A Review on the Role of SPRY4-IT1 in the Carcinogenesis

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Sprouty RTK signaling antagonist 4-intronic transcript 1 (SPRY4-IT1) is a long non-coding RNA (lncRNA) encoded by a gene located on 5q31.3. This lncRNA has a possible role in the regulation of cell growth, proliferation, and apoptosis. Moreover, since SPRY4-IT1 controls levels of lipin 2, it is also involved in the biosynthesis of lipids. During the process of biogenesis, SPRY4-IT1 is produced as a primary transcript which is then cleaved to generate a mature transcript which is localized in the cytoplasm. SPRY4-IT1 has oncogenic roles in diverse tissues. A possible route of participation of SPRY4-IT1 in the carcinogenesis is through sequestering miRNAs such as miR-101-3p, miR-6882-3p and miR-22-3p. The sponging effect of SPRY4-IT1 on miR-101 has been verified in colorectal cancer, osteosarcoma, cervical cancer, bladder cancer, gastric cancer and cholangiocarcinoma. SPRY4-IT1 has functional interactions with HIF-1α, NF-κB/p65, AMPK, ZEB1, MAPK and PI3K/Akt signaling. We explain the role of SPRY4-IT1 in the carcinogenesis according to evidence obtained from cell lines, xenograft models and clinical studies.

Keywords: SPRY4-IT1, cancer, biomarker, expression, carcinogenesis

INTRODUCTION

SPRY4 Intronic Transcript 1 (SPRY4-IT1) is a long non-coding RNA (lncRNA). This transcript is encoded by a gene on the cytogenetic band 5q31.3. During the process of biogenesis, SPRY4-IT1 is produced as a primary transcript which is then cleaved to generate a mature transcript which is localized in the cytoplasm (1). Since the complete size and structure of the primary and cleaved transcripts of SPRY4-IT1 are not clear, it has been speculated that the primary transcript is an alternatively spliced variant of SPRY4 (https://www.ncbi.nlm.nih.gov/gene/100642175).

A pioneer study in this field has suggested that SPRY4-IT1 is originated from an intronic region of the SPRY4 gene. In silico studies have predicted that SPRY4-IT1 has numerous long hairpins in its secondary configuration. Based on the results of RNA-FISH experiments in the melanoma cells, SPRY4-IT1 is mainly localized in the cytoplasm. Since SPRY4-IT1 silencing has altered growth, differentiation, and apoptosis in melanoma cells, it has been suggested that SPRY4-IT1 has a role in the etiology of melanoma (2). Subsequent studies have provided further evidence for participation of SPRY4-IT1 in other types of cancers as well. In normal cells, this lncRNA can regulate cell cycle
progression and cell proliferation. In the current review, we explain the role of SPRY4-IT1 in the carcinogenesis based on evidence obtained from cell lines, xenograft models and clinical studies.

CELL LINE STUDIES

SPRY4-IT1 has been found to up-regulated in colorectal cancer cells. SPRY4-IT1 regulates growth and glycolysis of these cells through enhancing expression of PDK1. SPRY4-IT1 has affected glucose intake, lactic acid synthesis, and levels of ATP in colorectal cancer cells (3). SPRY4-IT1 has also been demonstrated to increase proliferation, migratory potential and invasiveness of colorectal cancer cells. Most notably, SPRY4-IT1 enhances expression of epithelial-mesenchymal transition (EMT)-associated genes. Mechanistically, SPRY4-IT1 negatively regulates expression of miR-101-3p in these cells through binding with this miRNA (4). SPRY4-IT1 up-regulation in a colorectal cancer cell line has resulted in differential expression of several genes among them has been TCEB1. This transcription elongation factor subunit can interact with the Alu element in the 3′ untranslated region (UTR) of SPRY4-IT1. Besides, SPRY4-IT1 binds with STAU1 to increase STAU1 recruitment to the 3′-UTR of TCEB1 transcript. It subsequently modulates stability and expression of TCEB1, leading to up-regulation of HIF-1α. STAU1 is attributed to the family of double-stranded RNA-binding proteins. It participates in the transport of transcripts to various subcellular localizations. Expression of SPRY4-IT1 is also activated by NF-κB/p65 (5).

