CircMTO1: A circular RNA with roles in the carcinogenesis

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ABSTRACT

Circular RNAs (circRNAs) have a closed loop structure which endows them high stability. These transcripts are made through back splicing instead of classical splicing and are abundant in the human transcriptome. Recent advances in the development and implementation of high-throughput sequencing methods in cooperation with novel bioinformatics tools have shown contribution of circRNAs in the developmental processes, physiological settings and pathoetiology of cancers. CircMTO1 is a circRNA which was firstly identified as a down-regulated circRNA in hepatocellular carcinoma through circRNA profiling using microarray technique. Subsequent independent studies in lung adenocarcinoma, colorectal cancer, bladder cancer, glioblastoma, prostate cancer, osteosarcoma, gastric cancer and ovarian cancer have verified down-regulation of circMTO1 in neoplastic tissues compared with non-neoplastic ones. However, expression of circMTO1 has been found to be up-regulated in cervical and gallbladder cancers. miR-17, miR-9, miR-221, miR-6893, miR-92, miR-219a-5p, miR-337, miR-630, miR-3200-5p and miR-199a-3p have been shown to be sequestered by circMTO1. This circRNA can regulate activity of Notch, Wnt/β-Catenin, TGF-β/Smad, JAK1/STAT3 and AMPK signaling pathways. In the current study, we review the literature on the role of circMTO1 in the tumorigenesis.

1. Introduction

Circular RNAs (circRNAs) are a group of transcripts with a closed loop structure which endows them high stability [1]. As a class of RNAs with abundant expression in eukaryotes, they are expressed in a site- and stage-specific manner [2]. It has been estimated that up to 10% of expressed genes can make circRNAs [3]. Nearly all regions of the genome such as intergenic, intronic, antisense and untranslational areas can be the origin of circRNAs [4]. Similar to linear RNAs, circRNAs are produced from precursor mRNAs, yet circRNAs are mainly produced through back-splicing instead of classical splicing [5]. Not yet being considered as sole futile derivatives of aberrant RNA splicing, circRNAs have been found to affect gene expression events through serving as miRNA sponges [6]. In addition, they can cooperate with RNA binding proteins, influence transcription or splicing of genes or even translate proteins [7].

Recent advances in the development and implementation of high-throughput sequencing methods of transcripts and parallel improvement in bioinformatics tools [8] have shown contribution of circRNAs in the developmental processes and physiological settings in eukaryotes [2,5]. Most importantly, circRNAs have been shown to be involved in the pathogenesis of cancers [9] where they regulate tumor growth, metastatic ability, stemness and resistance to therapeutics [10, 11]. They can regulate carcinogenesis via different routes. CircRNAs have been identified as both tumor suppressor and oncogenic transcripts. For instance, hsa_circ_0007534 has been found to inhibit proliferation of colorectal cancer cells through stimulating cell apoptosis [12]. On the other hand, circUBAP2 has been reported to be up-regulated in osteosarcoma cells, where it enhances cell proliferation and inhibits cell apoptosis through binding with miR-143, therefore increasing expression of Bcl-2 [13]. Several of cancer-related circRNAs have been identified up to now (reviewed in [7,14]).

