Chapter 6
Role and Fate of TCTP in Protein Degradative Pathways

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Abstract This chapter focuses on published studies specifically concerning TCTP and its involvement in degradation or stabilization of various proteins, and also in its own degradation in different ways. The first part relates to the inhibition of proteasomal degradation of proteins. This can be achieved by masking ubiquitination sites of specific partners, by favoring ubiquitin E3 ligase degradation, or by regulating proteasome activity. The second part addresses the ability of TCTP to favor degradation of specific proteins through proteasome or macroautophagic pathways. The third part discusses about the different ways by which TCTP has been shown to be degraded.

Abbreviations

Bre5	Brefeldin A sensitivity 5
CMA	Chaperone-mediated autophagy
DHA	Dihydroartemisinin
HIF1α	Hypoxia-inducible factor 1α
HRF	Histamine releasing factor
Hsp27	Heat shock protein 27
Mcl-1	Myeloid cell leukemia 1
Mdm2	Murine double minute 2
Mmi1	Microtubule and mitochondria interacting protein
Mss4	Mammalian suppressor of yeast Sec4
Mst-1	Mammalian sterile twenty-1
NTHK1	Tobacco histidine kinase-1
Pim-3	Serine/threonine-protein kinase Pim-3
PRX1	Peroxiredoxin-1
Rpn	26S proteasome regulatory subunit
Rpt	Proteasome regulatory particle base subunit

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UPS	Ubiquitin–proteasome system
TCTP	Translationally controlled tumor protein
Ubp3	ubiquitin specific protease 3
VHL	von Hippel–Lindau protein

6.1 Introduction

Translationally controlled tumor protein (TCTP), also known as fortilin or HRF (histamine releasing factor), is a multifunctional protein implicated in diverse processes such as apoptosis (Yang et al. 2005; Liu et al. 2005; Susini et al. 2008), survival (Lucibello et al. 2011; Diraison et al. 2011), the cell cycle (Gachet et al. 1999; Cucchi et al. 2010; Burgess et al. 2008), proliferation and growth (Chen et al. 2007b; Hsu et al. 2007), development (Le et al. 2016; Roque et al. 2016), and DNA repair (Zhang et al. 2012; Hong and Choi 2013). TCTP has been shown to be subjected to various posttranslational modifications that can change its intracellular behavior. It is a cytosolic protein which was also found to be functionally associated with subcellular compartments such as mitochondria, nucleus, and microtubules (Susini et al. 2008; Hong and Choi 2013; Bazile et al. 2009). TCTP interactome was recently characterized and about a hundred interacting proteins were identified (Li et al. 2016). From a functional standpoint, TCTP often regulates protein behavior by favoring stabilization of protein partners or, on the contrary, promoting degradation of others. Regarding its own expression, TCTP has been shown to be transcriptionally and translationally regulated (Bommer et al. 2002, 2010, 2015; Amson et al. 2012). Moreover, TCTP can be unconventionally secreted in the extracellular space while exhibiting cytokine-like activity (MacDonald et al. 1995) or released within exosomes and resulting in a decrease in its intracellular levels (Amzallag et al. 2004).

6.2 TCTP as Protein Stabilizer

TCTP has often been described as a chaperone protein due to its stabilizing effect on protein partners. TCTP does not have foldase or holdase characteristics like those of classical chaperone proteins, although it has been reported that human and parasite (*Schistosoma mansoni*) TCTP can bind to a variety of denatured proteins and protect them from thermal shock (Gnanasekar et al. 2009). Note also that TCTP was shown to be structurally close to the mammalian suppressor of yeast Sec4 (Mss4) protein that binds to the GDP/GTP free form of Rab proteins, which is called the guanine nucleotide-free chaperone (Thaw et al. 2001). Moreover, TCTP has been reported to inhibit, in different ways, degradation of specific proteins by the ubiquitin–proteasome system (UPS).