SPRY4-IT1 has also been reported to be over-expressed in MCF-7 cancer stem cells compared with MCF-7 cells. Up-regulation of SPRY4-IT1 has enhanced proliferation and stemness of breast cancer cells. Moreover, SPRY4-IT1 silencing has inhibited renewal capacity of breast cancer stem cells and maintenance of their stemness. Mechanistically, SPRY4-IT1 acts as a sponge for miR-6882-3p to affect expression of TCF7L2 (6). SPRY4-IT1 silencing in breast cancer cells has significantly inhibited their proliferation and prompted cell apoptosis. ZNF703 has been found to be a target of SPRY4-IT1 in these cells (7). The encoded protein by this gene is involved in nucleic acid binding and DNA-binding transcription factor binding. Figure 1 shows the oncogenic effect of SPRY4-IT1 in colorectal and breast cancers.

Cao et al. has shown that SPRY4-IT1 silencing significantly constrains proliferation of gastric cancer cells through inducing G1 arrest and enhancing apoptosis. SPRY4-IT1 acts as a sponge for miR-101-3p to increase expression of AMPK (8). On the other hand, Xie et al. have shown tumor suppressor role of SPRY4-IT1 in gastric cancer. DNA methylation has been found to be the main mechanism of control of SPRY4-IT1 expression in these cells. Besides, SPRY4-IT1 has been shown to affect EMT in gastric cancer cells (9). In osteosarcoma cells, SPRY4-IT1 has been shown to promote cancer progression through sequestering miR-101 and enhancing expressions of ZEB1 and ZEB2 (10). Figure 2 shows the effect of SPRY4-IT1 in the pathogenesis of gastric cancer and osteosarcoma.

**FIGURE 1** | Oncogenic effect of SPRY4-IT1 in colorectal and breast cancers.
In lung cancer, SPRY4-IT1 has been shown to reverses resistance to cisplatin through decreasing expression of MPZL-1 and suppression of EMT process (11). MPZL-1 is functionally related with tyrosine kinases/adaptors and adhesion. Moreover, EZH2-related epigenetic down-regulation of SPRY4-IT1 has promoted proliferation and metastatic ability of lung cancer cells through influencing EMT (12). Contrary to these studies, Zhang et al. have stated that SPRY4-IT1 increases migration and invasiveness of lung adenocarcinoma cells (13).

In cervical cancer, SPRY4-IT1 can increase EMT influencing activity of the miR-101-3p/ZEB1 axis (14). In testicular germ cell tumors, SPRY4-IT1 has been found to suppress growth of cancer cells and phosphorylation of Akt (15). Figure 3 shows the role of SPRY4-IT1 in the pathogenesis of lung, cervical and testicular cancers.

SPRY4-IT1 levels have been found to be elevated in melanoma cells lines when compared to the normal skin cell line. Up-regulation of this lncRNA has been attended by down-regulation of miR-22-3p. Dual luciferase reporter assay has confirmed the interaction between SPRY4-IT1 and miR-22-3p. Under-expression of SPRY4-IT1 has blocked proliferation, invasiveness, migration, and EMT of melanoma cells. Overexpression of miR-22-3p has been shown to decelerate phosphorylation of p38MAPK, MAPKAPK and Hsp27, thus miR-22-3p decreases activity of the p38MAPK/MAPKAPK/Hsp27 signaling (16). In glioma, SPRY4-IT1 has been revealed to stimulate cell proliferation and invasion via up-regulating SKA2 (17). It has a role in enhancement of EMT of glioma cells as well (18). Moreover, SPRY4-IT1 enhances proliferation and invasiveness of pancreatic cancer cells through regulation of Cdc20 (19). Figure 4 shows oncogenic role of SPRY4-IT1 in melanoma, glioma and pancreatic cancer.