CircMTO1 (hsa_circRNA_0007874/hsa_circRNA_104135: chr6:741 75931-74176329) has been firstly identified as a down-regulated circRNA in hepatocellular carcinoma (HCC) through circRNA profiling using microarray technique [15]. This circRNA is produced through a
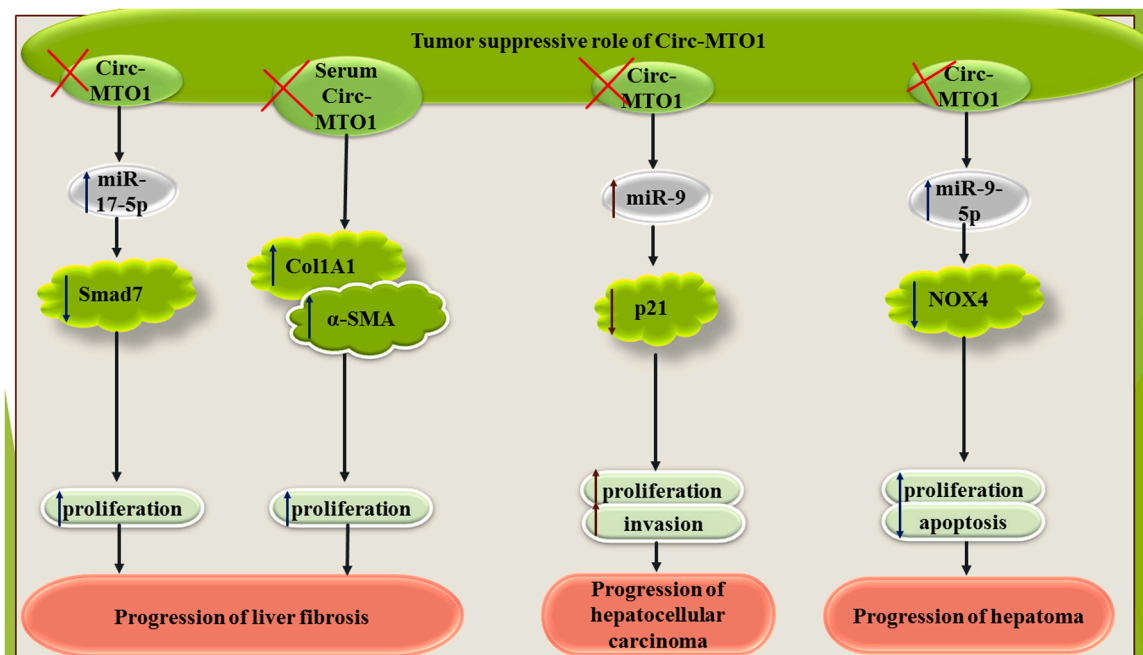

Fig. 1. The role of circMTO1 in liver cancer and liver fibrosis (Upward arrows show enhancement, while downward arrows show suppression, crosses show down-regulation).

back splicing event from the *Mitochondrial tRNA translation optimization 1* (*MTO1*) gene is located 6q13, thus lacking polyadenylated tail or 5–3′ polarity. Being originated from exons 2 and 3 of *MTO1* gene, this circRNA has a 318 bp size [16]. While it is produced by non-linear splicing of the MTO1 pre-mRNA, it is not clear whether it can control transcription amounts of the linear transcript [17]. CircMTO1 is predominantly located in the cytoplasm [18].

In the current study, we review the literature on the role of circMTO1 in the tumorigenesis. The first type of evidence has come from experiments in cell lines when researches have evaluated the function of circMTO1 through knock-in or knock-out studies. Second type of

evidence has originated from investigations in animal models, where circMTO1 over-expressing/under-expressing cancer cell liens have been transplanted to nude mice and the consequences of up-/down-regulation of this circRNA have been evaluated in these animal model. Finally, the impact of deregulation of circMTO1 has been evaluated in clinical samples.

