CircITCH: A Circular RNA With Eminent Roles in the Carcinogenesis

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Circular RNAs (circRNAs) are a group of long non-coding RNAs with enclosed structure generated by back-splicing events. Numerous members of these transcripts have been shown to affect carcinogenesis. Circular RNA itchy E3 ubiquitin protein ligase (circITCH) is a circRNA created from back splicing events in ITCH gene, a protein coding gene on 20q11.22 region. ITCH has a role as a catalyzer for ubiquitination through both proteolytic and non-proteolytic routes. CircITCH is involved in the pathetiology of cancers through regulation of the linear isoform as well as serving as sponge for several microRNAs, namely miR-17, miR-224, miR-214, miR-93-5p, miR-22, miR-7, miR-106a, miR-10a, miR-145, miR-421, miR-224-5p, miR-197 and miR-199a-5p. CircITCH is also involved in the modulation of Wnt/β-catenin and PTEN/PI3K/AKT pathways. Except from a single study in osteosarcoma, circITCH has been found to exert tumor suppressor role in diverse cancers. In the present manuscript, we provided a comprehensive review of investigations that reported function of circITCH in the carcinogenesis.

Keywords: circular RNA, circITCH, cancer, expression, ncRNAs

INTRODUCTION

Circular RNAs (circRNAs) are a group of long non-coding RNAs with enclosed structure. This structure is created through establishment of a covalent bond between 5’ and 3’ termini through a back-splicing event in exons of a certain pre-mRNA (1). Several studies have indicated broad expression of circRNAs in mammalian cells in a cell type- or tissue-specific manner (1). CircRNAs have been shown to affect different cellular and biological processes, namely cell proliferation (1), differentiation, pluripotency (2) and epithelial-mesenchymal transition (EMT) (3). Moreover, they can participate in the remodeling of endoplasmic reticulum stress, autophagy and phagocytosis, DNA repair mechanisms as well as drug efflux (4). Different mechanisms have been suggested for circRNAs effects in these processes with the most appreciated one being their function as decoys for microRNAs (miRNAs) or RNA-binding proteins. Through this mechanism, circRNAs can influence expression of genes or translation of proteins with regulatory functions (1). CircRNA have the ability to base pair with other types of RNAs as well (5). Moreover, circRNAs can suppress activity of certain proteins, particularly cell cycle proteins through interacting with them (6). While circRNAs are mainly considered as non-coding RNAs, they might be served as a template for production of proteins under some conditions (5). Cumulatively, circRNAs can influence
expression of cellular proteins, interfere with RNA-binding proteins to affect transcription of genes, regulate gene transcription in cis, and modulate splicing events (5). Yet, the competing endogenous function of circRNAs is the chief way through which they exert their biological effects (5). Several studies have emphasized on the role of circRNAs in cancer development and induction of chemo/radioresistance (4, 5).

Circular RNA itchy E3 ubiquitin protein ligase (circITCH) is an example of cancer-related circRNAs which can be used as a target for therapeutic interventions. It is created from back splicing events in ITCH gene, a protein coding gene on 20q11.22 region. ITCH has a role as a catalyst for ubiquitination through both proteolytic and non-proteolytic routes (7). It has been shown to affect tumorigenesis in a context-dependent manner (7). Recent studies have shown involvement of the circRNA from this locus in the carcinogenesis process. In the present manuscript, we provided a comprehensive review of investigations that reported function of circITCH in this process. The evidence regarding the role of circITCH in cancers is classified based on the samples/models used in the original papers to in vitro, in vivo and clinical studies.

CELL LINE STUDIES

Bladder Cancer
CircITCH has been found to be down-regulated in bladder cancer cell lines. Forced over-expression of circITCH could inhibit proliferation, migratory potential, invasive properties and metastatic ability of bladder cancer cells. Functionally, circITCH acts as a sponge for miR-17 and miR-224 to up-regulate expression of their target genes p21 and PTEN. Cumulatively, circITCH functions as a tumor suppressor circRNA in bladder cancer (8).

Breast Cancer
Expression of circITCH has also been shown to be decreased in triple negative breast cancer cell lines. Stable transfection of MDA-MB-231 and BT-549 cells with circITCH-expressing vectors has resulted in inhibition of proliferation, invasiveness and metastatic ability of these cells. Mechanistically, circITCH serves as a molecular sponge for miR-214 and miR-17 leading to enhancement of expression of the linear form of ITCH. This circRNA functionally inactivates Wnt/β-catenin signaling (9).

