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REVIEW ARTICLE

The role of C-terminal tensin-like (Cten) gene in cancer metastasis

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ABSTRACT

C-terminal tensin-like (cten, also known as tensin4, TNS4) is the fourth member of the tensin family. all tensin family members localizes in focal adhesion sites. Cten shares the sequence homology with other tensins at its C-terminal region by having the SH2 and PTB domains. Cten is expressed in some normal tissue such as prostate and placenta while down-regulated in prostate cancer. The overexpression of cten was found associates with tumors of breast, colon, lung, stomach, skin and pancreas. It interacts with growth factors and cytokines as regulators. Also it has been found that cten expression promotes cell motility and enhances tumorigenicity. The collective findings support that cten is having a role in carcinogenesis and promising biomarker. It can be a candidate for a therapeutic target for solid cancers.

Keywords: Cten, colorectal cancer, tensin, metastasis

Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries (1). Metastasis and recurrence are frequent among cancer patients, despite the advances in treatment and diagnosis. Upon the development of metastatic deposits, the prognosis for cancer patients is dramatically worsened and cure is unlikely (2).

Numerous approaches have been undertaken to tackle the early steps of metastasis including cell migration and invasion. However, most of the agents are in the pre-clinical stage or have failed during clinical trials (such as the failure of matrix metalloproteinase inhibitors in clinical trials) (3). Further research is necessary to search for potential diagnostic biomarkers or molecular targets.

A full understanding of the aberrant molecular changes behind the emergence of metastatic cells such as certain activated pathways, increased expression of certain molecules, or epigenetic changes that drive metastatic capacities, would enable the development of a targeted therapy that would abate their metastatic capabilities early at the primary site.

One of the molecules which recently has been the focus of cancer metastasis research is C-terminal tensin-like (Cten), which is part of the tensin family that is located in focal adhesions (FAs).

The Tensin Family

The tensins constitute a family of intracellular proteins that are coming to the fore as novel regulators of cell motility and growth. They are localized to the cytoplasmic side of the FA (4). Tensin was first isolated in 1991 from chicken cardiac muscle (5). Ten years later, human tensin2 was discovered and found to have strong homology with tensin at both C and T terminus. Later the tensin gene family was thought to be composed of four highly homologous members, based on the genomic structure and protein sequence, tensin1, tensin2, tensin3, and tensin4 (TNS1, TNS2, TNS3, and TNS4) each with discrete expression patterns in the human body (6,7).

Structure of Tensin Molecules

Lo et al. characterized the structure of tensin molecules using light scattering electron microscopy and gel filtration; they found that tensin could form a dimer (8,9). Tensins are multi-domain, containing proteins that have the ability to bind to many structural and signaling molecules. All tensin isoforms contain a phosphotyrosine-binding domain (PTB), which plays the role of interacting with the cytoplasmic tail of the β-integrin (10). Also, they all contain, at the C-terminal end, an Src homology-2 domain (SH2 domain) (5). While tensin1, tensin2,

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and tensin3 interact with actin at multiple sites in the N-terminus, tensin4 (Cten) lacks the N-terminal actin-binding domain (ABD) (7,10) (Figures 1 and 2).

Tensin can be divided into three regions that are each involved in mediating protein–protein interactions. The N-terminus contains the ABD Ia and Ib that interact with actin filaments. This region also contains a FA-binding (FAB) activity and the PTEN homologous sequence. The center region of tensin contains the ABD II that retards the actin polymerization rate. The C-terminus contains an SH2 domain, PTB domain, and another FAB site. The SH2 domain binds to the tyrosinephosphorylated PI3 kinase, FA kinase (FAK), and p130Cas. The PTB domain interacts with integrin tails of β1, 3, 5, and 7. Amino acid numbers are based on the chicken tensin sequence (7).

Human tensin, tensin2, tensin3, and Cten are highly conserved at N- and C-terminal regions. A C1 domain (protein kinase C conserved region 1) is found in tensin2 only. The center regions of tensin members show no sequence homology (7).

Function of Tensin

In normal cells, tensin1, tensin2, and tensin3 serve as bridges linking the extracellular matrix, to the actin cytoskeleton, via integrins (11,12). These proteins can interact with the cytoplasmic tail of β-integrin through their PTB and bind to the actin cytoskeleton via their ABDs (5). It has been reported that tensin interacts with AXL receptor tyrosine kinase (AXL RTK) within the C-terminal region. This interaction indicates that tensin may itself be a direct substrate for tyrosine phosphorylation by AXL when activated by its ligand Gas6 (13,14). Tensins also function as a platform for assembly/disassembly of signaling complexes at FAs by recruiting tyrosine-phosphorylated signaling molecules through their SH2 domain and providing interaction sites for other SH2-containing proteins (5,8). Therefore, tensins may facilitate signal transduction through direct participation in the signaling pathway and through enabling interaction of other signaling molecules.

