CTHRC1, a novel gene with multiple functions in physiology, disease and solid tumors (Review)

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Received July 20, 2022; Accepted March 1, 2023

DOI: 10.3892/ol.2023.13852

Abstract. Collagen triple helix repeat containing 1 (CTHRC1) is a gene discovered in 2005; it is highly conserved, and no homologous proteins have been disclosed thus far. A number of studies have shown that CTHRC1 is present in normal tissues and organs, and it has vital functions in physiological processes, including participating in the regulation of metabolism, arterial remodeling, bone formation and myelination of the peripheral nervous system. It has been reported that abnormal expression of CTHRC1 is involved in the carcinogenesis of various human organs, such as the breast, colon, pancreas, lung, stomach and liver. Therefore, the present review aims to collate all known findings and results on the regulation of CTHRC1 expression and related signaling pathways. To conclude, this review also provides a hypothesis of the functional mechanism of this gene.

Contents

1. Discovery and identification of CTHRC1

Collagen triple helix repeat containing 1 (CTHRC1) was first identified in 2005 in a screen for differentially expressed genes between normal and balloon-wounded rat arteries (1). The CTHRC1-related gene was subsequently discovered in two distant cnidarian species, the jellyfish *Nematostella vectensis* and the hydrozoan *Clytia hemisphaerica*, both of which contained multiple copies of the gene. In addition, an attempt was made to trace the origin of CTHRC1 by studying the C-terminal domains of CTHR and CTHRC1, but this remains unclear (2). Located at chromosome position 8q22.3, the CTHRC1 gene encodes a 28-kDa secretory glycosylated protein (1,3).

The evolutionarily conserved structure of CTHRC1 has been elucidated among several species, with no homologous proteins discovered (1). It is composed of a leucine-rich hydrophobic signal peptide at the N-terminus, a short 12 repeat Gly-X-Y collagen motif responsible for triple helix formation, and a number of highly conserved amino acids at the C-terminus (1,4).

In vitro detection of CTHRC1 using antibodies specific to the corresponding domain of recombinant CTHRC1 expressed in *Escherichia coli* resulted in the detection of five lower molecule weight forms of CTHRC1, ranging between 10 and 30 kDa, of which only one form was not cleaved by plasminase (5). The abundance of processed CTHRC1 implies that CTHRC1 may appear in a differentially modified form. In dedifferentiated smooth muscle cells (SMCs), monomeric CTHRC1 was found to bind with cytoplasmic proteins, suggesting a potential functional regulation of CTHRC1 (5). Plasmin was reported to cleave a putative propeptide of CTHRC1 to generate an N-terminally truncated molecule capable of regulating procollagen synthesis (5). N-glycosidase is capable of cleaving CTHRC1 into minor fragments, which are the active form of CTHRC1 involved in some signaling transductions (6). As the name may suggest, CTHRC1 is susceptible to cleavage by collagenases.

2. Expression pattern of CTHRC1

Immunohistochemical studies on cell types from a number of organs have shown the localized expression of CTHRC1 in the cytoplasm (7-11). One particular study has suggested that CTHRC1 is membrane-anchored (3).

Comprehensive expression analysis revealed that CTHRC1 was present in a number of tissues and organs of embryonic and

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Key words: collagen triple helix repeat containing 1, physiology, disease, tumor, mechanism

postnatal mice (3). CTHRC1 was also found to be expressed in differentiated SMCs of arterioles, large veins, the uterus and gastrointestinal tract, as well as in myoepithelial cells, neurons, Purkinje cells and parafollicular cells of the thyroid gland (5). In particular, CTHRC1 has also been found in calcified atherosclerotic plaques in a rat model of carotid balloon catheter-induced injury (1).

In addition to endogenous detection in normal tissues, the presence of CTHRC1 has been observed in a number of malignancies. The expression levels of CTHRC1 in 24 different tumor tissues were analyzed by the UALCAN database, and the transcription level in all 24 tumor tissues was abnormally elevated compared with that in normal tissues (8). Additionally, CTHRC1 is typically expressed at epithelial-mesenchymal interfaces, such as the epidermis and dermis, the epithelium of the basal cornea, airway and esophagus, and the choroid plexus and meninges (12).

