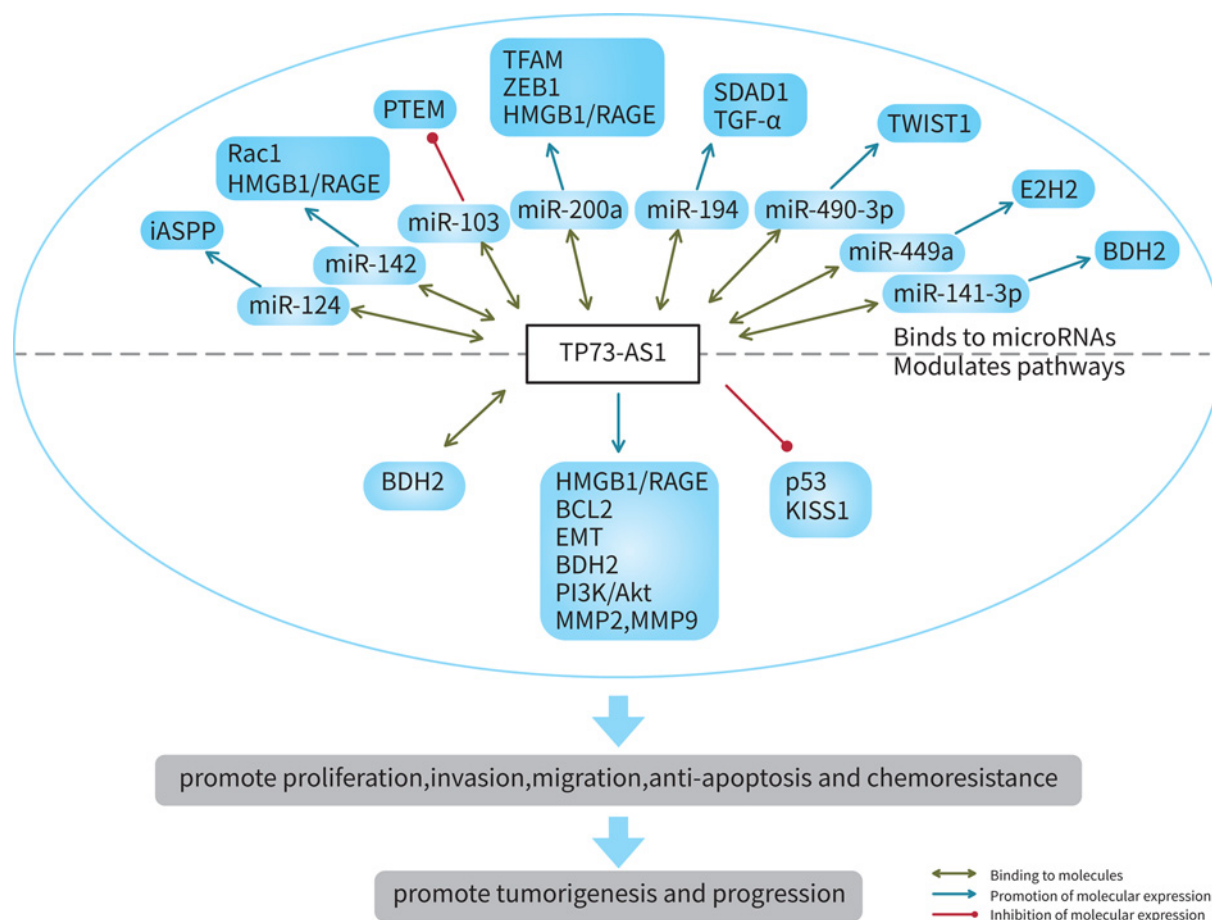


Figure 3. Main mechanisms of lncRNA TP3-AS1 in tumorigenesis and progression

mechanisms of this lncRNA contributing to drug resistance remain largely unknown. Noteworthy, studies on the expression of TP3-AS1 in glioma and CRC tissues have shown contradictory results, probably due to diverse functions of different splice variants of TP3-AS1 or sex-related differences between samples. Further researches should be done to find other methods of detection, identify the complex mechanism of regulating responses to chemotherapy, and a larger cohort of cancer samples should be included in the study so that the reasons for the inconsistent research results in the same tumor type might be identified and TP3-AS1 can be used as a biomarker for early diagnosis and therapy of cancer in the clinic.