6.2.1 TCTP Masks the Ubiquitination Sites of Its Partners

A widely described function of TCTP relates to its anti-apoptotic activity (Susini et al. 2008; Graidist et al. 2004; Baudet et al. 1998). This anti-apoptotic function is partly due to TCTP-induced p53 downregulation (Amson et al. 2012), preventing transcriptional activation of the pro-apoptotic gene Bax. However, TCTP has been shown to inhibit apoptosis in other ways, such as via stabilization of the extremely labile anti-apoptotic protein Mcl-1, thus counteracting Bax dimerization (Susini et al. 2008). TCTP interaction with Mcl-1 was found by two-hybrid screening and confirmed in GST pull-down and co-immunoprecipitation experiments (Liu et al. 2005). It was shown that a mutant form of Mcl-1 unable to bind to TCTP was much more susceptible to ubiquitination and, conversely, that TCTP overexpression blocked Mcl-1 from undergoing ubiquitination. TCTP has also been shown to be involved in protecting cells against ROS-mediated apoptosis independently of p53. TCTP protects the antioxidant enzyme peroxiredoxin-1 (PRX1) from inactivation by the kinase Mst-1 (mammalian sterile twenty-1) by masking phosphorylation sites when physically interacting with PRX1 (Chattopadhyay et al. 2016). TCTP-shielded PRX1 is enzymatically active, and it was shown that TCTP overexpression in mouse liver enhanced the peroxidase activity protecting mice against alcohol-induced ROS-mediated liver damage. Concomitantly, TCTP binding to PRX1 was also demonstrated to protect PRX1 from ubiquitin–proteasome degradation. TCTP depletion by shRNA induced PRX1 downregulation which was reversed by adding the proteasome inhibitor MG-132. Accordingly, TCTP overexpression in the U2OS cell line or in mouse liver induced a decrease in PRX1 polyubiquitination (Chattopadhyay et al. 2016). In the same line, TCTP has been identified through a yeast two-hybrid screen and shown to interact with Pim-3, a proto-oncogene with serine/threonine kinase activity (Zhang et al. 2013). TCTP is not phosphorylated by Pim-3 but modulates the protein kinase stability. Actually, depletion of TCTP by siRNA in the human pancreatic carcinoma cell line PCI55 increases Pim-3 degradation, which is abrogated by the proteasome inhibitor MG132. Accordingly, Pim-3 ubiquitination was promoted by TCTP siRNA treatment.

TCTP is a highly conserved protein identified in a wide range of eukaryotic organisms, across animal and plant kingdoms and in yeast. Cultivated tobacco (*Nicotiana tabacum*) NtTCTP has been shown to regulate seedling growth through control of cell proliferation. Ethylene is a phytohormone that inhibits vegetative growth. This inhibition is regulated by a feedback mechanism, in which ethylene-induced NtTCTP binds to and stabilizes ethylene receptor tobacco histidine kinase-1 (NTHK1) and reduces the plant response to ethylene, promoting plant growth by increasing cell proliferation (Tao et al. 2015). Interaction of NtTCTP with NTHK1 was identified by two-hybrid screening and confirmed by GST pull-down and co-immunoprecipitation experiments (Tao et al. 2015). In the presence of cycloheximide, NtTCTP overexpression in plants stabilized NTHK1 compared to wild-type plants, while this decrease in NTHK1 levels in wild-type plants was abolished by proteasome inhibitor treatment. It is thus tempting to speculate that in all of these

cases (Mcl-1, PRX1, PIM-3, and NTHK1), ubiquitination sites on TCTP partners are masked by TCTP interaction, thus avoiding ubiquitination and further degradation by the proteasome.

6.2.2 TCTP Binding Leads to E3 Ligase Degradation

TCTP can also stabilize protein by inducing degradation of the specific E3-ubiquitin ligase involved, thus inhibiting ubiquitination of the protein. This has been described for TCTP stabilization of hypoxia-inducible factor 1α (HIF1α). The tumor suppressor von Hippel–Lindau protein (VHL) functions as an E3 ligase that can interact with and ubiquitinate HIF1α (Chen et al. 2013). It has been shown that TCTP specifically binds to the β-domain responsible for substrate recognition by VHL, while competing with HIF1α. However, TCTP is not ubiquitinated by VHL, as suggested by the constant TCTP protein levels observed when VHL is either overexpressed or depleted. Conversely, TCTP promotes K48-linked ubiquitination of VHL and its further degradation by proteasomes. TCTP thus competes with HIF1α for binding to VHL, reduces E3 ligase stability, inducing upregulation of the HIF1α protein level.