A number of studies have demonstrated CTHRC1 expression in a variety of human solid tumors; however, a previous study has suggested that cells from a pancreatic tumor did not express CTHRC1 (8,13). The aforementioned study also noted that expression of CTHRC1 was only present in the stroma surrounding tumor cells, which includes vessel and skeletal muscle cells, as well as fibroblasts. There are four explanations for this paradox: i) Endogenous CTHRC1 has been revealed to exist in a number of molecular weight forms, meaning it may exist in different forms with a variety of sequences after some modification; hence, each modified CTHRC1 protein may contain a different epitope map; ii) the combination of CTHRC1 with undetermined cytoplasmic proteins may prevent the exposure of specific epitopes on CTHRC1, although when, where and how this binding occurs remains unknown; and iii) the specificity of anti-CTHRC1 antibodies may vary between institutions, possibly leading to different epitope recognition.

3. Regulation of the expression of CTHRC1

Transforming growth factor-β (TGF-β) and bone morphogenetic protein 4 (BMP-4) are involved in regulating the expression of CTHRC1. The mRNA expression levels of CTHRC1 have been shown to be gradually increased under TGF-β1 and BMP-4 stimulation (1). Sequence analysis of the CTHRC1 promoter region revealed a Smad protein-binding site, which is a downstream member of the TGF-β1- and BMP-4-mediated pathways (14). In keloid fibroblasts, CTHRC1 expression was revealed to be upregulated in a concentration-dependent manner by TGF-β1 (15). CTHRC1 and phosphos-Smad 3 form a negative feedback loop in the TGF-β pathway. CTHRC1 is specifically induced by TGF-β1 by phosphorylating Smad3 and binding to the H promoter, which in turn accelerates the degradation of phosphorylated Smad3 (16).

Dolichyl-phosphate N-acetylglucosaminephosphotransferase (DPAGT1). DPAGT1 is an N-glycosylation gene that functions as the primary regulator of the metabolic pathway in protein N-glycosylation (17). The amplification of CTHRC1 is positively associated with its own hyperglycosylation, which is modulated by DPAGT1. In oral squamous cell carcinoma (OSCC), DPAGT1 and CTHRC1 were shown to be upregulated simultaneously, and the inhibition of DPAGT1 by small interfering RNA led to decreased CTHRC1 expression (18). Partial inhibition of DPAGT1 expression in OSCC cells downregulated CTHRC1 abundance by reducing its half-life (18).

Hepatitis B virus (HBV) infection. In hepatocytes, HBV was shown to stimulate CTHRC1 mRNA and protein levels in a time- and dose-dependent manner (19). Two sequences were found to be involved in HBV-activated CTHRC1 expression by constructing full-length promoters or mutants of CTHRC1, regulated by nuclear factor-κB (NF-κB) and cAMP response element binding protein (19). Overexpression of CTHRC1 in turn promoted HBV replication (20).

Proto-oncogene, Wnt-3a. Wnt3a is a member of a diverse family of secreted lipid-modified signaling glycoproteins that act as ligands to activate the Wnt/β-catenin pathway (21). In OSCC, Wnt3a was shown to markedly increase the mRNA transcript and protein levels of CTHRC1, and increased recruitment and binding of β-catenin to the T-cell factor sites at the CTHRC1 promoter contributed to this observation (18).

MicroRNAs (miRNAs/miRs). miRNAs are associated with individual life activities, such as cell growth, tissue differentiation, and tumor transformation and metastasis. miR-30c is an important member of the miR-30 family, and its expression was found to be significantly lower in breast cancer (BC) compared with in normal tissue (22). Notably, the expression of miR-30c has been revealed to be negatively associated with CTHRC1, and miR-30c may inhibit CTHRC1 activation of the GSK-3β/β-catenin signaling process, reduce β-catenin protein in the nucleus and inhibit BC cell proliferation, invasion and migration (23). In BC, miR-30e can negatively regulate CTHRC1 (24). In gastric cancer, overexpression of let-7b, a miRNA belonging to the let-7 family has been shown to reduce the levels of CTHRC1 protein. Conversely, in cells treated with a let-7b inhibitor, CTHRC1 expression was higher compared with that in control cells (25). It was reported that let-7b suppressed the activity of CTHRC1 through binding position 20-26 in the 3'-untranslated region (3'-UTR) of CTHRC1 mRNA (25). In melanoma, both miR-134 and CTHRC1 have been reported to be highly expressed, but there is a negative interaction between the two: miR-134 can directly target the 3'-UTR of CTHRC1 to downregulate CTHRC1, thereby limiting the migration and invasion ability of melanoma cells (26). The same regulation was discovered for miR-509-3p, which can bind to the potential binding site of CTHRC1 to reduce the expression of CTHRC1. miR-509-3p can also increase the levels of a-catenin and E-cadherin, and reduce mesenchymal markers such as waveform and fibronectin levels to inhibit melanoma metastasis and invasion (27). In human ovarian cancer, miR-30b-3p, through targeting of the CTHRC1 3'-UTR, can increase E-cadherin and β-catenin expression, and inhibit the epithelial-mesenchymal transition (EMT) process in ovarian cancer cells to suppress tumor invasion and metastasis (28). In prostate cancer, miR-30e-5p can also play a role in regulating the CTHRC1/EMT axis to inhibit the proliferation and invasion of PCa cells by targeting the CTHRC1 3'-UTR (29).