In bladder cancer cells, SPRY4-IT1 sequesters miR-101-3p to increase proliferation and metastatic ability of neoplastic cells via enhancing expression of EZH2 (20). In hepatocellular carcinoma cells, SPRY4-IT1 silencing has attenuated cell proliferation, colony formation, invasiveness and migratory potential. SPRY4-IT1 silencing has led to cell cycle arrest at G0/G1 stage and stimulated cell apoptosis. Moreover, SPRY4-IT1 silencing has inhibited expression of estrogen-related receptor α (ERRα) at transcript and protein level (21). Upregulation of SPRY4-IT1 has also been shown to increase viability of esophageal squamous cell carcinoma cells through inducing expression of zinc finger 703 (22). Figure 5 shows impact of SPRY4-IT1 in the pathoetiology of bladder, liver and esophageal cancers.

Table 1 summarizes the effect of SPRY4-IT1 in cancers based on cell line studies.

### ANIMAL STUDIES

Experiments in animal models of cancers have verified the influence of SPRY4-IT1 in the carcinogenesis. For instance, up-regulation of SPRY4-IT1 has enhanced proliferation and stemness of breast cancer cells in animal models. Besides, investigations in animal models have shown that SPRY4-IT1 silencing inhibits renewal capacity of breast cancer stem cells and reduces their stemness (6). In xenograft models of gastric cancer, two different studies have reported conflicting results. While in BALB/c nude mice, SPRY4-IT1 silencing has decreased...
FIGURE 3 | Effect of SPRY4-IT1 in the pathogenesis of lung, cervical and testicular cancers.

FIGURE 4 | Oncogenic role of SPRY4-IT1 in melanoma, glioma and pancreatic cancer.
malignant behavior of neoplastic cells (8), another study in male athymic mice has shown the reverse results (9). In animal models of lung cancer, concomitant up-regulation of SPRY4-IT1 and cisplatin treatment has attenuated tumor growth and metastasis (11). However, in other types of cancers, xenograft models have shown oncogenic roles of SPRY4-IT1 (Table 2).

**HUMAN STUDIES**

Using a panel of colon, breast, and ovarian cancer tissues, Zhao et al. have found that elevation of SPRY4-IT1 expression is associated with aggressive behavior and poor clinical outcome of patients (5). Another study has shown that SPRY4-IT1 overexpression in breast cancer tissues is associated with a larger neoplasm bulk and higher pathological stage (7).

SPRY4-IT1 has also been reported to be increased in gastric cancer tissues and serum exosomes. Notably, up-regulation of SPRY4-IT1 in serum exosomes has been correlated with metastatic ability of this cancer (8). On the other hand, Xie et al. have reported down-regulation of SPRY4-IT1 in gastric cancer tissues in association with greater tumor dimension, higher pathological stage, higher depth of tumor invasion and lymphatic metastasis. Down-regulation of SPRY4-IT1 has been associated with poor prognosis of gastric cancer patients in this cohort (9).

Elevation of SPRY4-IT1 in patients with hepatocellular carcinoma has been associated with poor five year survival of patients. Besides, expression of SPRY4-IT1 in these patients has been correlated with TNM stage (21). Table 3 summarizes the role of SPRY4-IT1 in cancers based on clinical studies.

Expression of SPRY4-IT1 in tissues and peripheral blood might be used for separation of healthy tissues/blood samples from those obtained from patients with neoplastic conditions (Table 4).

**DISCUSSION**

SPRY4-IT1 has oncogenic roles in diverse tissues. A possible path of participation of SPRY4-IT1 in the carcinogenesis is through decreasing bioavailability of miRNAs such as miR-101-3p, miR-6882-3p and miR-22-3p. The sponging effect of SPRY4-IT1 on miR-101 has been verified in colorectal cancer, osteosarcoma, cervical cancer, bladder cancer, gastric cancer and cholangiocarcinoma. Thus, this miRNA is the main target of SPRY4-IT1 in the carcinogenesis process. In spite of the bulk of evidence pointing to the oncogenic roles of SPRY4-IT1 in diverse tissues, single studies in lung, ovarian and gastric cancers have reported a tumor suppressor role for this lncRNA. Notably, in gastric cancer, animal studies have also shown contradictory results. The number of passages of the cancer cell lines and other in vitro and in vivo conditions should be compared between these studies to find the underlying causes of such inconsistent results.
TABLE 1 | Effect of SPRY4-IT1 in cancers based on cell line studies.