2. Cell line studies

A pioneer study in this field has shown that up-regulation of circMTO1 can decrease proliferation rate of HCC cells. On the other
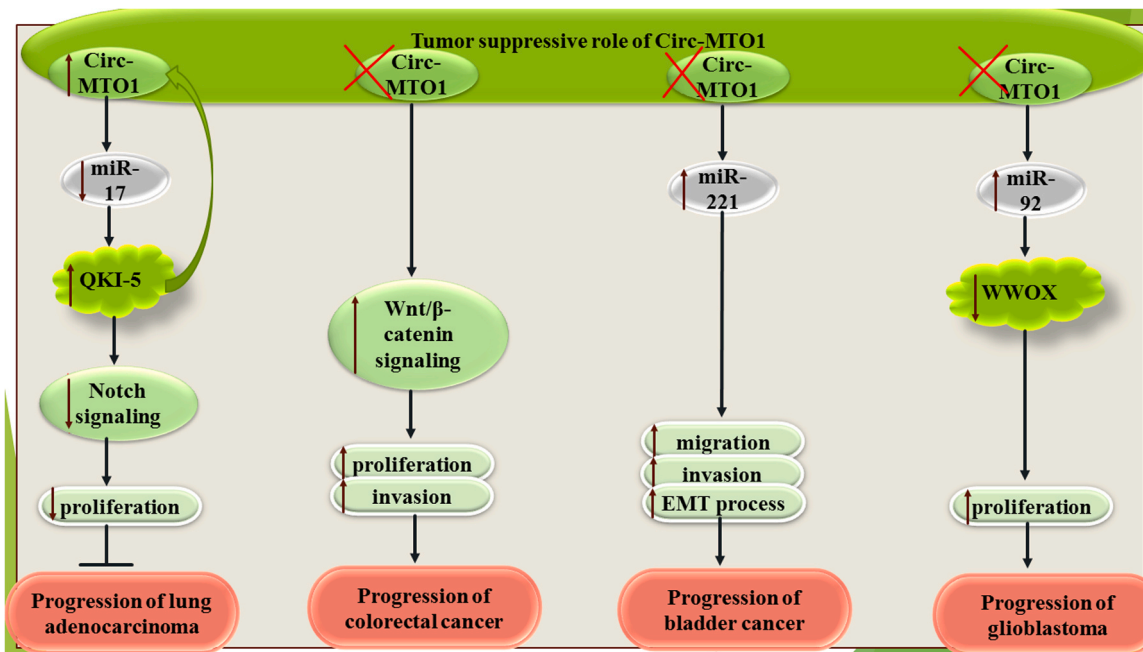

Fig. 2. Summary of tumor suppressor role of circMTO1 in lung cancer, colorectal cancer, bladder cancer and glioblastoma (Upward arrows show enhancement, while downward arrows show suppression, crosses show down-regulation).
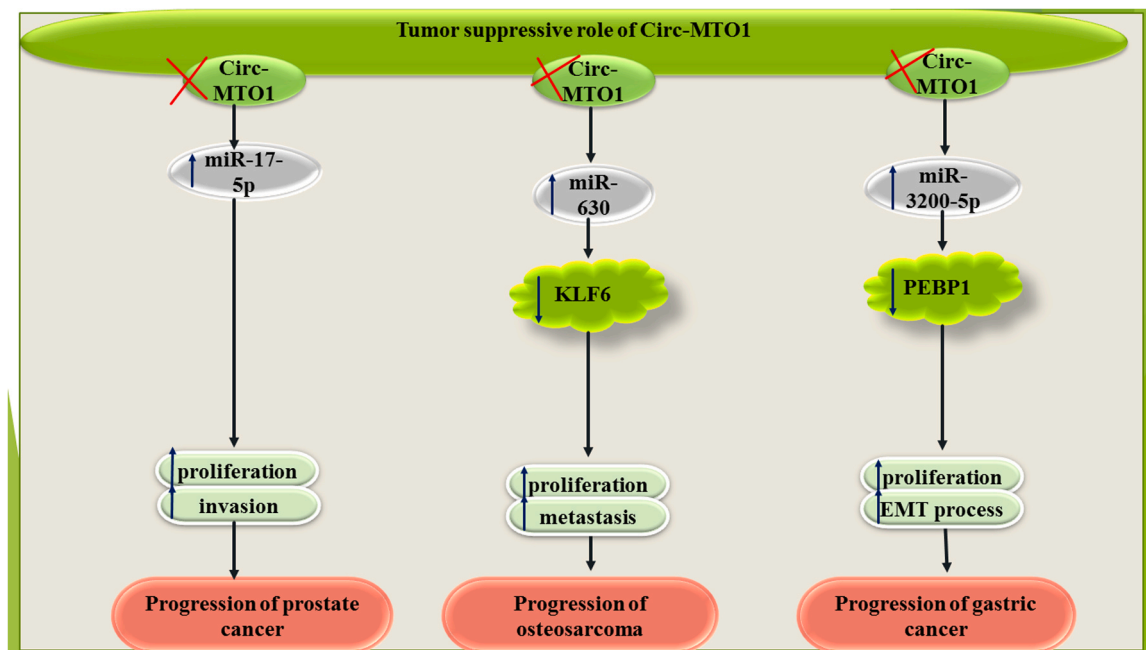
Fig. 3. Tumor suppressor role of circMTO1 in prostate cancer, osteosarcoma and gastric cancer (Upward arrows show enhancement, while downward arrows show suppression, crosses show down-regulation).