Author Contribution

Caizhi Chen and Long Shu wrote the manuscript. Wen Zou was responsible for manuscript revision.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

BC, breast cancer; BDH2, butyrate dehydrogenase 2; CCA, cholangiocarcinoma; ccRCC, clear cell renal cell carcinoma; ceRNA, competitive endogenous RNA; CRC, colorectal cancer; EMT, epithelial-to-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HMGB1, high mobility group box 1 protein; LAD, lung adenocarcinoma; lncRNA, long non-coding RNA; miRNA, microRNA; NSCLC, non-small cell lung cancer; OS, overall survival; PDAM, p53-dependent apoptosis modulator; RAGE, receptor for advanced glycation end product; Rb, retinoblastoma;

RNA Pol II, RNA polymerase II; SDAD1, SDA1 domain containing 1; TNM, tumor lymph node metastasis; TP53, tumor protein 53; TP73-AS1, P73 antisense RNA 1T; TWIST1, twist family bHLH transcription factor 1; 5-FU, 5-Fluorouracil.

References

- Chen, W., Zheng, R., Zhang, S., Zeng, H., Xia, C., Zuo, T. et al. (2017) Cancer incidence and mortality in China, 2013. *Cancer Lett.* **401**, 63–71, <https://doi.org/10.1016/j.canlet.2017.04.024>
- Chen, W., Zheng, R., Baade, P.D., Zhang, S., Zeng, H., Bray, F. et al. (2016) Cancer statistics in China, 2015. *CA Cancer J. Clin.* **66**, 115–132
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **68**, 394–424
- Siegel, R.L., Miller, K.D. and Jemal, A. (2019) Cancer statistics, 2019. *CA Cancer J. Clin.* **69**, 7–34
- Quinn, J.J. and Chang, H.Y. (2016) Unique features of long non-coding RNA biogenesis and function. *Nat. Rev. Genet.* **17**, 47–62, <https://doi.org/10.1038/nrg.2015.10>
- Djebali, S., Davis, C.A., Merkel, A., Dobin, A., Lassmann, T., Mortazavi, A. et al. (2012) Landscape of transcription in human cells. *Nature* **489**, 101–108, <https://doi.org/10.1038/nature11233>
- Fatima, F. and Nawaz, M. (2017) Vesiculated long non-coding RNAs: offshore packages deciphering trans-regulation between cells, cancer progression and resistance to therapies. *Noncoding RNA* **3**, 10
- Yoon, J.H., Abdelmohsen, K., Kim, J., Yang, X., Martindale, J.L., Tominaga-Yamanaka, K. et al. (2013) Scaffold function of long non-coding RNA HOTAIR in protein ubiquitination. *Nat. Commun.* **4**, 2939, <https://doi.org/10.1038/ncomms3939>
- Orom, U.A., Derrien, T., Beringer, M., Gumireddy, K., Gardini, A., Bussotti, G. et al. (2010) Long noncoding RNAs with enhancer-like function in human cells. *Cell* **143**, 46–58, <https://doi.org/10.1016/j.cell.2010.09.001>
- Chiu, H.S., Somvanshi, S., Patel, E., Chen, T.W., Singh, V.P., Zorman, B. et al. (2018) Pan-cancer analysis of lncRNA regulation supports their targeting of cancer genes in each tumor context. *Cell. Rep.* **23**, 297–312.e212, <https://doi.org/10.1016/j.celrep.2018.03.064>
- Long, Y., Wang, X., Youmans, D.T. and Cech, T.R. (2017) How do lncRNAs regulate transcription? *Sci. Adv.* **3**, eaao2110, <https://doi.org/10.1126/sciadv.aao2110>
- Xiao, H., Tang, K., Liu, P., Chen, K., Hu, J., Zeng, J. et al. (2015) lncRNA MALAT1 functions as a competing endogenous RNA to regulate ZEB2 expression by sponging miR-200s in clear cell kidney carcinoma. *Oncotarget* **6**, 38005–38015, <https://doi.org/10.18632/oncotarget.5357>
- Latos, P.A., Pauler, F.M., Koerner, M.V., Senergin, H.B., Hudson, Q.J., Stocsits, R.R. et al. (2012) Airn transcriptional overlap, but not its lncRNA products, induces imprinted Igf2r silencing. *Science* **338**, 1469–1472, <https://doi.org/10.1126/science.1228110>
- Dotsch, V., Bernassola, F., Coutandin, D., Candi, E. and Melino, G. (2010) p63 and p73, the ancestors of p53. *Cold Spring Harb. Perspect. Biol.* **2**, a004887, <https://doi.org/10.1101/cshperspect.a004887>