6.2.3 Mmi1/ScTCTP Modulates Proteasome Activity

The microtubule and mitochondria interacting protein (Mmi1), the yeast homologue of mammalian TCTP, is described as a stress sensor and stress-response regulator (Rinnerthaler et al. 2006). In high-throughput studies, Mmi1 was found to be a putative interactor of various proteasomal subunits such as Rpn1, Rpt5, and Rpn11 (Guerrero et al. 2008). Using fluorescence imaging, Mmi1-GFP was found to be uniformly distributed in the cytoplasm of exponentially growing yeast cells. However, when yeasts were submitted to robust heat stress, Mmi1-RFP partially colocalized with the proteasome (labeled using Rpn1-GFP) in the nucleus and gradually returned to its diffusely cytoplasmic location as cells recovered from the heat shock (Rinnerthaler et al. 2013). The partial relocalization of Mmi1 to the nucleus in heat-stressed cells was confirmed by immunogold electron microscopy. By comparing the proteasomal activity of WT yeast cells or Mmi1-deleted mutants, at low temperature or after heat shock, it was shown that Mmi1 slightly but consistently inhibited proteasome activity. Moreover, Mmi1 was found to interact with other components that potentially modulate proteasome degradation. Indeed, Bre5 and Ubp3 can form a complex to specifically de-ubiquitinate proteins by cleaving off the first conjugated ubiquitin, thus modifying their turnover, as shown for Sec23 (Cohen et al. 2003). This Bre5-Ubp3 de-ubiquitination complex was shown to colocalize with Mmi1 in association with stress granules in the cytoplasm of heat-stressed yeast cells (Rinnerthaler et al. 2013).

6.3 TCTP as Degradation Inducer

The tumor suppressor p53 is tightly controlled by the E3-ubiquitin ligase Mdm2 protein. Interaction with Mdm2 maintains p53 at low levels under basal conditions through different mechanisms, including proteasomal degradation after ubiquitination. In response to stress, the cellular level of p53 is elevated through a posttranslational mechanism, leading to cell cycle arrest or apoptosis. It has been demonstrated that TCTP binds to the p53–Mdm2 complex and increases the Mdm2-mediated ubiquitination and proteasome degradation of p53, concomitantly with Mdm2 autoubiquitination inhibition (Amson et al. 2012). TCTP overexpression or knockdown in HCT116 cells, respectively, resulted in a decrease or increase in p53 protein levels. Accordingly, analysis of tissues from *Tctp* heterozygous ($Tctp^{+/-}$) mice revealed readily detectable p53 levels, contrary to *Tctp* WT mice in which basal p53 levels were undetectable. TCTP-induced p53 degradation is inhibited by the proteasome inhibitor MG132 and antagonized by NUMB, a regulator of p53 that was previously shown to bind to the p53–Mdm2 complex, therefore preventing p53 ubiquitination and degradation (Colaluca et al. 2008). Co-immunoprecipitation experiments on endogenous proteins in HCT116 cells demonstrated that TCTP forms complex with p53–Mdm2 and NUMB (Amson et al. 2012). Importantly, high TCTP levels were found to be correlated with breast cancer aggressiveness, for which it is an independent prognostic factor (Amson et al. 2012).

Hepatocellular carcinoma is also a cancer in which TCTP overexpression was detected and associated with the advanced tumor stage (Chan et al. 2012). It was shown that the chromodomain helicase/ATPase DNA binding protein1-like gene binds to the promoter region of *TCTP* and activates its transcription. TCTP overexpression was shown to contribute to the mitotic defects of tumor cells by inducing a decrease in Cdc25, leading to failure in the dephosphorylation of Cdk1 and its dysfunction during mitosis. TCTP-induced Cdc25 downregulation was shown to occur at the protein rather than mRNA level. TCTP overexpression in cell lines induced Cdc25 ubiquitination and degradation, which was abolished by MG132 treatment. Conversely, TCTP depletion by shRNA increased Cdc25 levels, which in turn increased Cdk1 activity (Chan et al. 2012).

Besides regulating proteasome degradation of various proteins, as seen above, TCTP has recently been shown to be involved in macroautophagy regulation. Macroautophagy is a self-degradative process through which macromolecules and even organelles are transported to lysosomes for degradation by the prominent formation of autophagic vesicles in the cytoplasm. This process is important for balancing sources of energy at critical times in development and in response to nutrient stress. Macroautophagy is orchestrated by a series of core autophagy proteins (ATG proteins) that are evolutionarily conserved (Tsukada and Ohsumi 1993; Ohsumi 2014). By studying long-term artificial selection of pigs (wild vs domestic species), *TCTP*/*TPT1* genes have been found to be upregulated during artificial selection, concomitantly with an increase in female fecundity (Chen et al. 2014). It is suggested that this could be related to macroautophagy that takes place during

oogenesis in ovarian granulosa and cumulus cells. TCTP was shown to regulate AMPK and mTORC1 activities, both of which were involved in macroautophagy activation under hypoxic conditions. In line with this, it was shown that the phosphatidylethanolamine-conjugated form of ATG8 (ATG8-PE, also named LC3-II), a key molecular component initiating and contributing to autophagic vacuole elongation, was increased in TCTP knockdown COS-7 cells cultured in normoxic conditions, but decreased in the same cells cultured in hypoxic conditions. Similar results were obtained under serum starvation conditions. Moreover, by co-immunoprecipitation, TCTP was found to interact with ATG5, ATG12, and ATG16, three ATG proteins forming a complex in charge of ATG8 phospholipid conjugation and autophagic vacuole formation (Walczak and Martens 2013). These data suggest that TCTP could positively regulate macroautophagy to generate energy during oogenesis.

