A long non-coding RNA with important roles in the carcinogenesis

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Long non-coding RNAs are demonstrated to contribute to carcinogenesis. TMPO Antisense RNA 1 (TMPO-AS1) is an example of lncRNAs with crucial roles in this process. This lncRNA serves as a sponge for miR-320a, miR-383-5p, miR-329-3p, miR-126, miR-329, miR-199a-5p, miR-577, miR-4731-5p, miR-126-5p, miR-383-5p, let-7c-5p, let-7g-5p, miR-199a-5p, miR-200c, miR-204-3p, miR-126-5p, miR-383-5p, miR-498, miR-143-3p, miR-98-5p, miR-140 and miR-143. It can also affect activity of PI3K/Akt/mTOR pathway. The current review summarizes the role of TMPO-AS1 in the carcinogenesis and assessment of its potential as a marker for certain types of cancers.

KEYWORDS
lncRNA, TMPO-AS1, cancer, biomarker, expression

Introduction

Long non-coding RNAs (lncRNAs) are a class of RNAs with sizes more than 200 nt and some similar features with mRNAs, yet they do not encode large polypeptides. These transcripts have critical functions in the embryonic development (Kung et al., 2013), DNA damage response (Thapar, 2018; Ghafouri-Fard et al., 2021) and carcinogenic processes (Schmitt and Chang, 2017; Ghafouri-Fard et al., 2020). Based on the latest reports from GENCODE and FANTOM projects, there are approximately 18,000 and 28,000 lncRNA genes, respectively (Hon et al., 2017; Frankish et al., 2019). The role of these transcripts in the development of human disorders, particularly cancers is being elucidated in recent years. The vast majority of investigations are focused on identification of the impact of lncRNAs in the development of cancers, since cancers constitute a major cause of mortality. In fact, lncRNAs can affect all features of cancer development, including cell proliferation/differentiation, cell cycle transition, metastatic ability and invasiveness.
of cancer cells, epithelial-mesenchymal transition (EMT) and angiogenesis (Ghafouri-Fard et al., 2019; Ghafouri-Fard and Taheri, 2019).

TMPO Antisense RNA 1 (TMPO-AS1) is an example of lncRNAs with crucial roles in the carcinogenesis. Genomic location for this lncRNA is chr12:98,510,417–98,516,454 (GRCh38/hg38), minus strand. Expression of this lncRNA has been appraised in numerous types of cancers, revealing its important roles in the oncogenesis. The current review aims at identification of the impact of TMPO-AS1 in the carcinogenesis and evaluation of its potential as a marker for certain types of cancers.

**Cell line studies**

TMPO-AS1 has been noticeably upregulated in nasopharyngeal cancer cells. TMPO-AS1 silencing has restrained aggressive behaviors of these cells, while its overexpression has led to the opposite results. Mechanistically, TMPO-AS1 acts as a molecular sponge for miR-320a, leading to up-regulation of the mRNA target of miR-320a, i.e. SOX4. Taken together, TMPO-AS1/miR-320a/SOX4 axis has been shown to enhance progression of nasopharyngeal carcinoma (Xing et al., 2021).

This lncRNA has also been shown to be up-regulated in bladder cell lines and facilitate cell growth. Moreover, TMPO-AS1 could boost migration and invasive features of bladder cancer cells. Expression of TMPO-AS1 has been found to be induced by EBF transcription factor 1 (EBF1). This cytoplasmic lncRNA serves as a sponge for miR-98-5p. EBF1 has been verified to be a target of miR-98-5p whose expression is negatively correlated with expression of miR-98-5p. EBF1 up-regulation restores the suppressive role of TMPO-AS1 silencing in the development of bladder cancer (Luo et al., 2020). Another study in bladder cancer has confirmed the role of TMPO-AS1 in enhancement of cell proliferation, migratory potential, and invasion and suppression of cell. Mechanical studies have also shown that E2F1 up-regulates TMPO-AS1. In addition, TMPO-AS1 has been found to facilitate the interaction between E2F1 and OTUB1. This interaction leads to deubiquitination of E2F1 and its stabilization facilitating the role of TMPO-AS1 in induction of malignant phenotypes in bladder cancer. Further studies have confirmed that TMPO-AS1 induces growth of bladder cancer through an E2F1-dependent manner. This study has verified the importance of a TMPO-AS1/E2F1 positive regulatory circuit in the development of bladder cancer (Zhang et al., 2021).