Cten (TNS4)

Cten is the fourth member of the tensin family and is also called tensin4 (TNS4) (HGNC: 24352 and OMIM ref. No. 608385). The Cten/TNS4 gene was cloned and found to be a distant member of the tensin family; therefore, given the name Cten (COOH-terminal tensin-like molecule) (15). The gene is about 21 kb in length with a coding sequence of 4,015 base pair (bp) and an open reading frame encoding a 715 amino acid protein. The 418–715 amino acids are very similar with the COOH termini of tensin1 and tensin2 with about 48% identity or 62% similarity. There are six potential tyrosine phosphorylation sites found in Cten but the gene product lacks the NH2-terminal homologous regions found in other tensins (Figures 1 and 3). It was found that the human Cten gene is located on the chromosome 17q12–21 and has 12 exons. The splice

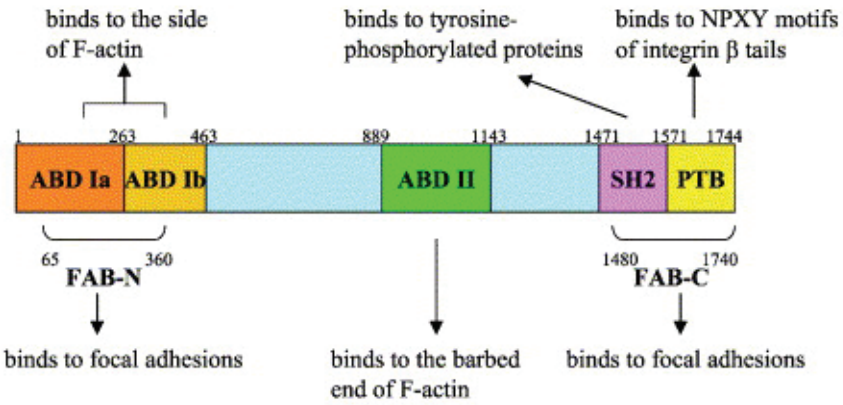

Figure 1. *Structure and functions of Tensins domain.*

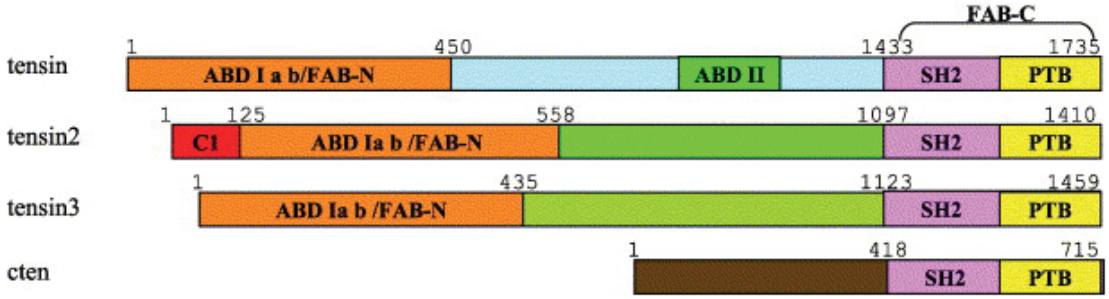

Figure 2. *Similarities between Tensin family members.*

Exon Number	Codon phase	3′Splice acceptor	Exon size (bp)	5′ Splice donor	Intron size(bp)
E1	N	tttc**ag**ATCCTG	534	CCTTGG**gt**aagg	7019
E2	I	ccaa**ag**ACATAA	424	TGGAAG**gt**aggt	1087
E3	II	ctgc**ag**CAGCCC	425	CAGAGG**gt**acgt	2030
E4	I	ctcc**ag**GTCCCG	[86 90] 87	AGCAAG**gt**aaaa	313
E5	I	ttcc**ag**CAATCG	[133 125] 126	GACCAG**gt**atgc	2069
E6	I	gtcc**ag**GTGAGG	[93 93] 93	ACTTTG**gt**gaga	119
E7	I	tttc**ag**GGAGCC	[78 78] 78	AGAGAG**gt**gggt	1362
E8	I	gctc**ag**AACTGG	[72 78] 69	CTGCGG**gt**gagt	859
E9	I	ccac**ag**GCTGCC	[169 169] 169	GAGGAA**gt**aagg	1027
E10	II	tcct**ag**GGTGTT	[69 69] 69	ACGGAA**gt**aagt	248
E11	II	ctac**ag**GTGGCA	[33 30] 27	CTCCTG**gt**aagg	579
E12	II	cacc**ag**GATCTT	1883		