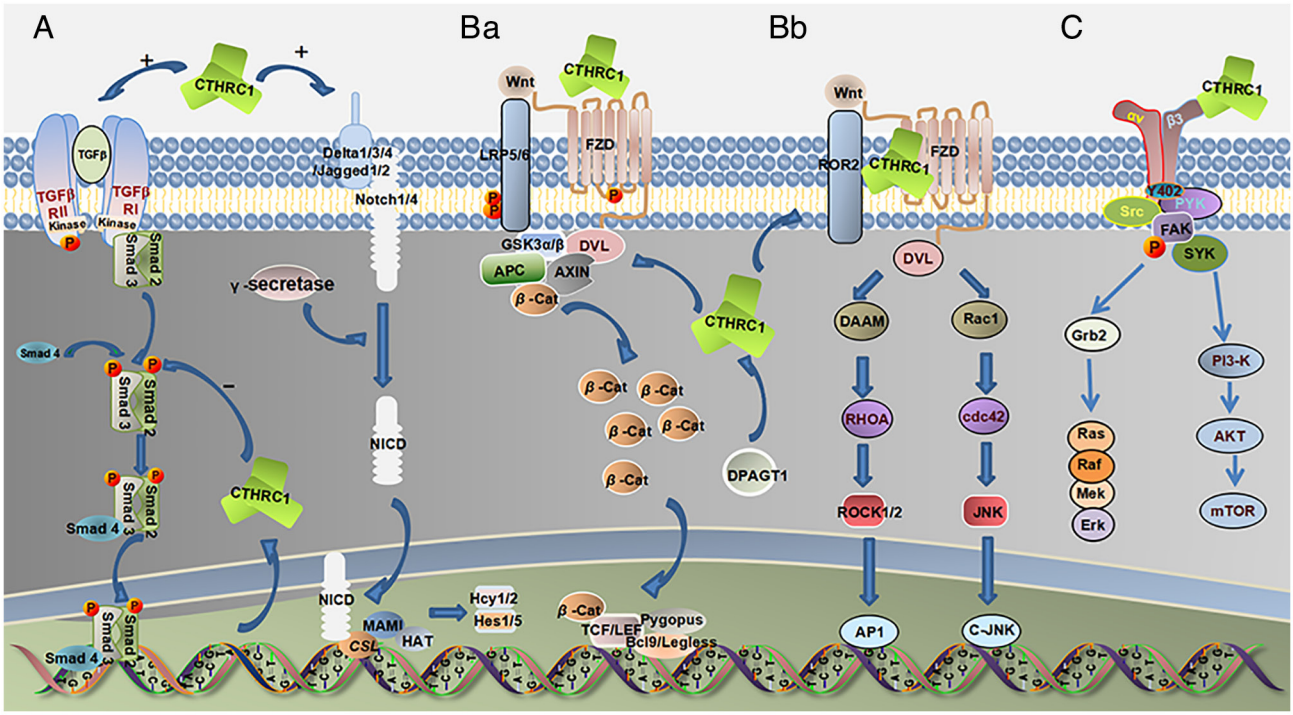

Figure 1. (A) In wound healing, CTHRC1 can recruit additional M2 macrophages to the wound site to promote skin repair and activate the TGF-β and Notch pathways. DPAGT1 can regulate the activation of CTHRC1, and CTHRC1 activates the TGF-β pathway; simultaneously, there is a key negative feedback loop. The increased phosphorylation level of Smad2/3 in the TGF-β downstream signaling pathway stimulates the expression of CTHRC1. However, overexpression of CTHRC1 in turn suppresses Smad2/3 phosphorylation. WNT signaling includes the WNT/β-catenin classical pathway and the β-catenin atypical pathway. (Ba) In the WNT/β-catenin classical pathway, CTHRC1 can activate this pathway and significantly increase β-catenin stability and transcriptional activity. (Bb) In non-classical WNT/PCP signaling, CTHRC1 can promote and stabilize the formation of the CTHRC1-Wnt-FZD/Ror2 complex, thereby selectively activating the WNT/PCP pathway, whose downstream molecules include the GTPase family, such as Rac1, RhoA and JNK. CTHRC1 can enhance RhoA and Rac1 activities, and increase JNK phosphorylation, and DPAGT1 can regulate the activation of CTHRC1 on the Wnt/PCP pathway. (C) Upregulation of CTHRC1 activates Src-FAK signaling, which is associated with cancer progression and metastasis.