TMPO-AS1 has also up-regulated in glioma cell lines parallel with down-regulation of miR-383-5p. TMPO-AS1 silencing has intimidated proliferation, migration and invasive abilities of glioma cells. Further experiments have shown that miR-383-5p is a target of TMPO-AS1 (Liu et al., 2020a).

Expression of TMPO-AS1 has also been elevated in hepatocellular carcinoma cell lines. TMPO-AS1 silencing has suppressed viability, migration aptitude and invasiveness of these cells. This lncRNA has mainly located in the cytoplasm of hepatocellular carcinoma cells, where it sponges miR-320a and facilitates up-regulation of SERBP1 (Wang et al., 2020). Another study in this type of cancer has shown that TMPO-AS1 boosts both proliferation and EMT through targeting the miR-126-3p/β-catenin axis (Huang et al., 2021) (Figure 1).

In osteosarcoma cells, TMPO-AS1/miR-329/E2F1 axis has been acknowledged as an importatnt regulator of cell proliferation and apoptosis. Inhibition of TMPO-AS1, overexpression of miR-329 and inhibition of E2F1 could defeat proliferation and invasiveness of osteosarcoma cells and enhance their apoptosis. Moreover, TMPO-AS1 could regulate EMT process in osteosarcoma cells via the mentioned axis (Liu et al., 2020b). Another study in this type of cancer has revealed the importance of TMPO-AS1/miR-199a-5p/WNT7B axis in the enhancemnet of tumorigenic properties (Cui and Zhao, 2020).

Likewise, Wei and his colleagues showed that E2F1-regulate TMPO-AS1 lncRNA affects lung cancer cell proliferation through controlling the miR-326/SOX12 pathway (Wei et al., 2020). They revealed that advanced clinical stage and poor prognosis in Lung adenocarcinoma (LUAD) were linked to increased TMPO-AS1 expression. Furthermore, reducing TMPO-AS1 expression could slow LUAD cell growth by stopping the cell cycle at the G0/G1 stage and triggering apoptosis. Similarly, Li et al. reported that inhibiting TMPO-AS1 through the miR-143-3p/CDK1 pathway causes increasing apoptosis process in Lung cancer cells (Li et al., 2021) (Figure 2).

Meanwhile, TMPO-AS1/miR-577/RAB14 (Yang et al., 2019) and TMPO-AS1/miR-143-3p/ZEB1 (Gang et al., 2020) axes have been identified as important regulator of malignant phenotyps of cervical cancer cells.

In breast cancer cell lines, TMPO-AS1 has been found to sponge for miR-4731-5p (Wang et al., 2021), miR-140-5p (Zhu et al., 2021) and miR-1179 (Ning et al., 2021) and up-regulate oncogenic targets of these miRNAs. Besides, TMPO-AS1 has been found to be over-expressed in endocrine therapy-resistant MCF-7 cells compared with estrogen inducable parental cells. Mechanistically, TMPO-AS1 enhances proliferative ability and viability of estrogen receptor (ESR)-positive breast cancer cells. Moreover, expression of this lncRNA is linked with the estrogen signaling cascade. TMPO-AS1 can also up-regulate expression of ESR1 through stabilizing its transcripts. Up-regulation of ESR1 transcript by this lncRNA has a crucial impact in the proliferation of ESR-positive breast cancer (Miéote et al., 2019).