Cervical Cancer
Expression of circITCH has also been shown to be down-regulated in cervical cancer cell lines. Up-regulation of circITCH in cervical cancer cells has inhibited their proliferation, migration, and invasiveness. Mechanically, circITCH acts a sponge for miR-93-5p to regulate expression of FOXK2 (10).

Osteosarcoma
Down-regulation of circITCH has also been verified in osteosarcoma cells. Overexpression of circITCH has induced cell apoptosis and decreased cell viability, proliferation, migratory potential and invasive properties of MG63 and Saos-2 osteosarcoma cells. This circRNA could decrease expression of miR-22 in osteosarcoma cells, thus suppressing PTEN/PI3K/AKT and SP-1 signals (11). On the other hand, another study in the hFOB1.19 osteoblast cell line and multiple osteosarcoma cell lines has shown up-regulation of circITCH in neoplastic cells compared with the osteoblast cells. Functionally, circITCH enhanced migration, invasive properties, and growth of these neoplastic cells through sponging miR-7 and increasing expression of EGFR (12).

Figure 1 shows the tumor suppressor role of circITCH in bladder, breast and cervical cancers as well as dual role of this circRNA in osteosarcoma.

Thyroid Cancer
In thyroid cancer cells, forced over-expression of circITCH inhibits cell proliferation and invasive properties, while promoting cell apoptosis. These effects are mediated through sponging miR-22-3p and subsequent up-regulation of levels of CBL, an E3 ligase of nuclear β-catenin. Cumulatively, circITCH affects activity of the Wnt/β-catenin pathway through modulation of CBL levels, therefore suppressing progression of thyroid cancer (13).

Ovarian Cancer
Expression of circITCH expression has been found to be down-regulated in numerous epithelial ovarian cancer cell lines versus normal ovarian epithelial cells. This circRNA could inhibit proliferation of SKOV3 and OVCAR-3 cells, while enhancing their apoptosis (14). Another study has shown the role of circITCH in suppression of proliferation, invasiveness, and glycolytic process in ovarian cancer cells through sequestering miR-106a and enhancing expression of CDH1 (15). miR-10a-alpha has also been identified as a target of circITCH in ovarian cancer cells through which circITCH exerts its tumor suppressor effects (16). Moreover, circITCH has been shown to suppress progression of this cancer via influencing miR-145/RASA1 axis (17). Finally, circITCH has been suggested to suppress proliferation of ovarian cells through deceasing expression of HULC (18). Figure 2 shows the tumor suppressor role of circITCH in thyroid and ovarian cancers.

Hepatocellular Carcinoma
CircITCH has also been shown to have tumor suppressor roles in hepatocellular carcinoma. In fact, the effects of lidocaine on inhibition of proliferation of hepatocellular carcinoma cells have been shown to be mediated through restoration of circITCH in these cells. Mechanistically, circITCH modulates expression of CPEB3 through sponging miR-421 (19). CircITCH can also affect progression of hepatocellular carcinoma through sponging miR-224-5p and increasing expression of MafF (20). CircRNAITCH levels have been found to be down-regulated in several hepatocellular cancer cell lines compared with normal hepatic L-02 cell line. Up-regulation of circRNAITCH has
FIGURE 1 | Tumor suppressor role of circITCH in bladder, breast and cervical cancers as well as dual role of this circRNA in osteosarcoma.

FIGURE 2 | Tumor suppressor role of circITCH in thyroid and ovarian cancers.
inhibited proliferation of these cells, suppressed their colony formation aptitude and induced their apoptosis. CircRNA/ITCH could be used as a sponge for miR-7 and miR-214. Through this route, it regulates Wnt/β-catenin signals and suppresses c-myc and cyclin D1 levels (21).

Glioma
CircITCH has also been shown to inhibit proliferation and invasive potential of glioma cells via sequestering miR-106a-5p and enhancing expression of SASH1 (22). Moreover, it has been reported to serve as a sponge for miR-214 and promote expression of linear ITCH in glioma cells (23).

Oral Squamous Cell Carcinoma
The miR-421/PDCD4 axis has been shown as the downstream axis mediating the role of circITCH in modulation of progression of oral squamous cell carcinoma by regulating (24).