4. Participation in multiple signaling pathways

CTHRC1 and TGF-β signaling. TGF-β signaling has been shown to be highly active at locations where CTHRC1 is transiently overexpressed, implying a linkage between the two (1). In a transgenic mouse animal model, increased phosphorylation of Smad2/3 in the downstream TGF-β signaling pathway stimulated the expression of CTHRC1 mRNA and protein. Conversely, overexpression of CTHRC1 significantly inhibited TGF-β signaling transduction by reducing phospho-Smad2/3 activity (1,30). Therefore, it is possible that CTHRC1 may regulate the TGF-β signaling cascade through a negative feedback loop. Similarly, an experiment with polyvinylalcohol sponge found that during the middle stage of wound healing, CTHRC1 can recruit additional M2 macrophages by activating the TGF-β/Smad pathway to promote wound healing. TGF-β expression may be downregulated by CTHRC1 during the later remodeling stage of wound healing (31) (Fig. 1A). These results are not inconsistent with each other, suggesting that TGF-β and CTHRC1 interact to maintain tissue morphology and homeostasis.

CTHRC1 and Wnt/planar cell polarity (Wnt/PCP) signaling pathway. CTHRC1 has been shown to promote and stabilize formation of the CTHRC1-Wnt-Fzd/Ror2 complex, thus selectively activating the Wnt/PCP pathway (Fig. 1Bb). A highly conserved 200-amino acid region in the C-terminal domain of CTHRC1 was discovered to be responsible for this biological selection (32). DPAGT1 has been demonstrated to regulate the activation effect of CTHRC1 on the Wnt/PCP pathway; the interaction between Wnt protein and CTHRC1 was revealed to be more intensive and the downstream effector of the Wnt/PCP pathway was more abundant in DPAGT1-transfected cells (18). The Wnt/PCP signaling pathways affect the development of various types of cancer. In gastrointestinal stromal tumors (GISTs), CTHRC1 may activate human umbilical vein endothelial cells (HUVECs) in the Wnt/PCP signaling pathway to promote ERK phosphorylation and JNK to promote tumor angiogenesis (33). Western blotting showed that overexpression of CTHRC1 in cervical cancer tissue and HeLa cells increased Wnt5a, Ror2 and p-c-Jun, thereby activating the Wnt/PCP signaling pathway and promoting tumor invasion and metastasis (34).

CTHRC1 and Wnt/β-catenin signaling pathway. The relationship between CTHRC1 and the Wnt/β-catenin pathway has been shown to be cell type-dependent. In placental trophoblastic cells and cancer-associated fibroblasts, CTHRC1 can function as an activator by significantly increasing the stability and transcriptional activity of β-catenin, a hallmark of Wnt/β-catenin signaling activation (Fig. 1Ba) (35). However, in GISTs, CTHRC1 functions as an inhibitor by promoting the degradation of β-catenin (35-37). The mechanism by which CTHRC1 influences the Wnt/β-catenin

pathway in an opposing way in different cell types needs to be further explored.

CTHRC1 in Notch and other signaling pathways. The Notch signaling pathway allows communication between two adjacent cells and triggers a variety of downstream responses to maintain a stable cell state. A number of studies have shown that the Notch pathway is activated in wound macrophages (31,38). It may also be involved in tissue repair processes, and CTHRC1 may promote wound healing by activating it and the TGF-β pathway (31). Furthermore, the Notch signaling pathway is expressed in tumor cells, but it remains to be investigated whether CTHRC1 can participate in the development and progression of tumors through activation of the Notch signaling pathway.

It is well known that the proto-oncogene tyrosine-protein kinase Src, focal adhesion kinase (FAK), mitogen-activated protein kinase kinase (MEK) and ERK are key molecules in their respective signaling pathways and participate in tumorigenesis in various types of cancer (39-41). Overexpression of CTHRC1 has been shown to activate these pathways by increasing their phosphorylation level in numerous studies (Fig. 1C) (39,41-43). However, the detailed roles of CTHRC1 in these pathways have yet to be elucidated.