6.4 TCTP Degradation

As seen above, numerous studies have shown that TCTP regulates protein degradation by the ubiquitin–proteasome system or through the macroautophagy pathway (Fig. 6.1). Surprisingly, very few studies have examined the specific degradation of TCTP. One explanation is that TCTP is very efficiently and finely regulated at transcriptional and translational levels (Bommer et al. 2010, 2015). Intuitively, it is difficult to imagine TCTP as a component that could regulate proteasome degradation, while itself being a specific target for UPS degradation. As a matter of fact, TCTP can physically interact with E3-ligases (e.g., Mdm2, VHL) but is not a substrate for these ubiquitin ligases, and accordingly TCTP has been shown to have a quite long half-life (Tuynder et al. 2002; Baylot et al. 2012).

However, it was reported that in some cases TCTP degradation by UPS can be upregulated. Dihydroartemisinin (DHA) is a metabolite of artemisinin, a molecule originally used as an antimalarial drug. The anticancer activity of dihydroartemisinin was examined in human ovarian cancer cells (Jiao et al. 2007). It was found that DHA induced cell growth inhibition via the induction of apoptosis with a decrease in Bcl-xL/Bcl-2 and an increase in Bax/Bad, while also blocking cell cycle progression. Subsequently, DHA was found to bind to TCTP and shorten its half-life, a process that is blocked by MG132. TCTP was shown to be ubiquitinated in a DHA-dose dependent manner, likely after a structural change induced by DHA binding (Fujita et al. 2008).

The TCTP half-life has also been shown to be shortened after depletion of the heat shock protein 27 (hsp27) in the prostate carcinoma cell line (Baylot et al. 2012). It was first shown that hsp27 knockdown using antisense oligonucleotides and siRNA induced apoptosis and enhanced chemotherapy in prostate cancer (Rocchi et al. 2006). Hsp27 is highly overexpressed in castration-resistant prostate cancer, and TCTP was found to be a client protein of the chaperone in co-immunoprecipitation experiments. Overexpression of hsp27 increased TCTP

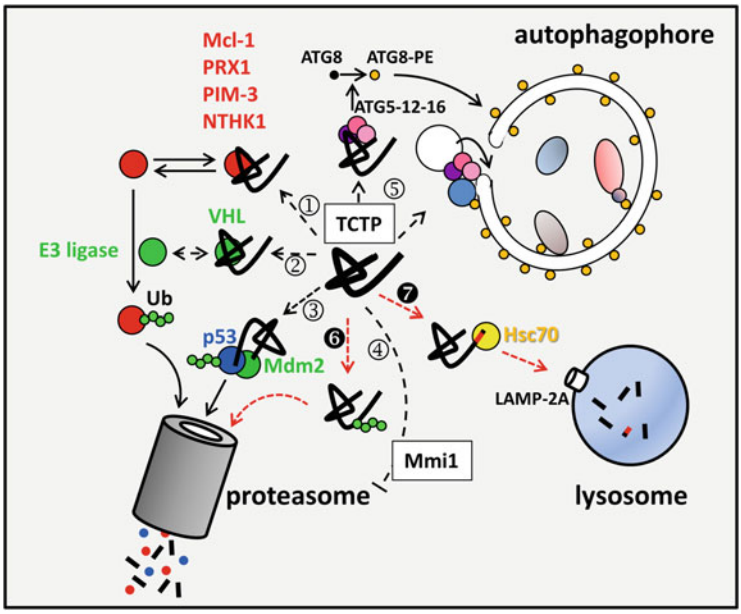

Fig. 6.1 Schematic representation of the different types of involvement of TCTP in protein degradative pathways discussed in the review. References for steps: ①: Liu et al. (2005), Susini et al. (2008), Chattopadhyay et al. (2016), Zhang et al. (2013) and Tao et al. (2015); ②: Chen et al. (2013); ③: Amson et al. (2012), Chan et al. (2012); ④: Guerrero et al. (2008) and Rinnerthaler et al. (2013); ⑤: Chen et al. (2014); ❻: Jiao et al. (2007) and Fujita et al. (2008) ; ❼: Bonhoure et al. (2017)

levels, while hsp27 knockdown led to a decrease in TCTP protein levels without affecting expression of its mRNA. Moreover, the proteasome inhibitor MG132 was found to reverse the effect of hsp27 knockdown and prolonged the TCTP half-life (Baylot et al. 2012).