| Tumor type                  | Targets/Regulators and Signaling Pathways | Cell line | Function | Reference |
|-----------------------------|------------------------------------------|-----------|----------|-----------|
| Colorectal cancer           | PDK1, NCM460, T84, HT-29, SW480           | HCT116, LoVo, RKO, SW620, SW480, 293T | Δ SPRY4-IT1: ↓ growth, ↓ viability, ↓ colony formation, ↓ glycolysis | (3)        |
|                            | mR-101-3p                                | LoVo, RKO, SW620, and SW480 | Δ SPRY4-IT1: ↓ proliferation, ↓ growth, ↓ invasion, ↓ EMT process, ↑ G0/G1 phase arrest, ↑ apoptosis | (23)       |
|                            | TCEB1, HIF-1 signaling pathways, Nf2/p65  | HCT116, Caco-2, HT-29, SW480, SW620 | Δ SPRY4-IT1: ↓ proliferation, ↓ invasion, ↓ EMT process | (4)        |
| Breast cancer               | mR-6882-3p, TCF7L2, SDF-1/CXCR4 axis, NT21MP, SKA2 | MCF-7, T47D | Δ SPRY4-IT1: ↑ stemness | (6)        |
|                            | TCEB1, HIF-1 signaling pathways, Nf2/p65  | MCF-7, T-47D, MDA-MB-231 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (25)       |
| Gastric cancer              | mR-101-3p, AMPK                           | MCF-7, T47D, MDA-MB-231 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (7)        |
| Ovarian cancer              | mR-101, ZEB1, ZEB2                        | MCF-7, T47D, MDA-MB-231 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (5)        |
| Osteosarcoma                | mR-101, ZEB1, ZEB2, ZNF703, SKA2          | Caov-3, SK-OV-3, HEK293T, OVCAR-3 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (9)        |
| Lung cancer                 | MP2L-1, A549, A549                        | HOS, Saos-2, U2OS, MG-63, NH osteosarcoma | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (10)       |
| Pancreatic cancer           | Cdc20                                     | H23, H1299, A549, SPC-A1, HLF | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (11)       |
| Pancreatic ductal adenocarcinoma | mR-101-3p, EZH2, Dnmt1                   | BxPC-3, Panc-1, Capan-2, Panc-1, SW1990 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (12)       |
| Cholangiocarcinoma          | Sp1, mR-101-3p, Klf2, Lats2, EzH2, Lsd1, Dnmt1 | RBE and HCC-9810, HIBEC, CCLP-1, HuCCT1, Huh-28, HMBC, BCC939 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (13)       |
| Gastric cancer              | mR-101-3p, EZH2                           | EH-G8, GBC-SO, SGC-996, NOZ, 293T | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (14)       |
| Bladder cancer              | mR-101-3p, EZH2                           | SV-HUC-1, EJ, UMUC3, T24T | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (15)       |
| Hepatocellular carcinoma    | ERα                                       | J82, T24, SW780, SV-40, SV-HUC-1 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ G0/G1 phase arrest, ↓ apoptosis | (16)       |

(Continued)
SPRY4-IT1 has functional interactions with HIF-1α, NF-κB/p65, AMPK, ZEB1, MAPK and PI3K/Akt signaling, thus it can influence the carcinogenesis from different aspects.

Diagnostic value of SPRY4-IT1 has been assessed in cervical malignancy, melanoma and esophageal squamous cell carcinoma, with the best values being reported in the malignancy, melanoma and esophageal squamous cell carcinoma. Since this lncRNA has been identified in serum exosomes of patients with cancer, it represents a possible candidate in non-invasive diagnostic strategies. Yet, these results should be confirmed in large cohorts of patients with different stages of cancers to appraise this potential application.

Except for three types of cancers, namely lung, ovarian and gastric cancers which have contradictory results, elevation of SPRY4-IT1 in other types of cancers has been associated with poor prognosis of patients.