Prostate Cancer
CircITCH exerts tumor suppressor roles in prostate cancer via influencing miR-17-5p/HOXB13 axis (25). Moreover, circITCH can inhibit proliferation, migratory aptitude, and invasiveness of human prostate cancer cells through sequestering miR-17. This circRNA can also down-regulate expression levels of several proteins in the Wnt/β-catenin and PI3K/AKT/mTOR signal transductions in LNCaP and PC-3 cells, as representatives of androgen receptor (AR)-positive and AR-negative cells, respectively (26). miR-197 is another target of circITCH in prostate cancer cells through which it regulates progression of this type of cancer (27).

Gastric Cancer
In addition, circITCH can suppress gastric carcinogenesis through modulation of miR-199a-5p/Klotho axis (28) as well as the Wnt/β-catenin pathway (29).

Melanoma
Finally, circITCH decreases expression of GLUT1 and inhibits uptake of glucose by melanoma cells to suppress their proliferation (30).

Other Cancers
miR-7 and miR-214 have been found to be sequestered by circITCH in lung (31) and esophageal cancers (32). In addition to mentioned cancer types, circITCH has tumor suppressor roles in renal cancer (33), multiple myeloma (34) and colorectal cancer (35). Table 1 summarizes expression and function of circITCH in cancer cell lines.

Table 1

| CircRNA | Expression and Function |
|---------|-------------------------|
| circITCH | Tumor suppressor role in hepatocellular carcinoma, glioma and oral squamous cell carcinoma. |
ANIMAL STUDIES

Subcutaneous injection of T24 bladder cancer cells transfected with circITCH into the nude mice has shown the impact of this circRNA in reduction of tumor volumes and tumor weight. Notably, expressions of p21 and PTEN have been up-regulated in the tumors originated from circITCH overexpressing cells (8). Other in vivo studies have consistently verified the tumor suppressor roles of circITCH in different animal models (Table 2). Similarly, over-expression of circITCH has increased sensitivity of bortezomib-resistant multiple myeloma cells to this drug in animal models (34).

CLINICAL STUDIES

Different studies in samples obtained from patients with diverse types of neoplasms have verified down-regulation of circITCH in neoplastic samples when compared with normal (non-affected) tissues (Table 3). Down-regulation of circITCH in bladder cancer tissues has been correlated with histological grade. In addition, bladder cancer patients who had circITCH down-regulation exhibited poor clinical outcome (8).

Expression of circITCH has also been reported to be lower in ovarian tumor tissues compared with corresponding non-tumoral tissues. Most notably, expression of circITCH has been inversely correlated with tumor size and FIGO stage in these patients. Based on multivariate Cox analyses, over-expression of circITCH has been identified as an independent predictor of favorable overall survival of patients with ovarian cancer (14).

Cumulatively, decreased levels of circITCH have been correlated with poor outcome in diverse types of cancers, suggesting this circRNA as a prognostic factor in human malignancies.

DISCUSSION

Except from a single study in osteosarcoma, circITCH has been found to exert tumor suppressor role in diverse cancers. This circRNA is involved in the pathobiology of cancers through regulation of the linear isoform as well as serving as sponge for several microRNAs, namely miR-17, miR-224, miR-214, miR-93-5p, miR-22, miR-7, miR-106a, miR-10a, miR-145, miR-421, miR-224-5p, miR-197 and miR-199a-5p. CircITCH also partakes in the modulation of Wnt/β-catenin and PTEN/P13K/AKT pathways.