In prostate cancer cells, TMPO-AS1 is mainly localized in the cytoplasm and directly down-regulated by androgen receptor. Up-regulation of TMPO-AS1 could increase cell proliferation through enhancing cell cycle progression (Huang et al., 2018) (Table 1). Figure 3 shows the expression pattern, targets and effects of TMPO-AS1 dysregulation in different types of cancer cells.
Animal studies

Results of studies in xenograft models of different cancer consistently support the oncogenic role of TMPO-AS1 (Table 2). All studies have confirmed that TMPO-AS1 silencing results in reduction of tumor burden in animal models. A single study in xenograft model of nasopharyngeal carcinoma SUNE1 cells has also verified the inhibitory effect of TMPO-AS1 knockdown on nasopharyngeal carcinoma cells growth. A notable reduction has been observed in tumor volume in the mice group injected with sh-TMPO-AS1. Based on the immunohistochemistry staining and qRT-PCR assays, substantial suppression in the expression of SOX4 and significant increase in miR-320a expression have been observed in mice injected with sh-TMPO-AS1-transfected cells. In vivo rescue experiments have also confirmed the sponging effect of TMPO-AS1 on miR-320a. miR-320a mimics-transfected SNUE1 cells have exhibited lower in vivo growth. Besides, TMPO-AS1 over-expression has reduced miR-320a levels in tumor tissues elevated by miR-320a mimics transfection (Xing et al., 2021).

Inoculation of stably transfected RT4 bladder cancer cells into nude mice has also verified that TMPO-AS1 can enhance bladder cancer growth through E2F1 in vivo. TMPO-AS1 silencing has substantially suppressed tumor growth, while up-regulation of E2F1 has eliminated the inhibitory effects on tumor growth resulted from TMPO-AS1 silencing. Besides, the immunohistochemistry staining has shown that TMPO-AS1 silencing results in a considerable reduction in Ki-67 and E2F1 levels and a prominent increase in caspase-3 expression (Zhang et al., 2021). Additionally, TMPO-AS1 has been shown to enhance proliferative ability and viability of ESR-positive breast cancer cells in animal models (Mitobe et al., 2019). Moreover, its silencing can decrease hormone-refractory tumor growth (Mitobe et al., 2019). In addition, experiments in animal models of ovarian cancer have confirmed a significant decrease in the angiogenic potential following TMPO-AS1 silencing (Zhao et al., 2020a). Finally, in animal models of esophageal squamous cell carcinoma, TMPO-AS1 silencing can suppress lymph node metastasis (Luo et al., 2022).