5. Biological function of CTHRC1

Arterial remodeling. Constitutive expression of CTHRC1 can significantly reduce adventitial collagen deposition, neointimal lesion formation and intimal SMC dedifferentiation in the repair process of injured arteries, suggesting that CTHRC1 may perform an important role in vascular remodeling (30). *In vitro* experiments suggested that overexpression of CTHRC1 inhibited collagen extracellular matrix (ECM) deposition in the adventitia of injured arteries by reducing the mRNA synthesis of α1 and α2 chains of collagen type I (1). *In vivo* experiments further confirmed that the adventitia of the carotid artery was 50% thinner in CTHRC1 transgenic mice than in wild-type littermates (30). In addition, an association between TGF-β and CTHRC1 has been reported. TGF-β plays an important role in promoting angiogenesis during arterial remodeling by activating Smad2/3 complex, upregulating collagen synthesis, and increasing collagen deposition and SMC proliferation (4). TGF-β stimulates upregulation of CTHRC1 expression; however, by reducing Smad2/3 phosphorylation, CTHRC1 inhibits the expression of the TGF-β target genes type I and type III collagen, thereby inhibiting collagen deposition, enhancing cell migration and promoting vascular repair (1,16).

Regulation in dystrophic muscle diseases. CTHRC1 has been shown to be a marker for the severity of disease progression in Duchenne muscular dystrophy (DMD) and congenital muscular dystrophy (CMD) (44). Gene expression of CTHRC1 was upregulated in DMD and CMD transgenic mice as well as in biopsy specimens of patients with DMD (44). The presence of CTHRC1 was associated with the deposition of type I collagen, and the collagen fibers adjacent to collagen and CTHRC1 were smaller, suggesting that CTHRC1 controlled collagen synthesis in DMD and CMD (44).

Regulation of metabolism. CTHRC1 has been detected in the plasma of CTHRC1 transgenic mice, exhibiting a half-life of ~2.5 h, which suggests it could be secreted into the circulatory system (45). CTHRC1 aids in regulating glucose and energy metabolism in the liver and skeletal muscle of animal models, suggesting that hepatocytes and myocytes may express CTHRC1 receptors (45). Moreover, constitutive expression of CTHRC1 was observed in some areas of the brain of rats and pigs, such as the chromophobe cells and colloid-filled follicles in the anterior pituitary lobe (45). Since no specific hormone has been reported to localize in chromophobe cells of the anterior pituitary lobe thus far, whether CTHRC1 is the first discovered hormone secreted from this site needs to be verified (45).

CTHRC1 can promote bone formation. A number of signaling pathways mediate bone homeostasis, including TGF-β and BMP, in which CTHRC1 is also involved. The regulation of bone formation and maintenance by CTHRC1 suggests that it interacts with TGF-β and BMP-Smad signaling (46). *In vitro* and *in vivo* studies have suggested that CTHRC1 is a positive regulator of bone formation, and can promote the differentiation and mineralization of bone progenitor cells, and the proliferation and differentiation of osteoblasts, thereby inducing high bone mass (46). The autonomy of CTHRC1 in promoting osteogenic differentiation depends on cell type, and CTHRC1 has been demonstrated to have an autonomous function in skull osteoblasts *in vitro* but not in bone marrow-derived mesenchymal stem cells (39). The identity of CTHRC1-producing cells remains controversial. CTHRC1 has been shown to serve a role in the coupling process of bone resorption to formation as a coupling factor of osteoclast secretion that regulates bone remodeling. However, studies have shown that CTHRC1 is not derived from osteoclasts but instead from osteoblasts and osteocytes, and can inhibit the formation of osteoclasts and their activity (39,47).

Role in the peripheral nervous system. Yamamoto *et al* (6) found that mice with complete CTHRC1 knockout showed no significant phenotypic abnormalities and remained fertile. The PCP homolog, Vangl2, was additionally introduced in the experiments. Concurrently, it was revealed that $CTHRC1^{LacZ}$ $Vangl2^{Lp/-}$ mouse embryos exhibited a weak PCP phenotype, while $CTHRC1^{LacZ/LacZ}$; $Vangl2^{Lp/+}$ mouse embryos showed complete closure of the neural tube, suggesting that CTHRC1 affects neural tube opening by modulating the PCP signaling pathway. However, no significant abnormal PCP pathway or neural tube closure was observed in mouse embryos with complete CTHRC1 knockout without enhanced PCP mutations, suggesting the presence of functional redundant genes; however, their true nature remains unknown and should be investigated. Furthermore, CTHRC1 has been shown to be active in peripheral nerve cells. Schwann cells serve an important role in peripheral nerve repair, and can guide axon growth through self-demyelination and directional differentiation (48). In Schwann cells, CTHRC1 is upregulated in axonal interactions. Upregulation of CTHRC1 stimulates Schwann cell proliferation and delays myelination through *in vitro* loss of function and *in vivo* gain of function (49). After