These studies showed that TCTP can be degraded by the ubiquitin–proteasome system. However, these are uncommon situations which probably do not account for physiologic regulation of TCTP downregulation. As noted earlier, TCTP has been shown to be posttranslationally modified through ubiquitination but also through acetylation, phosphorylation, and sumoylation. These modifications can change the behavior of TCTP, as demonstrated for TCTP phosphorylation by polo-like kinase-1 (PLK1), thus decreasing its microtubule-stabilizing activity (Yarm 2002) and promoting its nuclear localization (Cucchi et al. 2010). Relocalization is a way to rapidly switch off or promote protein function, in addition to transcription or translation regulation. Thus, we explored the possibility of TCTP degradation promoted by posttranslational modification and found that TCTP was degraded by chaperone-mediated autophagy (CMA) after acetylation (Bonhoure et al. 2017). In contrast to regular macroautophagy, CMA allows lysosomal degradation of specific cytosolic proteins on a molecule-by-molecule basis. The selectivity of this pathway is conferred through recognition by the cytosolic chaperone hsc70 of a pentapeptide

biochemically related to KFERQ in the CMA substrate sequence (Kaushik and Cuervo 2012). The substrate–chaperone complex is targeted to the lysosome and interacts with the cytosolic tail of lysosome-associated membrane protein type 2A (LAMP-2A). After unfolding, the substrate translocates into the lysosomal lumen through a multimeric complex formed by LAMP-2A assembly and is then rapidly degraded (Cuervo and Dice 2000). The TCTP interactome recently revealed various chaperones, including Hsc70/HSPA8, as binding partners (Li et al. 2016), and we confirmed this interaction by GST pull-down and by experiments using a tri-functional crosslinking reagent. Moreover, by using TCTP fused with a photoactivable PAmCherry protein, we observed fluorescent TCTP redistribution from a diffuse cytosolic to a punctate lysosomal pattern upon CMA upregulation in mouse embryo fibroblasts (MEF). Indeed, TCTP was found to be associated with CMA-competent lysosomes (LAMP-2A$^+$/hsc70$^+$) isolated from starved rat liver. In MEFs, TCTP downregulation induced by serum starvation was partly reversed by blocking lysosomal degradation, but not by proteasome or macroautophagy inhibition. LAMP-2A silencing in MEFs using siRNA decreased TCTP downregulation. The use of in vitro lysosomal assays indicated that, in the presence of hsc70 and ATP, recombinant TCTP translocated and was degraded by purified CMA-competent lysosomes. Very interestingly, no strict KFERQ-like motif was found in TCTP. However, acetylation endows Lys19 (Liu et al. 2014) with the status of critical (pseudo)glutamine in the ^{19}KIREI^{23} motif. This assumption was confirmed by showing that acetylation mimetic mutants (K19Q and K19 N) are efficiently targeted to the lysosomal (LAMP-2A$^+$) compartment, contrary to the acetylation ablative mutant (K19A). Accordingly, treatment of cells with deacetylase inhibitors decreased TCTP intracellular levels. Overall, these data show that CMA is involved in TCTP regulation, while its acetylation is critical for its degradation (Fig. 6.2).

6.5 Conclusion

TCTP relationships with protein degradative pathways thus appear to be very finely regulated, as a regulator of its partners' degradation but also of its own degradation.

It is thus tempting to speculate that acetylation/CMA sequential processing could be involved in the regulation of TCTP functioning by switching off interactions with partners and inducing its own degradation. Interestingly, the conditional KFERQ-like motif (^{19}KIREI^{23}) encompasses Arg21, which was shown to be critical for the interaction between TCTP and the Bcl-xL homolog Mcl-1 (Zhang et al. 2002). This is in keeping with interaction of TCTP with Mcl-1, which was reported to increase the TCTP half-life (Zhang et al. 2002). More broadly, the N-terminal sequence in TCTP, including the conditional KFERQ-like motif, was shown to mediate binding to the BH3 domain of Bcl-xL (Yang et al. 2005; Thebault et al. 2016).