Studies in clinical samples

Expression of TMPO-AS1 has been found to be elevated in all kinds of examined cancerous clinical samples (Table 3). In hepatocellular carcinoma samples, over-expression of TMPO-AS1 has been related to advanced stages and worse prognosis (Wang et al., 2020). Over-expression of TMPO-AS1 has also been related to large tumor size, lymphatic metastasis, and advanced stage in another study on patients with hepatocellular carcinoma (Guo and Wang, 2020). Meanwhile,
portal vein tumor thrombosis has been another feature that has been associated with up-regulation of this lncRNA in hepatocellular carcinoma (Huang et al., 2021). In silico analysis of TCGA database and expression assays in clinical specimens of bladder cancer have confirmed up-regulation of TMPO-AS1 in bladder cancer tissues compared with normal bladder samples. Notably, worse survival has been reported for patients with over-expression of this lncRNA. Moreover, up-regulation of TMPO-AS1 has been correlated with muscle invasiveness and advance TNM stage in these patients (He et al., 2020). RNA-sequencing data of breast cancer samples has shown correlation between TMPO-AS1 level and proliferative biomarkers. Moreover, TMPO-AS1 positivity has been significantly correlated with poor prognosis of patients with this type of cancer (Mitobe et al., 2019). TMPO-AS1 has also been suggested to be a valuable diagnostic and prognostic marker for prostate cancer, since its up-regulation has been associated with poorer prognosis of patients with prostate cancer. In silico studies have predicated associations between TMPO-AS1 and a number of biological processes participating in the progression of prostate cancer (Huang et al., 2018). Similar to other types of cancer, up-regulation of TMPO-AS1 has been associated with lymph node involvement and distant metastasis in patients with colorectal cancer (Mohammadrezakhani et al., 2020).
| Tumor type                        | Targets/Regulators and signaling pathways | Cell line                     | Function | References                        |
|----------------------------------|-------------------------------------------|-------------------------------|----------|-----------------------------------|
| Nasopharyngeal carcinoma         | miR-320a/ SOX4                            | SUNE-1 and C666-1             | △TMPO-AS1 ↓ cell growth ↓ invasion | Xing et al. (2021)                 |
| Bladder cancer                   | EBF1                                      | SV: HUC-1, T24 UMUC3, 5637, J82 | △ TMPO-AS1 ↓ cell growth ↓ invasion | Luo et al. (2020)                  |
|                                  | OTUB1/E2F1                                | 5637, T24, and RT4, BIU87, EJ | △ TMPO-AS1 ↓ cell growth ↓ invasion | Zhang et al. (2021)                |
| Glioma                           | miR-383-5p                                | NHA, U251, A172, LN229        | △ TMPO-AS1 ↓ cell growth ↓ invasion | Liu et al. (2020a)                 |
| Hepatocellular carcinoma         | miR-320a/ SERBP1                          | HepG2, SNU-387, HCCLM3, SMMC-7721, Huh7, LO2 | △ TMPO-AS1 ↓ cell growth ↓ invasion | Wang et al. (2020)                 |
|                                  | miR-329-3p/FOXK1                          | THLE-3, Huh7, Hep3B, LM3      | △ TMPO-AS1 ↓ cell growth ↓ invasion | Guo and Wang, (2020)              |
|                                  | miR-126-3p/LRP6/β-catenin axis            | Hep3B, Huh7, SMMC-7721, Bel-7402, SK-Hep-1, LM9, L-02 | △ TMPO-AS1 ↓ cell growth ↓ invasion | Huang et al. (2021)               |
| Osteosarcoma                     | miR-329/E2F1                              | Saos-2, (HCOs)                | △ PMPO-AS1 ↓ cell growth ↓ invasion | Liu et al. (2020b)                 |
|                                  | miR-199a-5p/WNT7B                         | U2OS, MG-63, SAOS-2 143B, FOB1.19 | △ TMPO-AS1 ↓ cell growth ↓ invasion | Cui and Zhao, (2020)              |
| Cervical cancer                  | miR-577/RAB14                             | HeLa, C-33a, SiHa, HCC94      | △ TMPO-AS1 ↓ cell growth ↓ invasion | Yang et al. (2019)                |
|                                  | miR-143-3p/ZEB1                           | HeLa, SiHa, CaSki, C-33A      | △ TMPO-AS1 ↓ cell growth ↓ invasion | Gang et al. (2020)                |
| Breast cancer                    | miR-4731-5p                              | Hs-578T, MCF7, ZR-75–30, HCC1937 | △ TMPO-AS1 ↓ cell growth ↓ invasion | Wang et al. (2021)                |
|                                  | miR-140-5p                                | MCF7, T47D, MDA-MB-231, SKBR3 | △ TMPO-AS1 ↓ cell growth ↓ invasion | Zhu et al. (2021)                 |
|                                  | miR-1179/TRIM37                           | MDA-MB-231, MCF7              | △ TMPO-AS1 ↓ cell growth ↓ invasion | Ning et al. (2021)                |
| Triple negative breast cancer    | E2F/TGF-β                                | MDA-MB-231 and MDA-MB-468     | △ TMPO-AS1 ↓ cell growth ↓ invasion | Mitsobe et al. (2020)             |
| Lung Carcinoma                   | miR-143-3p                               | H1299, A549, 95D, H125        | △ TMPO-AS1 ↓ cell growth ↓ invasion | Li et al. (2021)                  |

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TABLE 1 (Continued) Expression pattern of TMPO-AS1 in cancer cell lines (Δ: knock-down or deletion, DOC: docetaxel).