- Yu, H., Xu, Q., Liu, F., Ye, X., Wang, J. and Meng, X. (2015) Identification and validation of long noncoding RNA biomarkers in human non-small-cell lung carcinomas. *J. Thorac. Oncol.* **10**, 645–654, <https://doi.org/10.1097/JTO.0000000000000470>
- Pang, J.C., Li, K.K., Lau, K.M., Ng, Y.L., Wong, J., Chung, N.Y. et al. (2010) KIAA0495/PDAM is frequently downregulated in oligodendroglial tumors and its knockdown by siRNA induces cisplatin resistance in glioma cells. *Brain Pathol.* **20**, 1021–1032, <https://doi.org/10.1111/j.1750-3639.2010.00405.x>
- Xiao, S., Wang, R., Wu, X., Liu, W. and Ma, S. (2018) The long noncoding RNA TP73-AS1 interacted with miR-124 to modulate glioma growth by targeting inhibitor of apoptosis-stimulating protein of p53. *DNA Cell Biol.* **37**, 117–125, <https://doi.org/10.1089/dna.2017.3941>
- Zhang, R., Jin, H. and Lou, F. (2018) The long non-coding RNA TP73-AS1 interacted with miR-142 to modulate brain glioma growth through HMGB1/RAGE pathway. *J. Cell. Biochem.* **119**, 3007–3016, <https://doi.org/10.1002/jcb.26021>
- Zang, W., Wang, T., Wang, Y., Chen, X., Du, Y., Sun, Q. et al. (2016) Knockdown of long non-coding RNA TP73-AS1 inhibits cell proliferation and induces apoptosis in esophageal squamous cell carcinoma. *Oncotarget* **7**, 19960–19974, <https://doi.org/10.18632/oncotarget.6963>
- Li, S., Huang, Y., Huang, Y., Fu, Y., Tang, D., Kang, R. et al. (2017) The long non-coding RNA TP73-AS1 modulates HCC cell proliferation through miR-200a-dependent HMGB1/RAGE regulation. *J. Exp. Clin. Cancer Res.* **36**, 51, <https://doi.org/10.1186/s13046-017-0519-z>
- Cai, Y., Yan, P., Zhang, G., Yang, W., Wang, H. and Cheng, X. (2018) Long non-coding RNA TP73-AS1 sponges miR-194 to promote colorectal cancer cell proliferation, migration and invasion via up-regulating TGF α . *Cancer Biomark.* **23**, 145–156, <https://doi.org/10.3233/CBM-181503>
- Jia, Z., Peng, J., Yang, Z., Chen, J., Liu, L., Luo, D. et al. (2019) Long non-coding RNA TP73AS1 promotes colorectal cancer proliferation by acting as a ceRNA for miR103 to regulate PTEN expression. *Gene* **685**, 222–229, <https://doi.org/10.1016/j.gene.2018.11.072>
- Chen, X., Zhou, Y., Liu, S., Zhang, D., Yang, X., Zhou, Q. et al. (2018) lncRNA TP73-AS1 predicts poor prognosis and functions as oncogenic lncRNA in osteosarcoma. *J. Cell. Biochem.* **120**, 2569–2575, <https://doi.org/10.1002/jcb.27556>
- Yang, G., Song, R., Wang, L. and Wu, X. (2018) Knockdown of long non-coding RNA TP73-AS1 inhibits osteosarcoma cell proliferation and invasion through sponging miR-142. *Biomed. Pharmacother.* **103**, 1238–1245, <https://doi.org/10.1016/j.biopha.2018.04.146>
- Ding, Z., Lan, H., Xu, R., Zhou, X. and Pan, Y. (2018) lncRNA TP73-AS1 accelerates tumor progression in gastric cancer through regulating miR-194-5p/SDAD1 axis. *Pathol. Res. Pract.* **214**, 1993–1999, <https://doi.org/10.1016/j.prp.2018.09.006>
- Peng, J. (2018) si-TP73-AS1 suppressed proliferation and increased the chemotherapeutic response of GC cells to cisplatin. *Oncol. Lett.* **16**, 3706–3714
- Zhang, W., Zhai, Y., Wang, W., Cao, M. and Ma, C. (2018) Enhanced expression of lncRNA TP73-AS1 predicts unfavorable prognosis for gastric cancer and promotes cell migration and invasion by induction of EMT. *Gene* **678**, 377–383, <https://doi.org/10.1016/j.gene.2018.08.055>
- Liu, G., Zhao, X., Zhou, J., Cheng, X., Ye, Z. and Ji, Z. (2018) lncRNA TP73-AS1 promotes cell proliferation and inhibits cell apoptosis in clear cell renal cell carcinoma through repressing KISS1 expression and inactivation of PI3K/Akt/mTOR signaling pathway. *Cell. Physiol. Biochem.* **48**, 371–384, <https://doi.org/10.1159/000491767>