A number of miRNAs have been found to interact with circITCH in diverse tissues. For instance, miR-7 has been found to be sponged by circITCH in osteosarcoma, hepatocellular carcinoma, lung cancer and esophageal squamous cell carcinoma. Meanwhile, miR-17 has been detected as a target of this circRNA in bladder, breast, prostate, gastric and esophageal squamous cell cancers. Moreover, circITCH has been shown to sponge miR-214 in breast,
| Tumor type         | Targets/Regulators and Signaling Pathways | Cell line | Function                                      | Reference |
|-------------------|------------------------------------------|-----------|-----------------------------------------------|-----------|
| Bladder cancer    | miR-17, miR-224, p21, PTEN               | EJ, T24   | † circITCH: ↓ viability, ↓ migration, ↓ invasion, ↑ G1/S cell cycle arrest, ↑ apoptosis | (8)       |
| Breast cancer     | miR-214, miR-17, Wnt/β-catenin signaling | MCF-10A, MCF-7, T47D, SK-BR-3, MDA-MB-231, BT-549 | † circITCH: ↓ proliferation, ↓ migration, ↓ invasion | (9)       |
| Cervical cancer   | miR-93-5p, FOXK2                         | Hela      | † circITCH: ↓ proliferation, ↓ migration, ↓ invasion | (10)      |
| Osteosarcoma      | miR-22, PTEN/PI3K/AKT and SP-1 pathways  | MG63, U2OS, Saos-2, hFOB1.19 | † circITCH: ↓ proliferation, ↑ migration, ↑ invasion, ↑ apoptosis | (11)      |
| Thyroid cancer    | miR-7, EGFR                              | SJSA-1, U2OS, hFOB1.19 | † circITCH: ↓ proliferation, ↓ invasion, ↓ apoptosis | (12)      |
| Ovarian cancer    | miR-22-3p, CBL/β-catenin pathway         | K1, IHH4, TPC1 | † circITCH: ↓ proliferation, ↓ invasion, ↓ apoptosis | (13)      |
| Hepatocellular carcinoma | miR-106a, CDH1                  | SKOV3, OVCAr-3 | † circITCH: ↓ proliferation, ↓ apoptosis | (14)      |
|                   | miR-10a                                 | A2780 and OVCAr3, ISOE80 | † circITCH: ↓ proliferation, ↓ migration, ↓ invasion, ↓ glycolysis, ↓ apoptosis | (15)      |
|                   | miR-145, RASA1                           | SK-OV-3, Caov-3 | † circITCH: ↓ proliferation, ↓ migration, ↓ invasion | (16)      |
|                   | HULC                                    | UW1.289 + BRCA1 and UW1.289 | † circITCH: ↓ proliferation, ↑ apoptosis | (17)      |
|                   | miR-421, CPEB3                          | Huh7, Hep3B, THL-2 | Δ circITCH: ↓ suppressive effect of lidocaine on hepatocellular carcinoma development lidocaine treatment: ↑ circITCH, ↓ proliferation, ↓ migration, ↓ invasion | (19)      |
|                   | miR-224-5p, MafF                          | SMMC7721, Huh7, Hep3B | † circITCH: ↓ proliferation, ↓ apoptosis, ↓ MafF levels | (20)      |
|                   | miR-7, miR-214, Wnt/β-catenin signaling | HCC Huh-7, U251, HB811, SMMC-7721, L-02 | † circITCH: ↓ proliferation, ↓ colony formation ability, ↓ apoptosis | (21)      |
| Glioma            | miR-106a-5p, SASH1                       | U251, U87, SHG44, A172, HEB | † circITCH: ↓ proliferation, ↓ invasion | (22)      |
|                   | miR-214, linear ITCH, Wnt/β-catenin pathway | U87, U251, A172, SHG44, LN229, T983, SHG139, M059K | † circITCH: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process, ↓ apoptosis | (23)      |
| Oral squamous cell carcinoma | miR-421, PDCD4            | HOK, SCC6, SCC9, SCC25, HN4, HN6 | † circITCH: ↓ proliferation, ↑ apoptosis | (24)      |
| Prostate cancer   | miR-17-5p, HOXB13                        | C4-2, LNCaP, DU145, 22Rv1, PC-3 and VcaP, RWPE-1 | † circITCH: ↓ proliferation, ↓ apoptosis | (25)      |
|                   | miR-17, Wnt/β-catenin and PI3K/AKT/mTOR pathways | U 145, 22Rv1, VcaP, PC-3, RWPE-1 | † circITCH: ↓ proliferation, ↓ migration, ↓ invasion | (26)      |
| Gastric cancer    | miR-199a-5p, Klotho                     | HGC-27, AGS, MKN-45, MGC-803 and HEK-293 T, GES-1 | † circITCH: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process, effect on anticancer chemotherapy | (27)      |
| Melanoma          | miR-17, ITCH, Wnt/β-catenin pathway      | A375, M21 | † circITCH: ↓ proliferation, ↓ glucose uptake | (30)      |
| Lung cancer       | GLUT1                                   | A375, WM35 | Δ circITCH: ↓ proliferation, ↑ colony-forming ability | (36)      |
|                   | miR-520f                                | A549, NIC460 | † circITCH: ↓ proliferation | (31)      |
| Esophageal squamous cell carcinoma | miR-7, miR-17, miR-214, ITCH, Wnt/β-catenin signaling | Eco-109, TE-1 | † circITCH: ↓ proliferation, ↓ colony-forming ability | (32)      |
| Clear cell renal cell carcinoma | miR-106b-5p, PDCD4                  | HK-2, OSRC-2, A498, SW839, 786-O, Caki-1, GRC-1 | † circITCH: ↓ metastasis, ↓ migration, ↓ invasion | (33)      |
| Multiple myeloma  | miR-615-3p, PKRCD                       | U-266, OCI-H929, RPMI 8226, OCI-H929, RPMI 8226 | † circITCH: ↓ proliferation, ↓ apoptosis, sensitivity to BTZ | (34)      |
| Colorectal cancer | Linear ITCH, Wnt/β-catenin pathway      | HCT116, SW480 | † circITCH: ↓ proliferation | (35)      |