Figure 3. *Organization of human Cten gene.*

sites of acceptor and donor for the exons comply with the GT-AG rule. Exon 1 has the start codon, whereas the stop codon is in exon 12. Exon 12 is the largest exon having 1883 bp but only 142 bp comprise the coding sequence and the rest is the 3' untranslated region. Exon 11 is the smallest exon having 27 bp; exons 4–11 are similar to those of the other tensins (Figure 3).

Exon/intron boundaries were determined by comparison of sequences of genomic DNA and cDNA. In the splice site, uppercase letters indicate exon sequences, and intron sequences are indicated by lowercase letters. Codon phase refers to the codon split at the splice acceptor. Introns that do not split codon triplets are indicated by phase 0, interruption after the first nucleotide is indicated by codon phase I, and interruption after the second nucleotide is indicated by codon phase II. N indicates the noncoding region. Numbers in the brackets indicate the sizes of the corresponding exons in human tensin1 and tensin2, respectively (15).

Cten Expression in Tissue

While the TNS1 and TNS2 have shown to be broadly expressed in a wide variety of normal human tissues (12), Cten expression was reported initially (using Northern blot) in only prostate and placenta from a series of 15 different tissue types (15). Later in the same decade, Cten messenger RNA (mRNA) expression in normal tissues was evaluated by Sakashita et al. using the human total RNA master panel; this revealed that Cten is expressed at high levels in prostate, esophagus, breast, and salivary glands. Moderate Cten expression was found in the thyroid and trachea. In contrast, very low expression was reported in colon, lung, small intestine, spleen, kidney, stomach, and testis (16). Immunohistochemistry (IHC) staining showed no expression of Cten in normal breast tissues and was confirmed by a subsequent study by Albasri et al. (17). The discrepancy between the mRNA and protein expression may be due to the variations in the number of cases involved in both studies and variation of the techniques used.

The Role of Cten in Cancer

The role of Cten in cancer is not well defined. In prostate cancer, it is down-regulated, whereas in normal cells, it is localized to FAs recruiting the tumor suppressor deleted in liver cancer-1 (DLC-1), thus suppressing tumorigenesis (18). Similar to TNS1, Cten has been reported to be a caspase-3 substrate. Caspase-3 is able to cleave Cten at the $DSTD^{570}S$ site, thereby releasing Cten (571–715) fragment, which contains the PTB domain and is able to reduce cell growth by inducing apoptosis through binding to the β-integrin tails and disruption of the link between the integrins and actin fibers. This could disrupt the cell adhesions and eventually facilitate cell death (19). Therefore, the loss of Cten expression may lead to uncontrolled cell growth and result in cell transformation. Accordingly, in prostate cancer, Cten functions as a tumor suppressor protein.

On the other hand, Cten has been found to be up-regulated in a number of cancers. It is up-regulated in lung cancer and its expression relates with tumor progression (20). In breast cancer, the epidermal growth factor receptor (EGFR), which is involved in various cellular processes, including proliferation and motility, up-regulates Cten and down-regulates tensin3 (21)-a phenomenon known as the "tensin switch". Tenisn3 is localized in cell-matrix adhesions but it disappears upon EGF stimulation. Indeed, Cten in breast cancer is a potential marker of a poorly differentiated, relatively aggressive sub-population of invasive breast tumors (21). A recent study showed that the tensin3/Cten switch regulates RhoA inactivation via the activation of DLC1, decreasing cell migration. While tensin3 activates DLC1 Rho-GAP function by releasing an autoinhibitory interaction, Cten, which lacks the ABD, is not able to do so (22).

In colorectal cancer (CRC), Cten has also been found to be up-regulated and is localized to both cytoplasm and nucleus (23,24). CRC cell lines transfected with Cten have increased cell migration and invasion as tested

by appropriate assays (24). Correspondingly, a high expression of Cten was shown to be associated with worse prognosis and distant metastasis in a series of CRCs evaluated by IHC (25). However, the absence of "tensin switch" was noted in CRC cell lines, in which after stimulation by EGF, Cten, and tensin3 protein levels were evaluated using western blot; the results showed an increase in Cten expression following the EGF but a tensin switch was not observed (26).