sciatic nerve injury, the expression of CTHRC1 has been reported to be increased in Schwann cells overexpressing long non-coding RNA NONMMUG014387, which may promote the proliferation of Schwann cells by regulating the Wnt/PCP pathway (50). After peripheral nerve injury, most miRNAs are downregulated, and the downregulated expression of miR-9 is accompanied by upregulated expression of CTHRC1. A luciferase assay demonstrated that upregulated miR-9 could significantly downregulate CTHRC1 expression by directly targeting the CTHRC1 3'-UTR and reducing Schwann cell inhibition (51). These results suggested that CTHRC1 may be a novel myelination regulator in the peripheral nervous system (49-51).

6. Participation in the progression of solid tumors in humans

Melanoma. Melanoma is a type of skin cancer caused by malignant tumors of melanocytes. CTHRC1 was found to be expressed in invasive melanomas; however, in benign moles or noninvasive stage melanomas, it was not present, suggesting it may be associated with the invasion and metastasis of melanoma (14). It has been reported that CTHRC1 is involved in the tumorigenesis of melanoma mediated by miR-134-25 or miR-155-26 and miR-509-3p (26,27,52). In miR-509-3p-mediated melanoma, it was found that overexpressed CTHRC1 reduced the protein levels of α-catenin and E-cadherin, and enhanced the levels of vimentin and fibronectin, thus promoting the metastasis and invasion of melanoma (27).

BC. Upregulation of CTHRC1 was previously shown in BC, and its expression level was significantly associated with lymph node classification, histological grade and pathological Tumor-Node-Metastasis (pTNM) stage (23,36,53). It has been reported that CTHRC1 promotes BC cell invasion and metastasis by activating the Wnt/β-catenin signaling pathway between EMTs (23,36). CTHRC1 expression may also be associated with the prognosis of patients; in patients with elevated expression of CTHRC1, shorter overall survival (OS) and relapse-free survival times were observed, leading CTHRC1 to be considered an independent prognostic indicator for patients with BC (23).

Colorectal cancer (CRC). CTHRC1 has been indicated as a useful biomarker for CRC, as increased mRNA expression levels have been detected in CRC tissues compared with in normal tissues (54,55). CTHRC1 can affect the EMT process by inducing TGF-β signal transduction, thus enhancing the migration and invasion of CRC cells, and its high expression is associated with poor prognosis of patients with CRC (54,55). It has also been found that CTHRC1, which promotes liver metastasis of CRC, comes from CRC cells rather than hepatic stellate cells in patients with CRC exhibiting liver metastasis (55). It promotes tumor proliferation mainly through the TGF-β signaling pathway (55). Meanwhile, *in vivo* studies in mice showed that the combination of anti-CTHRC1 monoclonal antibody and anti-PD-1 monoclonal antibody reduced liver metastasis in CRC. Therefore, CTHRC1 may be a therapeutic target for CRC liver metastasis (55).

Gastric cancer (GC). An increased level of CTHRC1 has been discovered in GC (56,57). HIF-1α and CXCR4 perform important roles in GC metastasis, and the expression of CTHRC1 has been reported to increase the expression of activated HIF-1α/CXCR4 signaling pathways, which may result in GC cell migration and invasion (56). Upregulation of CTHRC1 in GC has been shown to be significantly associated with pTNM stage, tumor differentiation, depth of tumor invasion, lymph node metastasis, recurrence, vascular/lymphatic invasion, tumor size and peritoneal seeding (7,58). CTHRC1 expression may also be related to the prognosis of patients with GC, with higher CTHRC1 expression associated with a lower survival rate of patients with GC (57,58). Furthermore, a patient prognosis model based on CTHRC1 has been developed for stomach adenocarcinoma (59).

Pancreatic cancer (PC). Reverse transcription-PCR (RT-PCR) and immunohistochemical analysis revealed that CTHRC1 mRNA and protein levels were significantly increased in pancreatic ductal adenocarcinoma compared with in normal pancreatic ductal epithelium (42). Gene knock-in-and-out analysis suggested that high expression of CTHRC1 induced apparent metastatic spread to several secondary organs in PC, whereas abolishing expression of CTHRC1 predominantly decreased primary tumor progression and distant metastasis (42). By activating Src and ERK signaling pathways, CTHRC1 can induce cytoskeletal recombination, lamellar pseudopodia formation and sticky point increase in cell turnover in an autocrine manner, and enhance the motility and adhesion of PC cells (42). CTHRC1 can also activate the ERK/AP-1 signaling pathway to promote Ang-2 secretion, upregulate the Tie2 receptor ligand Ang-2 and lead to recruitment of Tie2-expressing monocytes in tumor tissues to induce tumor angiogenesis (42,43).