hand, circMTO1 silencing has resulted in down-regulation of p21, the direct target of miR-9 oncomiR [15]. Another study in liver cancer cell liens has indicated down-regulation of circMTO1 in these cells compared with normal controls. CircMTO1 has been shown to serve as a molecular sponge for miR-9-5p, and release NOX4 from inhibitory effects of miR-9-5p. Up-regulation of circMTO1 and NOX4 has suppressed proliferation and migration of hepatoma cells, whereas miR-9-5p up-regulation had the reverse impact. Both circMTO1 and NOX4 could induce cell apoptosis, while miR-9-5p exerted the opposite effect [19]. Fig. 1 shows the role of circMTO1 in liver cancer and liver fibrosis.

In lung cancer, circMTO1 acts as a tumor suppressor through several mechanisms. It has been reported to be down-regulated in lung cancer

cells. Forced over-expression of circMTO1 has inhibited proliferation of these cells. Functionally, circMTO1 acts as a sponge for oncogenic miR-17 to enhance levels of RNA-binding protein QKI-5, resulting in attenuation of activity of Notch signaling. Notably, circ-MTO1-medated over-expression of QKI-5 could result in up-regulation of circ-MTO1 [20]. Expression of circMTO1 has also been found to be decreased in colorectal cancer cells compared with a normal epithelial cell line. CircMTO1 silencing has enhanced proliferation and invasion aptitude of colon cancer cells through increasing activity of Wnt/β-catenin signaling [21].

CircMTO1 has a role in suppression of epithelial-to-mesenchymal transition (EMT) through sponging miRNAs. Expression of circMTO1
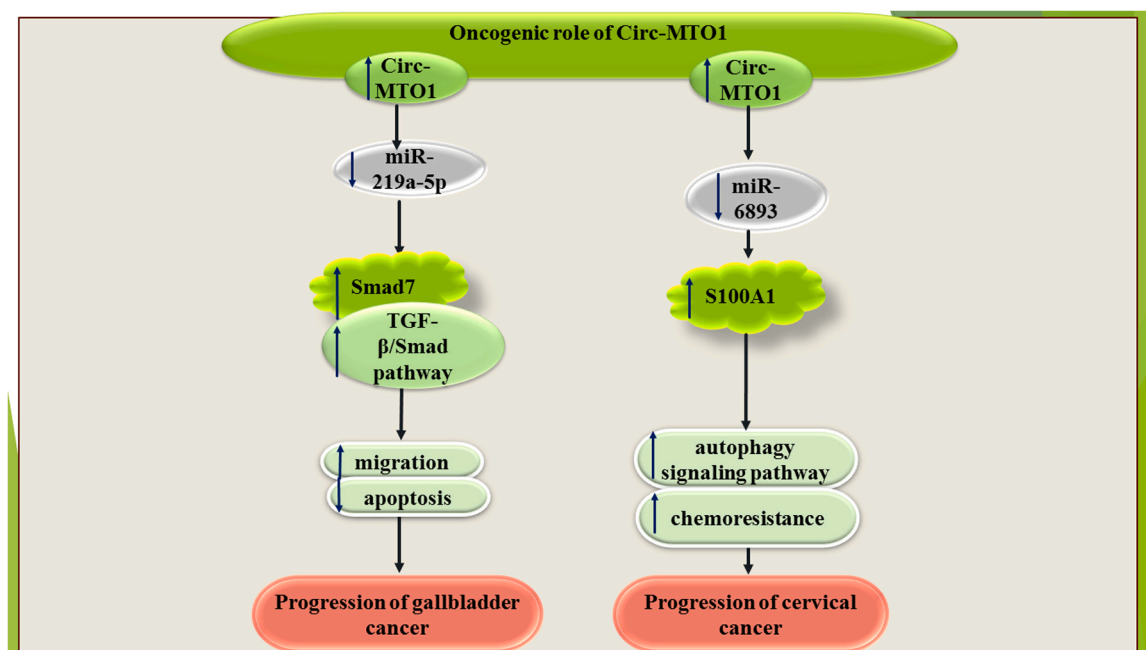