| Tumor type          | Targets/Regulators and signaling pathways | Cell line | Function | References |
|---------------------|-------------------------------------------|-----------|----------|------------|
| Lung adenocarcinoma | miR-326 /SOX12/E2F1                        | HCC827, A549, H838, H1299, SK-LU-1, H23 | Δ TMPO-AS1 cell cycle arrest | Wei et al. (2020) |
|                     | miR-383-5p                                | A549, H1299, H1975, H226, PC9, SPC-A1,6HBE | Δ TMPO-AS1 proliferation, invasion | Mu et al. (2020) |
|                     | let-7c-5p/STRIP2                          | h1650, A549, SPC-A1, and H1975, BEAS-2B | Δ TMPO-AS1/let-7c-5p/STRIP2 Adverse outcomes | Wang et al. (2022) |
| Retinoblastoma      | miR-199a-5p/HIF-1-1s                      | HXO-RB44, SO-Rb50 | TMPO-AS1 proliferation | Peng et al. (2020) |
| Ovarian cancer      | LCN2/E2F6                                 | SKOV3, A2780, HO-8910, OVCA2-3, CAOV3 | Δ TMPO-AS1 proliferation, migration, invasion | Zhao et al. (2020a) |
|                     | miR-200c /TMEFF2/PJ3K/Akt                 | HOSEpiC, SKOV3 | Δ TMPO-AS1 invasion, drug resistance to 5-FU | Li et al. (2020a) |
| Non-small cell lung cancer | miR-204-3p/ERBB2                              | BEAS-2B, A549, H226, H522 and H1299 | Δ TMPO-AS1 proliferation, migration, invasion | Yu et al. (2020) |
|                     | TMPO                                      | 95D, A549, H1299, H460, H1975, BEAS-2B | Δ TMPO-AS1 growth, invasion | Qin et al. (2019) |
| Gastric cancer      | miR-126-5p /PI3K/Akt/mTOR pathway/BRCC3   | MKN-45, AGS, SGC-7901 SNU-16, GE1 | Δ TMPO-AS1 proliferation, migration, angiogenesis | Hu et al. (2021) |
|                     | miR-140-5p/SOX4                           | GC-27, SGC-7901, BGC-823 AGS, GE1 | Δ TMPO-AS1 proliferation, migration, invasion | Sun and Han, (2020) |
| Cholangiocarcinoma  | let-7g-5p/HMGA1                           | HCCC9810, HuCCT1, RBE HIBEC | Δ TMPO-AS1 proliferation, apoptosis | Chang and Yao, (2022) |
| Pancreatic carcinoma| miR-383-5p/SOX11                          | HPDE6-C7, SW 1990 PANC-1 | Δ TMPO-AS1 migration, invasion | Xue et al. (2021) |
| Thyroid cancer      | miR-498                                   | TPC-1, HHI-4, A-PTC, CUTCS, nthy-ori3-1 | Δ TMPO-AS1 migration, invasion | Li et al. (2020b) |
| Colorectal cancer   | miR-143-3p                                | SW480, HCT15, SW1116, HCT116, NCM460 | Δ TMPO-AS1 proliferation, migration, invasion, EMT | Zhao et al. (2020b) |
|                     | miR-98-5p/BCAT1                           | HCT15, HT-29, HCT116, SW116, FHC | Δ TMPO-AS1 proliferation, apoptosis | Ye et al. (2022) |
| Gallbladder carcinoma| miR-1179/E2F2 axis                       | GC-996, GBC-SD, EH-GB1, NOZ, H69 | Δ TMPO-AS1 proliferation, migration, invasion | Sui and Sui, (2021) |

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TABLE 1 (Continued) Expression pattern of TMPO-AS1 in cancer cell lines (Δ: knock-down or deletion, DOC: docetaxel).