Cumulatively, SPRY4-IT1 is a potential cancer-related lncRNA which can be used as a possible therapeutic target for diverse malignancies. Several issues should be solved before

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TABLE 1 | Continued

| Tumor type | Targets/Regulators and Signaling Pathways | Cell line | Function | Reference |
|------------|------------------------------------------|-----------|----------|-----------|
| Esophageal squamous cell carcinoma | _ | KYSE-450, KYSE-510, KYSE-150, KYSE-180, KYSE-70s, and KYSE-140 | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion | (32) |
| Clear cell renal cell carcinoma | ZNF703 | TE-13 | 786-O, ACHN, Caki-1, Caki-2, HK-2 | Δ SPRY4-IT1: ↓ proliferation, ↓ viability | (22) |
|  |  |  |  | Δ SPRY4-IT1: ↓ proliferation, ↓ migration, ↓ invasion | (33) |

Δ, knock-down or deletion; DDP, cisplatin.

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TABLE 2 | Role of SPRY4-IT1 in cancers based on animal studies.

| Tumor Type | Animal models | Results | Reference |
|------------|---------------|---------|-----------|
| Breast cancer | 3- to 4-week-old female BALB/c nu/nu mice | Mice were divided into the four groups (n = 6 per group): NC-cDNA with MCF-7; SPRY4-IT1-cDNA with MCF-7; sh-NC with MCF-7 GSCs; and sh-SPRY4-IT1 with MCF-7 GSCs | Δ SPRY4-IT1: ↓ tumor weight, ↑ stemness, ↑ self-renewal capacity | (8) |
| Gastric cancer | 3- to 4-week-old male BALB/c nude mice | Mice injected with BGC823 cells transfected with sh-SPRY4-IT1 or sh-NC | Δ SPRY4-IT1: ↓ tumor weight, ↓ tumor growth, ↓ tumor size, ↓ metastasis | (9) |
| Osteosarcoma | 24 nude mice were divided into 4 groups (n=6/group); MG-63/shNC (control), MG-63/shSPRY4-IT1 (treatment), U2OS/shNC (control) and U2OS/shSPRY4-IT1 (treatment). | Mice were injected with MG-63 or U2OS cells transfected with shNC or shSPRY4-IT1. | Δ SPRY4-IT1: ↓ tumor volume, ↓ tumor weight | (10) |
| Lung cancer | 4-week old female athymic BALB/c nude mice | 10 Mice (n = 5 per group) were injected with A549/DDP cells transfected with pCDNA-SPRY4-IT1 and empty vector. | Δ SPRY4-IT1 + DDP Treatment: ↓ tumor volume, ↓ tumor weight | (11) |
| | | 4-week old female athymic BALB/c nude mice | Mice were injected with SPC-A1 cells transfected with pCDNA-SPRY4-IT1 and empty vector. | Δ SPRY4-IT1: ↓ tumor volume, ↓ tumor weight, ↓ metastasis | (12) |
| | | 4-week old male athymic mice | 9 mice were injected with A549 cells transfected with pCDNA-SPRY4-IT1 or empty vector. | Δ SPRY4-IT1: ↓ tumor volume, ↓ tumor weight, ↓ metastasis | (14) |
| Cervical cancer | 4-week old female BALB/c nude mice | Mice (n=6 per group) were injected with HeLa and CaSki cells transfected with SPRY4-IT1 shRNA or negative control. | Δ SPRY4-IT1: ↓ tumor volume, ↓ tumor weight, ↓ metastasis | (14) |
| Pancreatic ductal adenocarcinoma | 6-week old female nude mice | Mice (n=4 per group) were injected with PANCl cells transfected with control shRNA or SPRY4-IT1 shRNA. | Δ SPRY4-IT1: ↓ tumor weight | (28) |
| Cholangiocarcinoma | 6-week old female BALB/c nude mice | Mice (n=6 per group) were injected with HuCCT1 cells transfected with shSPRY4-IT1 or the scrambled control. | Δ SPRY4-IT1: ↓ tumor weight, ↓ tumor growth | (29) |
| Bladder cancer | 4-week old female BALB/c nude mice | Mice (n=6 per group) were injected with T24T cells transfected with SPRY4-IT1 shRNA or negative control. | Δ SPRY4-IT1: ↓ tumor volume, ↓ tumor weight | (23) |
| Esophageal squamous cell carcinoma | 4-week old male BALB/c nude mice | Mice (n=5 per group) were injected with KYSE-30 cells transfected with si-SPRY4-IT1 or si-NC. | Δ SPRY4-IT1: ↓ tumor weight, ↓ tumor growth | (33) |