Hepatocellular carcinoma (HCC). CTHRC1 expression in HCC tissues has been shown to be significantly higher than in adjacent tissues, and the expression level of CTHRC1 was associated with tumor size, extent of vascular invasion, TNM stage and Barcelona clinic liver cancer stage (60,61). CTHRC1 also performs a role in the precancerous microenvironment of HCC (62). Studies have shown that CTHRC1 is an independent factor affecting OS in HCC. The establishment of a HCC survival prediction model showed that CTHRC1 was negatively associated with patient prognosis, and was determined to be a key factor in predicting HCC OS (61,63). Patients with HCC with higher CTHRC1 expression had lower 10-year OS and disease-free survival rates (64).

GIST. Immunohistochemical staining of GISTs have shown that they exhibit increased CTHRC1 expression and microvascular density (33). HUVEC migration and invasion are increased in GISTs, suggesting that the overexpression of CTHRC1 could promote tumor angiogenesis (33). RT-PCR, western blotting and immunohistochemical analysis revealed that CTHRC1 expression was closely associated with the risk grade of National Institutes of Health classification and prognosis of GIST (37). Kaplan-Meier curve analysis showed that CTHRC1 expression was negatively associated with the OS and disease-free status (DFS) of patients with GIST (37).

Non-small-cell lung cancer (NSCLC). Proteomic analysis of multiple studies has shown that CTHRC1 protein and mRNA levels are significantly overexpressed in NSCLC tissues and cell lines compared with the levels in adjacent non-cancerous tissues and normal lung epithelial cells (65,66). CTHRC1 can activate c-Jun/MMP7, c-Jun/MMP9 and NF-κB/MMP9 signaling to enhance the invasive ability of NSCLC (66). Upregulation of CTHRC1 has been reported to be significantly associated with differentiation, TNM stage, lymph node status and smoking status, and to strengthen the invasive ability, increase the colony formation and increase the migration of NSCLC cells (65). In addition, the expression of CTHRC1 may be considered an independent prognostic factor for both OS and DFS in NSCLC. A previous study showed that the diagnostic value of CTHRC1 was only observed in patients with NSCLC with a history of cigarette smoking, suggesting that CTHRC1 may interact with tobacco-based compounds in the development of NSCLC (67).

Prostate cancer (PrCa). Although CTHRC1 has been found to perform an important role in proliferation and metastasis in a number of tumors, its role in PrCa has not been fully elucidated. It has been reported that CTHRC1 is significantly expressed in PrCa and plays an important role in the tumor microenvironment, promoting the proliferation and migration of PrCa cells and affecting the prognosis and treatment of PrCa, and CTHRC1 has also been shown to be related to the recurrence rate and survival rate of cancer following treatment (29,68). In the early detection of PrCa by ELISA, CTHRC1 has been shown to be a potential diagnostic marker for PrCa, but further studies are needed to determine its clinical utility as a diagnostic marker (69).

7. Conclusions

Cell specificity of CTHRC1 functioning. CTHRC1 has been reported to inhibit TGF-β signaling in SMCs, whereas this function has not been detected in endothelial cells (30). Overexpression of CTHRC1 can reduce the mRNA expression levels of collagen type I and decrease collagen deposition in SMCs, but not in osteoblasts (1,30). Notably, CTHRC1 promoted the migratory ability of SMCs in a wounded artery, but the function was reversed in Schwann cells (49). In addition, CTHRC1 can activate canonical Wnt/β-catenin signaling in NSCLC, whereas it inhibits it in GIST (66). Knockdown of CTHRC1 had no effect on the proliferation rate of PrCa cells, but significantly inhibited the proliferation and survival of HCC cells (3,42). Based on these findings, it is reasonable to assume that CTHRC1 functions with cellular specificity. It was previously reported that CTHRC1 is a hormone that may regulate cell function in an autocrine manner (42,45,49), which suggest that the types of membrane-anchored receptors specific to CTHRC1 may vary across cell types and cause differences in signal transduction, ultimately leading to distinctive outcomes.