The effect of Cten on cell migration and invasion occurs via modulation of downstream targets including down-regulation of E-cadherin (24) and induction of epithelial–mesenchymal transition. Cten was also found to affect tumorigenicity and invasion by binding to β-catenin in the nucleus (23,24), the significance of the interaction of Cten with β-catenin, which is integrated with the Wnt signaling pathway, is not clarified yet. In addition, Cten was found to induce resistance to staurosporine-induced apoptosis, which may explain the ability to survive in hostile environments such as sites of metastasis.

In thymomas and lung tumors, Cten has been found as an oncogene with progressive up-regulation correlating with increasing tumor stage. The Cten expression correlated with tumor progression and metastases (20,27). In addition, the expression of Cten in gastric cancer was evaluated using IHC revealed that Cten overexpression was significantly associated with histologically poorer grade, deeper invasion into the serosa, lymph node metastasis, and peritoneal dissemination (16). Additionally, in pancreatic cancer, Cten overexpression was positively associated with enhanced colony formation and cell motility, proving its role as an oncogene (28). Aratani et al. demonstrated the Cten molecular mechanisms in adenocarcinoma of the esophagogastric junction (AEG), 34% of AEG tumors tested showed a high expression of Cten and was associated with poorer prognostic and low overall survival. Cten also was overexpressed in NUGC4 and MKN45 cells out of five cell lines used (40%). Moreover, to assess the role in which Cten plays in AEG carcinogenesis, Cten was knocked down in NUGC4 and MKN45 cells by transfection using siRNA specific to Cten, this resulted in the inhibition of tumor cell migration, proliferation, and invasion (29). Cten functions may vary between cell types, which is why it is a tumor suppressor in one and an oncogene in another.

Nuclear Cten

Cten has also been seen in a number of studies to be localized in the nucleus. The interesting observation is that nuclear Cten expression correlates with advanced tumor stage and metastasis. This suggests a role of Cten beyond cellular adhesion foci (24). In the nucleus, Cten is bound to β-catenin, thus linking a FA molecule to the canonical Wnt-signalling pathway. It has been seen that a number of FA molecules travel to the nucleus and either act as regulators by binding to transcription factors or targeting of specific mRNAs to FAs for localized protein translation (23). The exact role of Cten in the β-catenin pathway, however, still needs investigating in the nucleus.

There may be a role of E-cadherin in the process of Cten's migration to the nucleus. It has been observed that the Cten expression decreases E-cadherin levels, leading us to propose that part of the Cten's role might be to disconnect β-catenin from cadherin junctions and take it into the nucleus. However, this area still needs much work to be validated.

Downstream Targets

Cten is an important component of FAs and it has been shown to have a number of different cellular functions.

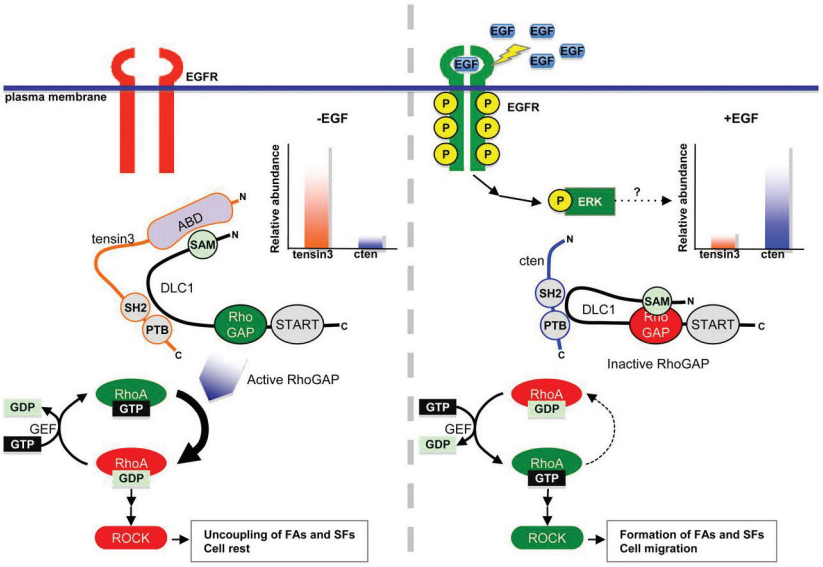

Figure 4. *A module for the tensin3/Cten-DLC1-RhoA signalling axis.*

There is a need to identify its relationship to other molecules in FAs and the downstream signaling pathway.