Fig. 4. Oncogenic role of circMTO1 in gallbladder and cervical cancers (Upward arrows show enhancement, while downward arrows show suppression).

Table 1

In vitro studies about the role of circMTO1 in the carcinogenesis (Δ: Knock-down).

Cancer type	Targets/ Regulators and Signaling Pathways	Cell line	Function	References
Hepatocellular carcinoma	miR-9, p21	HepG2, SMMC-7721, QGY-7701, SK-Hep1	Δ circMTO1: ↑ proliferation, ↑ invasion, ↓ apoptosis ↑ circMTO1: ↑ apoptosis	[15]
Lung adenocarcinoma	miR-17, QKI-5, Notch signaling pathway	A549, SPC-A1, HCC827, NCI-H1299, NCI-H23, HBE	↑ circMTO1: ↓ proliferation	[20]
Colorectal cancer	Wnt/β-Catenin Signaling Pathway	SW480, SW620, HT29, HCT-116, FHC	Δ circMTO1: ↑ migration, ↑ invasion	[21]
Bladder cancer	miR-221, E-cadherin, Ncadherin, vimentin	CCC-HB-2, UMUC3, SVHUC1, T24, J82, 5637	↑ circMTO1: ↓ migration, ↓ invasion, ↑ EMT process	[22]
Cervical cancer	miR-6893, S100A1, Beclin1, p62	HeLa, CaSki, C-33A, C-4 II, SiHa, Ect1/E6E7	Δ circMTO1: ↓ migration, ↓ invasion, ↓ autophagy signaling pathway, ↑ chemoresistance to cisplatin	[28]
Glioblastoma	miR-92, WWOX	NHA, A172, U251, U87, SNB19, SHG44	Δ circMTO1: ↑ proliferation	[23]
Gallbladder cancer	miR-219a-5p, TGF-β/Smad pathway, EGFR	GBC-SD, NOZ	Δ circMTO1: ↓ migration, ↑ apoptosis	[27]
Hepatoma	miR-9-5p, NOX4	Huh7, Hep3B, MHCC-97L, MHCC-97H, SMMC-7721, HepG2, L-02	↑ circMTO1: ↓ proliferation, ↓ migration, ↑ apoptosis	[19]
Prostate cancer	miR-17-5p	DU-145, VCaP, PC-3, RWPE-1	↑ circMTO1: ↓ proliferation, ↓ invasion	[24]
Osteosarcoma	miR-630, KLF6	hFOB 1.19, HOS, U2OS, Saos-2, MG63	↑ circMTO1: ↓ proliferation, ↓ migration, ↓ invasion, ↑ apoptosis	[25]
Gastric cancer	miR-3200-5p, PEBP1	GES-1, MKN-45, MGC-803, AGS	↑ circMTO1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process	[26]
	miR-199a-3p, PAWR	SGC-7901, BGC823, MKN-28, MGC-803, AGS, HGC-27, GES-1	↑ circMTO1: ↓ proliferation, ↓ migration, ↓ invasion, ↑ apoptosis	[29]
Ovarian cancer	miR-182-5p, KLF15	SKOV3, OVCAR3, IOSE80	Δ circMTO1: ↑ proliferation, ↑ migration, ↑ invasion ↑ circMTO1: ↓ proliferation, ↓ migration, ↓ invasion	[30]
Renal cell carcinoma	miR-9, LMX1A, P21	786-O, 767P, and GRC1, SN12C and A498	Δ circMTO1: ↑ proliferation, ↑ migration, ↑ invasion ↑ circMTO1: ↓ proliferation, ↓ migration, ↓ invasion	[17]