| Tumor type                      | Targets/Regulators and signaling pathways | Cell line                           | Function                      | References          |
|---------------------------------|-------------------------------------------|--------------------------------------|------------------------------|---------------------|
| Prostate cancer                 | AR                                        | LNCaP, DU145, 22Rv1, PC-3, WPMY       | ↑ TMPO-AS1 proliferation      | Huang et al. (2018) |
|                                 |                                            |                                      | ↓ apoptosis                  |                     |
| Esophageal cancer               | miR-498                                   | EC109 and KYSE70                      | ↑ TMPO-AS1                   | Gao et al. (2020)   |
|                                 |                                            |                                      | propofol effect on EMT       |                     |
| Esophageal squamous cell carcinoma | FUS, p300                                | Het-1A, NE-1, HEK293T, KYSE30, KYSE150, KYSE180, KYSE410, KYSE510, KYSE520 | ΔTMPO-AS1 proliferation     | Luo et al. (2022)   |
|                                 |                                            |                                      | migration                    |                     |
|                                 |                                            |                                      | invasion                     |                     |
| Endometrial cancer              | miR-140 & miR-143/GLUT1                   | Ishikawa and HHUA                    | ΔTMPO-AS1                    | Dong et al. (2022)  |
|                                 |                                            |                                      | Glycolysis                   |                     |
|                                 |                                            |                                      | resistance to Paclitaxel therapy |                     |

FIGURE 3
Signaling Pathways underling the role of TMPO-AS1 in Various Cancers.
Diagnostic role of TMPO-AS1 has been assessed in osteosarcoma and colorectal cancer, yielding better performance in the former type of cancer (Table 4).

**Concluding remarks**

TMPO-AS1 is an lncRNA with crucial roles in the carcinogenic processes. The best appreciated route of participation of TMPO-AS1 in these processes is its function as a molecular sponge for miRNAs. This lncRNA serves as a sponge for miR-383-5p, miR-320a, miR-329-3p, miR-126, miR-329, miR-199a-5p, miR-577, miR-4731-5p, miR-140-5p, miR-1179, miR-143-3p, miR-326, miR-383-5p, let-7c-5p, let-7g-5p, miR-199a-5p, miR-200c, miR-204-3p, miR-126-5p, miR-383-5p, miR-498, miR-143-3p, miR-98-5p, miR-140 and miR-143. Most of these miRNAs have anti-cancer effects through modulation of cell apoptosis, survival and differentiation. Thus, TMPO-AS1 has several routes of actions. Each of TMPO-AS1/miRNA axes has the potential to be used as diagnostic marker or therapeutic target. However, those being dysregulated in more than one type of cancer seem to be more appropriate, since they can be used in different types of cancers. Moreover, TMPO-AS1/miRNA/mRNA axes having specific roles in a certain type of cancer can be used for diagnostic marker for this type of cancer, particularly in the follow-up of patients after conduction of therapeutic modalities.