Δ, knock-down or deletion.
### TABLE 3 | Effect of SPRY4-IT1 in cancers based on clinical studies.

| Tumor type          | Samples                                  | Expression (Tumor vs. Normal) | Kaplan-Meier analysis (impact of SPRY4-IT1 up-regulation) | Univariate/Multivariate cox regression | Association of SPRY4-IT1 expression with Clinicopathologic characteristics | Reference |
|---------------------|------------------------------------------|-------------------------------|----------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------------------|-----------|
| Colorectal cancer (CRC) | 72 CRC tissues and normal tissues up poorer OS _ _ | (3)                           |   |   |   |   |
|                     | 106 CRC tissues and ANCTs up poorer OS SPRY4-IT1 levels are independent factors for CRC prognosis. |   |   |   |   | (23) |
|                     | 96 pair of CRC tissues and ANCTs up _ _  |   |   |   |   | (34) |
|                     | 84 pair of CRC tissues and ANCTs up worse OS SPRY4-IT1 level is an independent prognostic indicator for OS. |   |   |   |   | (24) |
|                     | 88 CRC serum samples and 98 healthy controls up _ _  |   |   |   |   |   |
|                     | 88 pair of CRC tissues and ANCTs up _ _  |   |   |   |   | (4) |
|                     | 113 CRC tissues up shorter OS and DFS _ _  |   |   |   |   | (5) |
| Breast cancer       | 101 breast cancer patients TCGA analysis: up in patients with CD44+/CD24- |   |   |   |   |   |
|                     | 102 pairs of tumor tissues and ANCTs up poorer OS and DFS SPRY4-IT1 level is an independent prognostic factor for both OS and DFS. |   |   |   |   | (35) |
|                     | 48 pairs of tumor tissues and ANCTs up _ _  |   |   |   |   | (7) |
|                     | 101 breast cancer tissues up shorter OS and DFS _ _  |   |   |   |   | (5) |
| Ovarian cancer      | 96 ovarian cancer tissues up shorter OS and DFS _ _  |   |   |   |   | (5) |
|                     | 15 pairs of tumor tissues and ANCTs down higher OS and DFS _ _  |   |   |   |   | (26) |
| Gastric cancer (GC) | 68 pairs of GC tissues and ANCTs up _ _  |   |   |   |   | (8) |
|                     | 61 pairs of GC tissues and ANCTs down higher OS and DFS _ _  |   |   |   |   | (9) |
| Osteosarcoma        | 56 pairs of tumor tissues and ANCTs up _ _  |   |   |   |   | (27) |
| Lung cancer         | TCGA analysis: up shorter OS _ _  |   |   |   |   | (13) |
|                     | 412 LUAD patients Levels of SPRY4-IT1 and histological grade were independent prognostic factors for OS. |   |   |   |   |   |
|                     | 88 pairs of tumor tissues and ANCTs up poorer prognosis _ _ _ _  |   |   |   |   |   | (Continued) |
| Tumor type                     | Samples                                                                 | Expression (Tumor vs. Normal) | Kaplan-Meier analysis (impact of SPRY4-IT1 up-regulation) | Univariate/Multivariate cox regression | Association of SPRY4-IT1 expression with Clinicopathologic characteristics | Reference |
|-------------------------------|------------------------------------------------------------------------|-------------------------------|----------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------|-----------|
| Cervical cancer               | 121 pairs of NSCLC tissues and ANCTs                                   | down                          | higher OS                                               | Low levels of SPRY4-IT1 were independent predictors of poor survival for NSCLC. | tumor size, advanced pathological stage, and lymph node metastasis              | (12)      |
|                               | 100 pairs of cervical cancer tissues and ANCTs                        | up                            | shorter OS                                              | Expression of SPRY4-IT1 was an independent prognostic factor for OS of cervical cancer patients. | tumor size, PGO stage, SCC-Ag, and lymph node metastasis                        | (36)      |
| Testicular germ cell tumor    | 13 TGCTs and 11 normal testis samples                                 | up                            | _                                                        | _                                     | _                                                                               | (15)      |
| Melanoma                      | 70 cases of malignant melanoma and 79 normal controls                 | up                            | poorer prognosis                                         | SPRY4-IT1 was found to be an independent prognostic factor for OS in patients.     | tumor site and TNM stage                                                        | (37)      |