has also been down-regulated in bladder cancer cells. Forced over-expression of circMTO1 in these cells has led to suppression of EMT and metastatic aptitude of bladder cancer cells. Functionally, circMTO1 could sponge miR-221 and regulate E-cadherin/N-cadherin pathway [22].

In addition, circMTO1 has been found to suppress proliferation of glioblastoma cells through influencing miR-92/WWOX cascade [23]. Fig. 2 summarizes the mechanisms of tumor suppressor role of circMTO1 in lung cancer, colorectal cancer, bladder cancer and glioblastoma.

In vitro experiments in prostate cancer cells have shown that circMTO1 inhibits proliferation and invasive aptitude of cells and down-regulates expression of miR-17-5p [24]. CircMTO1 has also been shown to suppress proliferation and metastatic ability of osteosarcoma cells via sponging miR-630 and up-regulating KLF6 [25]. The sponging effect of circMTO1 on miR-3200 and subsequent release of PEBP1 from the inhibitory effect of this miRNA has been identified as the molecular mechanism of circMTO1-mediated suppression of gastric cancer [26]. Fig. 3 depicts the tumor suppressor role of circMTO1 in prostate cancer, gastric cancer and osteosarcoma.

In gallbladder and cervical cancer cell lines, circMTO1 has oncogenic roles through sequestering miR-219a-5p [27] and miR-6893 [28], respectively (Fig. 4).

Table 1 summarizes the results of in vitro assessments of the role of circMTO1 in the carcinogenesis.

3. Animal studies

Intratumoral administration of small interfering RNA (siRNA) against circMTO1 has resulted in enhancement of tumor growth in xenograft models of HCC. Moreover, miR-9 has been identified as the target of circMTO1 through using biotin-labeled probes in animal models. These experiments have verified that circMTO1 inhibits progression of HCC through sequestering the oncogenic miR-9 [15]. The impact of circMTO1 on growth of lung cancer cells has been appraised in a xenograft model constructed by subcutaneous injection of stable circ-MTO1-overexpressing adenocarcinomic human alveolar basal epithelial cells into nude mice. Up-regulation of circ-MTO1 has led to attenuation of tumor growth as evident by reduced tumor weight and volume and significant decrease in proportion of Ki-67-positive cells

Table 2

Animal studies about the role of circMTO1 in the carcinogenesis.

Cancer Type	Animal models	Results	References
lung adenocarcinoma	nude mice	↑ circMTO1: ↓ tumor volume, ↓ tumor weight	[20]
Hepatocellular carcinoma	male nude mice	Δ circMTO1: ↑ tumor growth	[15]
Bladder cancer	BALB/c nude mice	↑ circMTO1: ↓ tumor volume	[22]
Cervical cancer	NOD-SCID immuno-deficient mice	Δ circMTO1: ↓ tumor growth	[28]
Gastric cancer	female BALB/c nude mice	↑ circMTO1: ↓ tumor volume, ↓ tumor weight, ↓ tumor growth	[29]

[20]. While tumor suppressor role of circMTO1 has been also validated in animal models of bladder [22] and gastric [29] cancers, a single study in cervical cancer has reported decrease in tumor growth following circMTO1 silencing [28]. Table 2 shows the results of animal studies about the role of circMTO1 in the carcinogenesis.