Possible mechanism by which CTHRC1 regulates the migration and invasion of solid tumors. CTHRC1 has been reported to be associated with multiple signaling cascades, suggesting that it performs a functional role in the physical and biological behavior of cells. However, CTHRC1 also promotes the carcinogenesis of solid tumors, as outlined in a number of studies. The present review sought to extract some possible mechanisms for how CTHRC1 is involved in carcinogenesis. First, CTHRC1 was found to control collagen type I deposition and thus regulate the formation of the ECM through crosstalk with the TGF-β signaling pathway. The ECM has been shown to be the basic skeleton of the tumor microenvironment, which performs a pivotal role in promoting cancer cell survival, invasion and metastasis (70,71). The suggestion that CTHRC1 regulates the tumor microenvironment is strengthened by the phenomenon that CTHRC1 expression is largely present in the interstitial region of tumor cells, such as stromal cells, vessels and fibroblasts, which are key components of the surrounding tumor environment. Second, activation of the Wnt/PCP pathway by CTHRC1 contributes to the migratory and invasive nature of tumors. The PCP signaling pathway regulates actin polymerization and cytoskeletal reorganization, which enables it to alter cellular morphology and increase cellular motility (72-74). Third, loss of intercellular adhesiveness, EMT, disruption of the basement membrane and degradation of the ECM are the four phases influencing the mobility and invasiveness of cancer cells (75). RT-PCR and immunoblotting indicated that some EMT-associated molecules, such as MMP9 and vimentin, were increased, whereas EMT inhibitory proteins, such as E-cadherin, were decreased in a cell line that highly expressed CTHRC1. Conversely, knockdown of CTHRC1 in this cell line markedly reversed the effect (27,28,66). Fourth, overexpression of CTHRC1 was shown to increase the phosphorylation level of the proto-oncogene tyrosine-protein kinases Src, FAK, MEK and ERK, which are key transmitters in promoting the migratory and invasive ability of numerous types of cancer (37,39,42).

The existence of a CTHRC1-related regulatory feedback loop. The expression sites of CTHRC1 on a cellular level were found to overlap considerably with those of TGF-β family members and interstitial collagens (12), which suggests a close relationship between CTHRC1 and TGF-β and ECM formation, as well as the pathway by which CTHRC1 performs its role. As aforementioned, a negative feedback regulatory loop possibly exists between CTHRC1 and TGF-β. Here, this review provides a hypothesis for how this feedback loop may work, although it is likely that the real network between these two would be much more complex. During the reparative process of tissue injury, TGF-β not only induces the production of collagen and ECM deposition through the activation of Smad-dependent signaling, but also simultaneously stimulates the expression of CTHRC1. With the negative feedback loop mechanism, the activity of TGF-β signaling transduction is accurately controlled by elevated levels of CTHRC1 in itself so that injured tissue can avoid excess repair; thus, the tissue normality is preserved. Nevertheless, *in vivo*, the expression of CTHRC1 may be delicately controlled by a variety of genetic signaling pathways rather than a single factor, which may also contribute to a series of pathological statuses, for example, luminal constriction during artery remodeling after injury and the occurrence of keloids during wound healing of the skin.

A study regarding the involvement of CTHRC1 in the development of Barrett's esophagus and esophageal adenocarcinoma revealed that CTHRC1 is expressed in

tissue repair processes. However, when CTHRC1 mutations occur, CTHRC1 loses its ability to form secondary structures and helix-loop-helix structures; therefore, collagen deposition, fibrosis and TGF-β/WNT signaling pathway involvement are disrupted so that the esophagus cannot be correctly repaired. This promotes gastroesophageal reflux disease, which may lead to an increased risk of developing esophageal adenocarcinoma (76). The negative feedback loop implies that the dynamic balance between TGF-β and CTHRC1 is a physiological behavior important in maintaining the morphology and homeostasis of tissue organisms.

Furthermore, in HBV-associated HCC, overexpression of CTHRC1 enhanced phospho-AKT in a concentration-dependent manner (19). AKT has been recognized as a key factor in the PI3K/AKT signaling cascade for regulating the activation of NF-κB (77,78). NF-κB has also been reported to elevate the expression of CTHRC1 (19). Therefore, in contrast to the relationship between CTHRC1 and the TGF-β signaling cascade, it is assumed that a positive feedback regulatory loop might be present among CTHRC1, AKT and NF-κB for promoting the carcinogenesis of HCC; however the mechanism needs to be further explored.

In summary, CTHRC1 not only participates in the physical and biological activity of normal cells, but also the carcinogenesis of various human solid tumors, dependent on the crosstalk with multiple cell signal transduction pathways. This may allow for the development of new therapies to treat related diseases by targeting CTHRC1.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

QZ and YJL completed the writing and revision of the first draft, and JD, JL and XPT all participated in the revision of the article. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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