| Glioma                        | 64 glioma specimens and 9 normal brain tissue specimens               | up                            | _                                                        | _                                     | _                                                                               | (17)      |
|                               | 163 glioma tissues and ANCTs                                          | up                            | poorer OS                                               | Expression of SPRY4-IT1 and WHO grade were independently significant prognostic factors. | WHO grade, and tumor size                                                       | (38)      |
|                               | 18 pairs of glioma tissues and ANCTs                                  | up                            | _                                                        | _                                     | _                                                                               | (18)      |
| Pancreatic ductal adenocarcinoma (PDAC) | 46 pairs of PDAC tissues and ANCTs                           | up                            | worse 5-year OS                                         | SPRY4-IT1 was an independent predictor of poor OS.                               | advanced tumor stages and poor differentiation grade                           | (28)      |
| Cholangiocarcinoma (CCA)      | 70 pairs of CCA tissues and ANCTs                                     | up                            | worse OS and PFS                                         | SPRY4-IT1 was an independent predictor of poor PFS and OS.                        | late tumor stage and advanced TNM stage                                         | (29)      |
| Gallbladder carcinoma (GBC)   | 38 pairs of GBC tissues and ANCTs                                     | up                            | _                                                        | _                                     | _                                                                               | (30)      |
| Bladder cancer                | 60 pairs of bladder cancer tissues and ANCTs                         | up                            | _                                                        | _                                     | _                                                                               | (23)      |
|                               | 68 pairs of UCB tissues and ANCTs                                     | up                            | shorter OS                                              | Expression of SPRY4-IT1, histological grade, cancer stage and lymph node involvement were found to be independent prognostic factors for patients with UCB. | advanced tumor stage, higher histological grade, and positive lymph node metastasis | (31)      |
| Hepatocellular carcinoma (HCC) | 87 pairs of HCC tissues and ANCTs                                   | up                            | _                                                        | _                                     | _                                                                               | (39)      |
|                               | Plasma of 60 HCC cases, 85 hepatitis B and cirrhosis patients, and 63 controls | up                            | higher in pre-operation than that at post-operation, hepatitis B and cirrhosis, and the control groups | _                                     | _                                                                               |          |
|                               | 82 pairs of HCC tissues and ANCTs                                     | up                            | poor 5-year OS                                          | _                                     | TNM stage and metastasis                                                        | (21)      |
| Esophageal squamous cell      | 92 pairs of ESCC tissues and ANCTs                                    | up                            | shorter OS                                              | SPRY4-IT1 expression, lymph node metastasis, and TNM stage were found to be independent | tumor differentiation, T classification, lymph node metastasis                 | (32)      |

(Continued)
application of SPRY4-IT1-targeting strategies in the clinical setting the most important one being the possible tissue-specific effect of this lncRNA in the carcinogenesis. Moreover, the impact of genetic variants within SPRY4-IT1 coding gene on susceptibility to cancer and response to therapeutic options should be appraised in future investigations.

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**AUTHOR CONTRIBUTIONS**

SG-F wrote the draft and revised it. MT designed and supervised the study. SS and TK collected the data and designed the figures and tables. All authors contributed to the article and approved the submitted version.

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