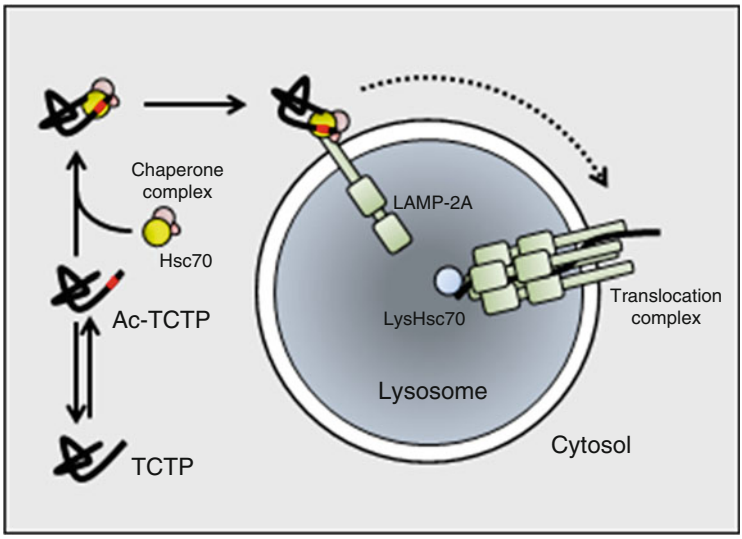

Fig. 6.2 Schematic representation of the different steps involved in TCTP degradation by chaperone-mediated autophagy

Note that Ku70 is another effector that is activated through deacetylation to enhance cell survival. Interestingly Ku70, like TCTP with which it interacts (Zhang et al. 2012), is involved in DNA double-strand break repair and apoptosis regulation in an acetylation sensitive-manner (Chen et al. 2007a; Subramanian et al. 2005). Importantly, it has been shown that CMA is upregulated in response to DNA damage and participates in the timely degradation of nuclear Chk1 subsequent to its phosphorylation by ATR kinase after DNA repair (Park et al. 2015). We could speculate a similar fate for TCTP with acetylation subsequent to DNA repair.

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Compliance with Ethics Guidelines

The author declares that he has no conflict of interest with the contents of this chapter.

References

Amson R, Pece S, Lespagnol A, Vyas R, Mazzarol G, Tosoni D et al (2012) Reciprocal repression between P53 and TCTP. Nat Med 18(1):91–99

Amzallag N, Passer BJ, Allanic D, Segura E, Thery C, Goud B et al (2004) TSAP6 facilitates the secretion of translationally controlled tumor protein/histamine-releasing factor via a nonclassical pathway. J Biol Chem 279(44):46104–46112

Baudet C, Perret E, Delpech B, Kaghad M, Brachet P, Wion D et al (1998) Differentially expressed genes in C6.9 glioma cells during vitamin D-induced cell death program. Cell Death Differ 5 (1):116–125

Baylot V, Katsogiannou M, Andrieu C, Taieb D, Acunzo J, Giusiano S et al (2012) Targeting TCTP as a new therapeutic strategy in castration-resistant prostate cancer. Mol Ther 20 (12):2244–2256. Epub 2012/08/16

Bazile F, Pascal A, Arnal I, Le Clainche C, Chesnel F, Kubiak JZ (2009) Complex relationship between TCTP, microtubules and actin microfilaments regulates cell shape in normal and cancer cells. Carcinogenesis 30(4):555–565. Epub 2009/01/27

Bommer UA, Borovjagin AV, Greagg MA, Jeffrey IW, Russell P, Laing KG et al (2002) The mRNA of the translationally controlled tumor protein P23/TCTP is a highly structured RNA, which activates the dsRNA-dependent protein kinase PKR. RNA 8(4):478–496

Bommer UA, Heng C, Perrin A, Dash P, Lobov S, Elia A et al (2010) Roles of the translationally controlled tumour protein (TCTP) and the double-stranded RNA-dependent protein kinase, PKR, in cellular stress responses. Oncogene 29(5):763–773

Bommer UA, Iadevaia V, Chen J, Knoch B, Engel M, Proud CG (2015) Growth-factor dependent expression of the translationally controlled tumour protein TCTP is regulated through the PI3-K/Akt/mTORC1 signalling pathway. Cell Signal 27(8):1557–1568. Epub 2015/05/06

Bonhoure A, Vallentin A, Martin M, Senff-Ribeiro A, Amson A, Telerman A et al (2017) Acetylation of translationally controlled tumor protein promotes its degradation through chaperone-mediated autophagy. Eur. J. Cell Biol. 96: 83–98

Burgess A, Labbe JC, Vigneron S, Bonneaud N, Strub JM, Van Dorsselaer A et al (2008) Chfr interacts and colocalizes with TCTP to the mitotic spindle. Oncogene 27(42):5554–5566

Chan TH, Chen L, Liu M, Hu L, Zheng BJ, Poon VK et al (2012) Translationally controlled tumor protein induces mitotic defects and chromosome missegregation in hepatocellular carcinoma development. Hepatology 55(2):491–505. Epub 2011/09/29