The correlation between expression levels of circITCH and clinicopathological data such as tumor size, local invasion, distant metastasis and different staging systems shows the importance of this circRNA in the development or progression of cancers, representing a novel biomarker role for it. Although the impact of circITCH in determination of prognosis of cancer patients is well established, its function as a diagnostic marker is not studied. Since circRNAs are stable transcripts in the circulation, they are expected to reflect cancer course. Thus, future investigations should focus on evaluation of levels of circITCH in plasma of patients with different stages of cancers.
### TABLE 2 | Summary of studies which assessed impact of circITCH up-regulation or silencing in animal models (Δ: knock-down or deletion, BTZ: Bortezomib).

| Tumor Type             | Animal models                                      | Results                                                                 | Reference |
|------------------------|----------------------------------------------------|-------------------------------------------------------------------------|-----------|
| Bladder cancer         | female athymic BALB/C nude mice                    | ↑ circITCH: ↓ tumor volume, ↓ tumor weight                             | (8)       |
| Breast cancer          | female BALB/c nude mice                            | ↑ circITCH: ↓ tumor volume, ↓ number of lung nodules                   | (9)       |
| Cervical cancer        | nude mice                                           | ↑ circITCH: ↓ tumor volume, ↓ tumor weight                             | (10)      |
| Thyroid cancer         | female BALB/c nude mice                            | ↑ circITCH: ↓ tumor size, ↓ tumor weight                              | (11)      |
| Ovarian cancer         | BALB/c nude mice                                    | ↑ circITCH: ↓ tumor volume, ↓ tumor weight                             | (12)      |
| Hepatocellular carcinoma | male BALB/c nude mice                               | ↑ circITCH: ↓ tumor volume, ↓ tumor weight under lidocaine treatment condition | (13)      |
| Glioma                 | BALB/c nude mice                                    | ↑ circITCH: ↓ tumor growth, ↓ tumor weight                             | (14)      |
| Prostate cancer        | female BALB/c nude mice                            | ↑ circITCH: ↓ tumor growth, ↓ tumor volume                             | (15)      |
| Gastric cancer         | male athymic nude mice                              | ↑ circITCH: ↓ tumor growth                                            | (16)      |
| Esophageal squamous cell carcinoma | female BALB/c nude mice                        | ↑ circITCH: ↓ tumor growth                                            | (17)      |
| Clear cell renal cell carcinoma | male BALB/c nude mice                          | ↑ circITCH: ↓ tumor volume, ↓ tumor weight                             | (18)      |
| Multiple myeloma       | BALB/c nude mice                                    | ↑ circITCH: ↓ tumor volume, ↓ tumor weight                             | (19)      |

### TABLE 3 | Results of studies that reported dysregulation of circITCH in clinical samples (ANCTs, adjacent non-cancerous tissues; OS, Overall survival; FIGO, International Federation of Gynecology and Obstetrics; DFS, disease-free survival; TNM, tumor-node-metastasis).