4. Human studies

In colorectal cancer, down-regulation of circMTO1 has been correlated with high TNM stage, lymph node involvement, and poor clinical outcome. In fact, circMTO1 serves as a tumor suppressor circRNA in colorectal cancer and a possible marker and therapeutic candidate for this type of cancer [21]. Similarly, circMTO1 has been found to be commonly down-regulated in bladder cancer tissues in correlation with higher probability of metastasis and poor survival [22]. In addition, a high throughput study using circRNA microarray has demonstrated down-regulation of circMTO1 in liver cancer tissues compared with normal controls [19]. Expression of circMTO1 has also been decreased in prostate cancer tissues compared with corresponding neighboring tissues. Over-expression of this circRNA has been correlated with lower pathological T and N stages as well as better overall and disease-free survival rates [24]. Table 3 shows summary of clinical studies that validated the expression pattern of circMTO1 in clinical samples.

Table 3

Clinical studies about the role of circMTO1 in the carcinogenesis (OS: overall survival, DFS: disease-free survival, PFS: progression-free survival, ANCT: adjacent non-cancerous tissue).

Cancer type	Numbers of clinical samples	Expression (Tumor vs. Normal)	Function	Kaplan-Meier analysis	Univariate cox regression	Multivariate cox regression	Ref
Lung adenocarcinoma	63 pairs of cancer and ANCTs	down	tumor suppressor	Low circMTO1 expression was correlated with a significantly shorter OS or PFS time.	_	_	[20]
Colorectal cancer	63 pairs of CRC tissues and ANCTs	down	tumor suppressor	CRC patients with low circMTO1 expression had significantly poor OS.	_	_	[21]
Hepatocellular carcinoma	261 HCC samples and ANCTs	down	tumor suppressor	_	_	_	[15]
	116 HCC samples and ANCTs	down	tumor suppressor	HCC patients with low circMTO1 expression in their tissues had significantly poor prognosis.			
Bladder cancer	117 bladder cancer tissues and ANCTs	down	tumor suppressor	Low circMTO1 expression was correlated with poorer OS and DFS.	_	_	[22]
	A Meta-Analysis: 1430 patients from 14 studies	_	tumor suppressor	High expression of circMTO1 was correlated with better clinical tumor characteristics such as TNM staging, lymph node metastasis, and histological grade.	_	_	[31]
Cervical cancer	TCGA analysis: 313 cervical cancer samples	up	oncogene	_	_	_	[28]
Glioblastoma	59 glioblastoma samples and ANCTs	down	tumor suppressor	Patients with lower expression of circMTO1 had poor OS.	_	_	[23]
Gallbladder cancer (GBC)	TCGA analysis: 36 tumor tissues and 9 normal tissues	up	oncogene	Patients with high expression of circMTO1 had poorer OS than those with low circMTO1 expression.	_	_	[27]
	100 GBC samples and ANCTs	up	oncogene	Patients with high expression of circMTO1 had significantly shorter OS and PFS than patients with low expression.	High circ-MTO1 expression was correlated with tumor size, differentiation, TNM stage, lymph node metastasis, and distant metastasis.	_	[32]
Liver fibrosis	360 CHB samples and ANCTs	down	tumor suppressor	High expression of circMTO1 was correlated with higher OS.	_	_	[18]
Hepatoma	20 pairs of liver tumor tissues and ANCTs	down	tumor suppressor	_	_	_	[19]
Prostate cancer	298 primary prostate cancer tissues and paired ANCTs	down	tumor suppressor	Patients with high levels of circMTO1 had more favorable OS and DFS compared to patients with low levels of circMTO1.	High levels of circMTO1 indicated improved DFS and better OS.	High levels of circMTO1 independently predicted increased DFS and more prolonged OS.	[24]
Osteosarcoma	70 osteosarcoma tissues and ANCTs	down	tumor suppressor	Patients with low circMTO1 expression showed significantly shorter OS time compared to those with high circMTO1 expression.	_	_	[25]
Gastric cancer (GC)	_	down	tumor suppressor	_	_	_	[26]
	68 pairs of GC tissues and ANCTs	down	tumor suppressor	Patients with low expression of circMTO1 showed advanced GC TNM staging, lymphatic invasion, larger tumor size, and poor OS.	_	_	[29]
Ovarian cancer	48 ovarian cancer tissues and ANCTs	down	tumor suppressor	_	_	_	[30]