Chattopadhyay A, Pinkaew D, Doan HQ, Jacob RB, Verma SK, Friedman H et al (2016) Fortilin potentiates the peroxidase activity of Peroxiredoxin-1 and protects against alcohol-induced liver damage in mice. Sci Rep 6:18701. Epub 2016/01/05

Chen CS, Wang YC, Yang HC, Huang PH, Kulp SK, Yang CC et al (2007a) Histone deacetylase inhibitors sensitize prostate cancer cells to agents that produce DNA double-strand breaks by targeting Ku70 acetylation. Cancer Res 67(11):5318–5327. Epub 2007/06/05

Chen SH, Wu PS, Chou CH, Yan YT, Liu H, Weng SY et al (2007b) A knockout mouse approach reveals that TCTP functions as an essential factor for cell proliferation and survival in a tissue- or cell type-specific manner. Mol Biol Cell 18(7):2525–2532

Chen K, Chen S, Huang C, Cheng H, Zhou R (2013) TCTP increases stability of hypoxia-inducible factor 1alpha by interaction with and degradation of the tumour suppressor VHL. Biol Cell 105 (5):208–218. Epub 2013/02/08

Chen K, Huang C, Yuan J, Cheng H, Zhou R (2014) Long-term artificial selection reveals a role of TCTP in autophagy in mammalian cells. Mol Biol Evol 31(8):2194–2211. Epub 2014/06/04

Cohen M, Stutz F, Belgareh N, Haguenauer-Tsapis R, Dargemont C (2003) Ubp3 requires a cofactor, Bre5, to specifically de-ubiquitinate the COPII protein, Sec23. Nat Cell Biol 5 (7):661–667

Colaluca IN, Tosoni D, Nuciforo P, Senic-Matuglia F, Galimberti V, Viale G et al (2008) NUMB controls p53 tumour suppressor activity. Nature 451(7174):76–80

Cucchi U, Gianellini LM, De Ponti A, Sola F, Alzani R, Patton V et al (2010) Phosphorylation of TCTP as a marker for polo-like kinase-1 activity in vivo. Anticancer Res 30(12):4973–4985

Cuervo AM, Dice JF (2000) Unique properties of lamp2a compared to other lamp2 isoforms. J Cell Sci 113(Pt 24):4441–4450

Diraison F, Hayward K, Sanders KL, Brozzi F, Lajus S, Hancock J et al (2011) Translationally controlled tumour protein (TCTP) is a novel glucose-regulated protein that is important for survival of pancreatic beta cells. Diabetologia 54(2):368–379. Epub 2010/11/11

Fujita T, Felix K, Pinkaew D, Hutadilok-Towatana N, Liu Z, Fujise K (2008) Human fortilin is a molecular target of dihydroartemisinin. FEBS Lett 582(7):1055–1060. Epub 2008/03/08

Gachet Y, Tournier S, Lee M, Lazaris-Karatzas A, Poulton T, Bommer UA (1999) The growth-related, translationally controlled protein P23 has properties of a tubulin binding protein and associates transiently with microtubules during the cell cycle. J Cell Sci 112(Pt 8):1257–1271

Gnanasekar M, Dakshinamoorthy G, Ramaswamy K (2009) Translationally controlled tumor protein is a novel heat shock protein with chaperone-like activity. Biochem Biophys Res Commun 386(2):333–337

Graidist P, Phongdara A, Fujise K (2004) Antiapoptotic protein partners fortilin and MCL1 independently protect cells from 5-fluorouracil-induced cytotoxicity. J Biol Chem 279 (39):40868–40875

Guerrero C, Milenkovic T, Przulj N, Kaiser P, Huang L (2008) Characterization of the proteasome interaction network using a QTAX-based tag-team strategy and protein interaction network analysis. Proc Natl Acad Sci USA 105(36):13333–13338. Epub 2008/09/02

Hong ST, Choi KW (2013) TCTP directly regulates ATM activity to control genome stability and organ development in Drosophila melanogaster. Nat Commun 4:2986. Epub 2013/12/20

Hsu YC, Chern JJ, Cai Y, Liu M, Choi KW (2007) Drosophila TCTP is essential for growth and proliferation through regulation of dRheb GTPase. Nature 445(7129):785–788

Jiao Y, Ge CM, Meng QH, Cao JP, Tong J, Fan SJ (2007) Dihydroartemisinin is an inhibitor of ovarian cancer cell growth. Acta Pharmacol Sin 28(7):1045–1056. Epub 2007/06/26

Kaushik S, Cuervo AM (2012) Chaperone-mediated autophagy: a unique way to enter the lysosome world. Trends Cell Biol 22(8):407–417