| Tumor type               | samples                                      | Expression (Tumor vs. Normal) | Kaplan-Meier analysis (Impact of circITCH down-regulation) | Univariate/Multivariate cox regression | Association of down-regulation of circITCH with clinicopathologic characteristics | Reference |
|--------------------------|---------------------------------------------|------------------------------|-----------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------------|-----------|
| Bladder cancer           | 72 pairs of tumor tissues and ANCTs          | down                         | shorter OS                                                | histological grade                   |                                                                                 | (8)       |
| Breast cancer            | 275 tumor tissues and 68 ANCTs               | down                         | shorter OS                                                | lymph node metastasis, larger tumor size and advanced TNM stage                  |                                                                                 | (9)       |
| Osteosarcoma             | 22 pairs of osteosarcoma tissues and paraosteosarcoma tissues | down                         | shorter OS                                                | clinical stage and lymph node metastasis                                          |                                                                                 | (10)      |
| Thyroid cancer           | 37 tumor tissues and 14 ANCTs                | down                         | shorter OS                                                | Larger tumor size, increased FIGO stage                                             |                                                                                 | (11)      |
| Ovarian cancer           | 77 tumor tissues and ANCTs                   | down                         | shorter OS                                                | CircITCH was found to be an independent predictive factor for favorable OS.      |                                                                                 | (12)      |
| Hepatocellular carcinoma | 40 tumor tissues and 34 ANCTs                | down                         | shorter OS                                                | Larger tumor size, increased FIGO stage                                             |                                                                                 | (13)      |
| Glioma                   | 48 pairs of tumor tissues and ANCTs          | down                         | shorter OS                                                | Larger tumor size, increased FIGO stage                                             |                                                                                 | (14)      |
| Oral squamous cell cancer | 103 pairs of tumor tissues and ANCTs         | down                         | shorter OS                                                |                                                                                 |                                                                                 | (15)      |
| Prostate cancer          | 52 pairs of tumor tissues and ANCTs          | down                         | poor OS                                                   | preoperative PSA, Gleason score, and tumor stage                                   |                                                                                 | (16)      |
| Gastric cancer           | 61 pairs of tumor tissues and ANCTs          | down                         | shorter DFS and OS                                        | advanced pathologic T stage and high risk of lymph node metastasis and invasion depth |                                                                                 | (17)      |

(Continued)
to find the suitability of this marker for diagnostic purposes as well as patients’ follow-up. The main question in this regard is whether expression level of circITCH is changed after chemo/radiotherapy or tumor excision. If so, it can be used as a marker for early detection of cancer recurrence.

Another question to be answered is the correlation between expression levels of the circular and linear form of ITCH in different types of cancers. The answer to this question can help in better understanding of the mechanism of dysregulation of circITCH in relation to cancer progression.

Since circITCH is mostly considered as a tumor suppressor circRNA, several groups have assessed the impact of forced over-expression of this transcript in cancer cells transplanted into animal models. The results have been mostly promising, yet needing to be approved in clinical settings.

The interactions between circITCH and RNA-binding proteins have not identified in the previous literature. However, the online database circular RNA Interactome (https://circinteractome.nia.nih.gov/) has listed a number of RNA-binding proteins possibly interacting with circRNAs originated from ITCH locus (Table 4).

**FUTURE PERSPECTIVES**

CircITCH, as a tumor suppressor circRNA can be utilized in therapeutic regimens for cancers. Delivery methods include nanoparticles and exosome-based methods (40). Artificial circRNAs have been successfully used as miRNA sponges in recent years (41). Thus, synthetic circITCH molecules with the potential of sponging oncogenic miRNAs can be used for attenuation of carcinogenic process. Yet, this method should be appraised in cell lines and animal models. Finally, the interactions between circITCH and RNA-binding proteins should be assessed in future investigations.

**AUTHOR CONTRIBUTIONS**

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

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**TABLE 3 | Continued**

| Tumor type | samples | Expression (Tumor vs. Normal) | Kaplan-Meier analysis (impact of circITCH down-regulation) | Univariate/Multivariate cox regression | Association of down-regulation of circITCH with clinicopathologic characteristics | Reference |
|------------|---------|-------------------------------|----------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------|-----------|
| Melanoma   | 56 pairs of tumor tissues and ANCTs | down | - | - | age and tumor grades (39) |
| Lung cancer | 78 pairs of tumor tissues and ANCTs | down | poor OS | - | lymph node metastasis (29) |
| Esophageal squamous cell carcinoma | 684 pairs of tumor tissues and ANCTs | down | - | - | - |
| Clear cell renal cell carcinoma | 54 pairs of tumor tissues and ANCTs | down | - | - | - |
| Multiple myeloma | 56 patients with MM and 56 HCs | down | shorter OS | - | - |

**TABLE 4 | Possible interactions between circITCH and RNA-binding proteins.**

| CircRNA ID | RNA-binding protein sites matching circRNA junction | RNA-binding protein sites matching flanking regions of circRNA |
|------------|---------------------------------------------------|-------------------------------------------------------------|
| hsa_circ_0001141 | – | EIF4A3, HuR, U2AF65 |
| hsa_circ_0003073 | – | DGR8, EIF4A3, PTB |
| hsa_circ_0005677 | EIF4A3 | EIF4A3, PTB |
| hsa_circ_0005868 | – | AG02, EIF4A3, PTB, U2AF65 |
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