5. Role of circMTO1 in non-malignant conditions

Moreover, serum levels of circMTO1 have been found to be decreased in patients with chronic hepatitis B. Notably, serum levels of this circRNA have been inversely correlated with fibrosis stages and hepatic activity index scores. Receiver operating characteristic curve analysis has indicated that serum circMTO1 levels can separate patients with liver fibrosis from healthy controls with area under curve, sensitivity and specificity values of 0.914, 75.8% and 90.0%, respectively. Mechanistically, circMTO1 suppresses TGF-β1-induced activation of hepatic stellate cells. CircMTO1 has also been shown to interact with miR-17-5p. Collectively, circMTO1 has been found to inhibit liver fibrosis through modulation of miR-17-5p and Smad7 [18].

6. Discussion

CircRNAs have been found to affect tumorigenesis process through different routes, particularly sponging miRNAs. CircMTO1 is a newly identified circRNA with tumor suppressor role in various tissues, but oncogenic role in cervical and gallbladder cancers.

The most important route of participation of circMTO1 in the suppression of carcinogenesis is its effect on sequestering oncogenic miR-NAs. miR-17, miR-9, miR-221, miR-92, miR-630, miR-3200-5p and miR-199a-3p are among miRNAs which are sequestered by circMTO1. On the other hand, circMTO1 has been found to sponge the tumor suppressors miRNAs miR-6893 and miR-219a-5p, thus promoting progression of cervical and gallbladder cancer.

CircMTO1 levels have also been used to predict survival of patients with different types of cancers. Globally, higher expression of circMTO1 has been associated with lower stage, reduced tumor size, better differentiation of tumors and lower rate of remote metastasis, therefore indicating better survival of patients. However, in cervical cancer where it serves as an oncogene, patients with high expression of circMTO1 had poorer overall survival than those with low circMTO1 expression [28].

Diagnostic role of circMTO1 has been assessed in liver fibrosis indicating high diagnostic power and specificity value. However, data regarding diagnostic application of circMTO1 in malignant conditions is scarce. Based on the stability of circRNAs in the circulation, this class of transcripts can serve as potential biomarkers for early detection of cancer. Therefore, upcoming studies should assess this aspect of circMTO1 in clinical settings.

Taken together, circMTO1 has a novel circRNA with prominent roles in the carcinogenic processes which are most probably dependent on the tissue type. The results of studies in animal models have been promising, since up-regulation of circMTO1 could significantly reduce tumor burden in most cases, yet based on the tissue-specific effects of circMTO1 translation of these results into clinical application should be accomplished with caution. Therefore, therapeutic application of circMTO1 is a potential modality which should be assessed in future, based on the role of this circRNA in each tissue. These modalities include either force up-regulation of this circRNA or short hairpin/ small interfering RNA-mediated silencing of its expression.

CRediT authorship contribution statement

SGF and MT wrote the draft and revised it. TK, AB and MH collected the data, designed the figures and tables. All the authors read and approved the submitted version.

Conflict of interest statement

The authors declare they have no conflict of interest.

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