Several studies have reported regulatory role of TMPO-AS1 on PI3K/Akt/mTOR pathway. Based on the importance of this pathway in cancer progression and availability of targeted
| Tumor type                  | Samples | Expression of TMPO-AS1 or other genes (tumor vs Normal) | Cancer/TNM stage | Kaplan-meier analysis (impact of TMPO-AS1 dysregulation) | Univariate/Multivariate Cox regression | Association of TMPO-AS1 expression with clinicopathologic features | Related pathways/targets | References |
|---------------------------|---------|--------------------------------------------------------|------------------|------------------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------|--------------------------|------------|
| Nasopharyngeal carcinoma (NPC) | 45 NPC tissue samples and 22 normal nasopharynx tissues | Upregulated (which sponges miR320-a) | I-IV | - | - | Associated with metastasis and advanced clinical stage | miR-320a/SOX4 axis | Xing et al. (2021) |
| Bladder cancer (BC) | 40 fresh cancer tissues and PANTs | Upregulated (which sponges miR-98-5p) | T1-T4 | Poor OS | - | - | - | EBF1 | Luo et al. (2020) |
| 6 cancerous and PANTs | Upregulated | I-IV | Poor OS | - | - | Associated with recurrence of BC + advanced tumor stage | OTUB1/E2F1 | Zhang et al. (2021) |
| Hepatocellular carcinoma (HCC) | 42 HCC samples and PANTs | Upregulated | I-IV | Poor OS | - | - | - | miR-320a/SERP1 axis | Wang et al. (2020) |
| 48 HCC samples and PANTs | Upregulated | I-IV | Poor OS | - | - | Associated with Tumor size, Lymphatic metastasis, TNM | miR-32-3p/FOXK1 axis | Guo and Wang, (2020) |
| 53 HCC samples and PANTs | Upregulated | - | Poor OS | - | - | Associated with TNM stage, portal vein tumor thrombosis | miR-126-3p/LRP6/β-catenin axis | Huang et al. (2021) |
| Osteosarcoma | 51 samples of cancer tissues and PANTs | Upregulated | - | Poor OS | - | - | - | miR-329/E2F1 axis | Liu et al. (2020b) |
| 56 cancer tissues and PANTs | Upregulated (which sponges miR-199a-5p) | - | - | - | - | - | miR-199a-5p/WNT7B axis | Cui and Zhao, (2020) |
| Breast cancer | 22 cancer tissues and PANTs | Upregulated (which sponges miR-4731-5p) | I-IV | Poor OS | - | - | - | miR-4731-5p | Wang et al. (2021) |
| 40 Breast cancer tissues+ 15 healthy controls | Upregulated (which sponges miR-140-5p) | - | Poor OS | - | - | - | miR-140-5p | Zhu et al. (2021) |
| 115 breast cancer tissues | Upregulation resulted in poor prognosis | I-III | Poor OS | - | - | Prognostic factor for OS and distant disease-free survival | Associated with stage, pathological T factor, histological grade and HER2 status | ESR1 | Mitobe et al. (2019) |
| Laryngeal squamous cell carcinoma (LSCC) | 187 cancer tissues and PANTs | Upregulated | I-IV | Poor OS | Independent prognostic biomarker for LSCC patients | - | Associated with clinical stage, LNM | - | Zhang et al., 19922020 |
| Lung Carcinoma (LC) | 50 cancer tissues and PANTs | Upregulated | - | Poor OS | - | - | - | miR-143-3p | Li et al. (2021) |

(Continued on following page)
| Tumor type   | Samples                                                                 | Expression of TMPO-AS1 or other genes (tumor vs Normal) | Cancer/TNM stage | Kaplan-meier analysis (impact of TMPO-AS1 dysregulation) | Univariate/ Multivariate cox regression | Association of TMPO-AS1 expression with clinicopathologic features | Related pathways/targets | References |
|-------------|-------------------------------------------------------------------------|--------------------------------------------------------|------------------|-----------------------------------------------------------|----------------------------------------|---------------------------------------------------------------|--------------------------|------------|
| Lung adenocarcinoma (LUAD) | 25 cancer tissues and PANTs + GEPIA | Upregulated | I-IV | Poor OS | - | Associated with TNM stage, LMN and high risk of mortality | miR-326/SOX12/ E2F1 axis | Wei et al. (2020) |
|             | 6 cancer tissues and PANTs | Upregulated | - | Poor OS | - | - | miR-383-5p | Mu et al. (2020) |
| Retinoblastoma | tissue samples from 33 children + normal retinal pigment epithelial tissue | Upregulated | A-E (Based on tumor progression) | - | - | - | HIF-1α/miR-199a-5p | Peng et al. (2020) |
| Cholangiocarcinoma | 36 cancer tissues and PANTs | Upregulated | I-IV | - | - | - | let-7g-5p/HMG1 | Chang and Yao, (2022) |
| Ovarian cancer | 86 cancer tissues and PANTs (promotes LCN2) | Upregulated | I-IV/G1-G3 (Fuhrman) | Poor OS | - | Associated with TNM stage, Fuhrman grade and tumor size | LCN2/E2F6 | Zhao et al. (2020a) |
| Non-small cell lung cancer | 30 cancer tissues and PANTs | Upregulated (which Sponges miR-204-3p) | - | Poor OS | - | - | miR-204-3p/ ERBB2 axis | Yu et al. (2020) |
|             | 40 cancer tissues and PANTs | Upregulated | I-III | Poor OS | Lymph node metastasis is an independent prognostic factor | Associated with TNM stage and LMN | TMPO | Qin et al. (2019) |
| Gastric cancer | 70 cancer tissues and PANTs | Upregulated (which Sponges miR-126-5p) | I-IV | Poor OS | - | Associated with TNM stage and LMN | miR-126-5p/PI3K/ Akt/mTOR pathway/BRCC3 | Hu et al. (2021) |
|             | 105 cancer tissues and PANTs | Upregulated (which Sponges miR-140-5p) | I-IV | Poor OS | - | Associated with larger tumor size and advanced TNM stage | miR-140-5p/SOX4 axis | Sun and Han, (2020) |
| Pancreatic carcinoma | 38 cancer tissues and PANTs | Upregulated | - | - | - | - | miR-383-5p/SOX11 axis | Xue et al. (2021) |
| Thyroid cancer | 40 cancer tissues and PANTs | Upregulated | - | - | - | - | miR-498 | Li et al. (2020b) |
| Gallbladder carcinoma (GBC) | 30 cancer tissues and PANTs | Upregulated | I-IV | Poor OS | Poor OS | - | miR-1179/E2F2 axis | Sui and Sui, (2021) |