Integrin-linked kinase (ILK) has been found to play a central role in the transduction of many of the signals from the cell-matrix to the nucleus via integrin molecules (30,31). ILK also regulates fundamental cell processes such as growth, proliferation, survival, differentiation, migration, invasion, and angiogenesis (32). It is overexpressed in human cancers and its expression correlates with tumor progression and patient survival (33,34). In colorectal carcinomas, a Cten/ILK pathway has shown to be possibly controlling cell motility and probably promoting metastasis. The data showed that Cten is regulating ILK and mediating Cten-induced cell motility. However, the knockdown of ILK inhibited the motility inducing effects of Cten expression, confirming the functional relevance of Cten/ILK relationship (25).

Moreover, FAK was discovered in the early 1990s as a tyrosine-phosphorylated protein and considered to be one of the FA molecules, which is located on the cytoplasmic tail of integrins (35). The location of FAK and Cten is close, although the relationship between them is not yet fully understood.

FAK is an important mediator of cell growth, proliferation, survival, and migration, which are all often dysfunctional in cancer cells (36). FAK may play the main role in cancer metastasis either by phosphorylation and association with Src or interaction with PI3K and the adaptor molecule Grb7 (37).

The overexpression of FAK seems to enhance cell migration, whereas the lack of FAK expression reduces cell migration (38,39). With the information about the role of Cten in cell motility, a relationship between the Cten and FAK may be expected as they both localize to FAs and both appear to down-regulate E-cadherin (24,40). Protein expression of phosphorylated-FAK was evaluated and proven to have a negative prognostic value in CRC, additionally, nuclear TNS4 and nuclear P-FAK were compared using immunostaining; the results showed that there was a positive association in the metastases tumors, however, not in the primary tumors (41).

The DLC1 tumor suppressor gene encodes a Rho GTPase activating protein that increases the intrinsic hydrolysis of GTP bound Rho to the inactive GDP bound form of Rho. It has been found frequently deleted or down-regulated in colon, breast, lung, liver, and prostate tumors (42). It has been seen to negatively regulate Rho GTPases, and thus prevents tumor proliferation, cell survival, and motility. It has been reported that DLC1 interact with the SH2 domain of Cten to perform its function as a tumor suppressor. This phenomenon is seen in prostatic cancer, which lacks Cten expression while it is expressed normally in the prostate (18).

It has been found that EGF-induced tensin3/Cten switch also occurs with DLC1 to regulate mammary cell migration. The lack of ABD domain in Cten would cause an inhibition of the Rho-GAP activity of DLC1 with its sterile alpha motif (Figure 4) (22,43).

Prior to EGF stimulation, mammary cells (such as MCF10A) express more tensin3 than Cten. The Rho-GAP activity of DLC1 is inhibited by an intramolecular interaction with its SAM domain. However, the binding of tensin3 ABD to the SAM domain releases this inhibition, resulting in an increase in DLC1 Rho-GAP activity, which in turn, leads to a decrease in the RhoA-GTP level and destabilization of FAs and stress fibers (SFs). EGF treatment activates EGFR and ultimately, ERK. Phosphorylated ERK down-regulates tensin3 but concomitantly up-regulates Cten expression. Without an ABD, Cten is incapable of releasing the autoinhibition of DLC1 Rho-GAP activity, leading to increased RhoA activity and enhanced formation of FAs and SFs, which together contribute to cell migration. The effect of the tensin3/Cten-DLC1-RhoA signaling axis on cell migration depends on ROCK (22).

Recently, a novel Snail/Cten signaling pathway has been proposed in CRC. Two cell lines, HTC116 and SW260, exhibit low and high endogens expression of Cten, respectively, in which HTC116 cell line was transfected with GFP-Cten and resulted in an increase in snail protein production. While in SW260 cells (initially having high Cten expression), Cten was knocked down, similarly, that resulted in a decreased snail levels. However, in both experiments, Cten regulation of snail was found to be occurring at a post-transcriptional level, in fact, Cten expression was associated with delayed snail protein degradation, thus suggesting that Cten regulates snail protein stability. Additionally, it has been found that the Cten regulation of snail was mediated by the SH2 domain. Moreover, an increase in cell migration, invasion, and colony formation was noted following GFP-Cten over-expression and was subsequently lost after snail depletion. This indicates that the up-regulation of snail protein by Cten induces cell migration, invasion, and colony formation (44).