- 29 Tao, W., Sun, W., Zhu, H. and Zhang, J. (2018) Knockdown of long non-coding RNA TP73-AS1 suppresses triple negative breast cancer cell vasculogenic mimicry by targeting miR-490-3p/TWIST1 axis. *Biochem. Biophys. Res. Commun.* **504**, 629–634, <https://doi.org/10.1016/j.bbrc.2018.08.122>
- 30 Yao, J., Xu, F., Zhang, D., Yi, W., Chen, X., Chen, G. et al. (2018) TP73-AS1 promotes breast cancer cell proliferation through miR-200a-mediated TFAM inhibition. *J. Cell. Biochem.* **119**, 680–690, <https://doi.org/10.1002/jcb.26231>
- 31 Zou, Q., Zhou, E., Xu, F., Zhang, D., Yi, W. and Yao, J. (2018) A TP73-AS1/miR-200a/ZEB1 regulating loop promotes breast cancer cell invasion and migration. *J. Cell. Biochem.* **119**, 2189–2199, <https://doi.org/10.1002/jcb.26380>
- 32 Tuo, Z., Zhang, J. and Xue, W. (2018) LncRNA TP73-AS1 predicts the prognosis of bladder cancer patients and functions as a suppressor for bladder cancer by EMT pathway. *Biochem. Biophys. Res. Commun.* **499**, 875–881, <https://doi.org/10.1016/j.bbrc.2018.04.010>
- 33 Wang, X., Yang, B., She, Y. and Ye, Y. (2018) The lncRNA TP73-AS1 promotes ovarian cancer cell proliferation and metastasis via modulation of MMP2 and MMP9. *J. Cell. Biochem.* **119**, 7790–7799, <https://doi.org/10.1002/jcb.27158>
- 34 Yao, Y., Sun, Y., Jiang, Y., Qu, L. and Xu, Y. (2018) Enhanced expression of lncRNA TP73-AS1 predicts adverse phenotypes for cholangiocarcinoma and exerts oncogenic properties *in vitro* and *in vivo*. *Biomed. Pharmacother.* **106**, 260–266, <https://doi.org/10.1016/j.biopha.2018.06.045>
- 35 Zhang, L., Fang, F. and He, X. (2018) Long noncoding RNA TP73-AS1 promotes non-small cell lung cancer progression by competitively sponging miR-449aEZH2. *Biomed. Pharmacother.* **104**, 705–711, <https://doi.org/10.1016/j.biopha.2018.05.089>
- 36 Liu, C., Ren, L., Deng, J. and Wang, S. (2019) LncRNA TP73-AS1 promoted the progression of lung adenocarcinoma via PI3KAKT pathway. *Biosci. Rep.* **39**, BSR20180999, <https://doi.org/10.1042/BSR20180999>
- 37 Cui, X.P., Wang, C.X., Wang, Z.Y., Li, J., Tan, Y.W., Gu, S.T. et al. (2019) LncRNA TP73-AS1 sponges miR-141-3p to promote the migration and invasion of pancreatic cancer cells through the up-regulation of BDH2. *Biosci. Rep.* **39**, BSR20181937, <https://doi.org/10.1042/BSR20181937>
- 38 Wong, K.Y., Li, Z., Zhang, X., Leung, G.K., Chan, G.C. and Chim, C.S. (2015) Epigenetic silencing of a long non-coding RNA KIAA0495 in multiple myeloma. *Mol. Cancer* **14**, 175, <https://doi.org/10.1186/s12943-015-0444-8>
- 39 Xia, Z., Yang, X., Wu, S., Feng, Z., Qu, L., Chen, X. et al. (2019) LncRNA TP73-AS1 downregulates miR-139-3p to promote retinoblastoma cell proliferation. *Biosci. Rep.* **39**, BSR20190475, <https://doi.org/10.1042/BSR20190475>
- 40 Mazor, G., Levin, L., Picard, D., Ahmadov, U., Caren, H., Borkhardt, A. et al. (2019) The lncRNA TP73-AS1 is linked to aggressiveness in glioblastoma and promotes temozolomide resistance in glioblastoma cancer stem cells. *Cell. Death Dis.* **10**, 246, <https://doi.org/10.1038/s41419-019-1477-5>
- 41 Hu, H., Liu, J.M., Hu, Z., Jiang, X., Yang, X., Li, J. et al. (2018) Recently evolved tumor suppressor transcript TP73-AS1 functions as sponge of human-specific miR-941. *Mol. Biol. Evol.* **35**, 1063–1077, <https://doi.org/10.1093/molbev/msy022>