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### TABLE 4 Diagnostic value of TMPO-AS1 in cancers.

| Tumor type         | Samples                           | Distinguish between                          | Area under curve | Sensitivity (%) | Specificity (%) | References                  |
|--------------------|-----------------------------------|----------------------------------------------|------------------|-----------------|----------------|----------------------------|
| Osteosarcoma       | 51 pairs of cancer tissues and adjacent tissues | Osteosarcoma tissues vs control tissues        | 0.8              | 70.59           | 82.35          | Liu et al. (2020b)          |
| Colorectal cancer  | 21 tumor samples and 21 margin samples | Tumor vs margin samples                       | 0.6973           |                 |                | Mohammadrezakhani et al. (2020) |
therapies against this pathway (Alzahrani, 2019), therapeutic modalities that affect expression of TMPO-AS1 are promising strategies for enhancement of the effects of PI3K/Akt/mTOR-targeting modalities.

Although dysregulation of TMPO-AS1 has been described in several cancers, diagnostic role of this lncRNA has only been assessed in two types of cancerous tissues versus non-cancerous tissues. Moreover, its application as a diagnostic marker in the peripheral blood has not been evaluated. Since assessment of expression profile of lncRNAs in the peripheral blood can facilitate identification of novel strategies for non-invasive detection of malignant conditions, further studies should evaluate expression of TMPO-AS1 in different stages of cancer progression to find its potential as early diagnostic marker and its relevance with progression of cancer. Based on the heterogeneity of expression profiles in the cancerous samples, a more applicable strategy is identification of panels of lncRNAs which can discriminate cancer patients from healthy controls with higher efficacy.

Several experiments have shown that TMPO-AS1 silencing can attenuate malignant behavior of cancer cells in cultures and in xenograft models of cancer. Thus, TMPO-AS1-targeting strategies have the potential to be used as therapeutic modalities for cancer treatment. Therefore, future investigations should find effective methods for specific delivery of anti-TMPO-AS1 modalities to cancer cells and evaluate their safety and efficacy in suppression of tumor growth in clinical settings.

Finally, preliminary studies have shown that TMPO-AS1 silencing can enhance sensitivity to paclitaxel (Dong et al., 2022) and docetaxel (Ning et al., 2021) in endometrial and breast cancers, respectively. Thus, targeted therapies against this lncRNA are promising strategies in defeating resistance breast cancers, respectively. Thus, targeted therapies against this lncRNA are promising strategies in defeating resistance breast cancers, respectively. Therefore, future investigations should find effective methods for specific delivery of anti-TMPO-AS1 modalities to cancer cells and evaluate their safety and efficacy in suppression of tumor growth in clinical settings.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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