Potential Upstream Regulators of Cten

The mechanisms by which Cten is regulated are not completely clear. Two main pathways have been implicated that may regulate Cten, i.e., the EGFR/RAS/MAPK pathway (21) and the STAT3 pathway (45).

The EGFR is one of the families of receptor tyrosine kinases which was found to be anchored in the cytoplasmic membrane and composed of an extracellular ligand-binding domain, a short hydrophobic transmembrane region, and an intracytoplasmic tyrosine kinase domain (46).

EGFR can be activated by receptor overexpression, ligand-dependent, and ligand-independent mechanisms. There are six known ligands that bind to the EGFR, including EGF itself. Ligand binding to the receptor induces a conformational change of the receptor ectodomain that leads to receptor dimerization and autophosphorylation of several tyrosine residues within the COOH-terminal tail of the receptors (47). This provides specific docking sites for cytoplasmic proteins containing SH2 and PTBs

(46). In a recent study, it has been found that Cten is able to interact with activated c-Cbl in a phosphotyrosine-SH2-dependent manner, thus reducing receptor ubiquitination, leading to the suppression of ligand-induced EGFR degradation (48).

K-RAS is a member of the RAS family of genes, situated on the inner face of the plasma membrane, and are activated by binding to GTP and inactivated by binding to GDP (49). K-RAS has many downstream effectors such as RAF serine/threonine kinases and the PI3Ks, which preferentially bind to activated RAS, and any abnormality in the RAS effector binding domain leads to defective attachment (50). By controlling its downstream effectors, many of the cellular signaling pathways that are involved in growth, migration, adhesion, cytoskeletal integrity, survival, and differentiation are regulated by RAS proteins (50).

It has been shown that EGF signaling positively regulates the Cten expression (21). A recent study showed that EGF stimulation was able to induce the Cten expression in CRC cell line (SW480), a K-RAS mutant cell line. These findings suggest a K-RAS-independent mechanism of Cten regulation by EGF (51). However, K-RAS being a part of the signaling pathway for EGFR; a microarray study showed that K-RAS mutation resulted in changes in Cten (52,53). In fact, a recent study revealed that the knockdown of K-RAS, in a K-RAS mutant colorectal and pancreatic cancer cell lines, resulted in the downstream regulation of Cten (54).

STAT3 is a member of the family known as signal transduction and activator of transcription (STAT). The STAT proteins are activated by various cytokines and growth factors and migrate to the nucleus where they function as transcription factors (55).

The main activation molecule of STAT3 signaling is Interleukin 6 (IL-6) (56). However, others, such as cytokines, growth factors, and kinases such as EGF, PDGF, IFNγ, and Src, can also activate STAT3 (57).

Interaction of Cten with STAT3 has been reported in a mouse breast cancer model, showing a functional loop of inflammation/STAT3-migration and metastasis by Cten (45). In this model, IL-6 causes increased Cten induction through STAT3 activation. This model is supported by the fact that there are increased Cten levels in inflammatory breast cancers (45). A study on lung cancer cells identified STAT3 pathway as a possible regulator of Cten expression; STAT3 activation likely contributes to EGF-mediated Cten expression and lung cancer invasion and metastasis (58). In contradiction, a study has shown that Cten is negatively regulated by STAT3 in colorectal cell lines, where the knockdown of STAT3 resulted in the up-regulation of Cten, and in further validation, the up-regulation of STAT3 through the stimulation with IL-6 eventually led to the down-regulation of Cten (26).

In constant with the above-mentioned findings, mutations in the SH2 domain of Cten have been shown to have negative impact on STAT3 activation in a model of tubulogenesis (59), i.e., Cten is regulating STAT3. The roles of STAT3 have been reported as both tumor suppressor and promoter too, which may explain the contradiction regarding Cten (60).

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None.

List of abbreviations

ABD	Actin-binding domain
AEG	Adenocarcinoma of the esophagogastric
CRC	Colorectal cancer
Cten	C-terminal tensin
EGFR	Epidermal growth factor receptor
FAs	Focal adhesions
FAB	Focal adhesion-binding
FAK	Focal adhesion kinase
IHC	Immunohistochemistry
ILK	Integrin-linked kinase
PTB	Phosphotyrosine-binding
RTK	Receptor tyrosine kinase
SFs	Stress fibers
STAT	Signal transduction and activator of transcription

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