Le TP, Vuong LT, Kim AR, Hsu YC, Choi KW (2016) 14-3-3 Proteins regulate Tctp-Rheb interaction for organ growth in Drosophila. Nat Commun 7:11501. Epub 2016/05/07

Li S, Chen M, Xiong Q, Zhang J, Cui Z, Ge F (2016) Characterization of the translationally controlled tumor protein (TCTP) interactome reveals novel binding partners in human cancer cells. J Proteome Res. Epub 2016/09/09

Liu H, Peng HW, Cheng YS, Yuan HS, Yang-Yen HF (2005) Stabilization and enhancement of the antiapoptotic activity of mcl-1 by TCTP. Mol Cell Biol 25(8):3117–3126

Liu Z, Wang Y, Gao T, Pan Z, Cheng H, Yang Q et al (2014) CPLM: a database of protein lysine modifications. Nucleic Acids Res 42(Database issue):D531–D536. Epub 2013/11/12

Lucibello M, Gambacurta A, Zonfrillo M, Pierimarchi P, Serafino A, Rasi G et al (2011) TCTP is a critical survival factor that protects cancer cells from oxidative stress-induced cell-death. Exp Cell Res 317(17):2479–2489. Epub 2011/08/02

MacDonald SM, Rafnar T, Langdon J, Lichtenstein LM (1995) Molecular identification of an IgE-dependent histamine-releasing factor. Science 269(5224):688–690

Ohsumi Y (2014) Historical landmarks of autophagy research. Cell Res 24(1):9–23. Epub 2013/12/25

Park C, Suh Y, Cuervo AM (2015) Regulated degradation of Chk1 by chaperone-mediated autophagy in response to DNA damage. Nat Commun 6:6823. Epub 2015/04/17

Rinnerthaler M, Jarolim S, Heeren G, Palle E, Perju S, Klinger H et al (2006) MMI1 (YKL056c, TMA19), the yeast orthologue of the translationally controlled tumor protein (TCTP) has apoptotic functions and interacts with both microtubules and mitochondria. Biochim Biophys Acta 1757(5–6):631–638

Rinnerthaler M, Lejskova R, Grousl T, Stradalova V, Heeren G, Richter K et al (2013) Mmi1, the yeast homologue of mammalian TCTP, associates with stress granules in heat-shocked cells and modulates proteasome activity. PLoS One 8(10):e77791. Epub 2013/11/10

Rocchi P, Jugpal P, So A, Sinneman S, Ettinger S, Fazli L et al (2006) Small interference RNA targeting heat-shock protein 27 inhibits the growth of prostatic cell lines and induces apoptosis via caspase-3 activation in vitro. BJU Int 98(5):1082–1089. Epub 2006/08/02

Roque CG, Wong HH, Lin JQ, Holt CE (2016) Tumor protein Tctp regulates axon development in the embryonic visual system. Development 143(7):1134–1148. Epub 2016/02/24

Subramanian C, Opipari AW Jr, Bian X, Castle VP, Kwok RP (2005) Ku70 acetylation mediates neuroblastoma cell death induced by histone deacetylase inhibitors. Proc Natl Acad Sci USA 102(13):4842–4847. Epub 2005/03/22

Susini L, Besse S, Duflaut D, Lespagnol A, Beekman C, Fiucci G et al (2008) TCTP protects from apoptotic cell death by antagonizing bax function. Cell Death Differ 15(8):1211–1220

Tao JJ, Cao YR, Chen HW, Wei W, Li QT, Ma B et al (2015) Tobacco translationally controlled tumor protein interacts with ethylene receptor tobacco histidine kinase1 and enhances plant growth through promotion of cell proliferation. Plant Physiol 169(1):96–114. Epub 2015/05/06

Thaw P, Baxter NJ, Hounslow AM, Price C, Waltho JP, Craven CJ (2001) Structure of TCTP reveals unexpected relationship with guanine nucleotide-free chaperones. Nat Struct Biol 8 (8):701–704

Thebault S, Agez M, Chi X, Stojko J, Cura V, Telerman SB et al (2016) TCTP contains a BH3-like domain, which instead of inhibiting, activates Bcl-xL. Sci Rep 6:19725. Epub 2016/01/28

Tsukada M, Ohsumi Y (1993) Isolation and characterization of autophagy-defective mutants of Saccharomyces cerevisiae. FEBS Lett 333(1–2):169–174. Epub 1993/10/25

Tuynder M, Susini L, Prieur S, Besse S, Fiucci G, Amson R et al (2002) Biological models and genes of tumor reversion: cellular reprogramming through tpt1/TCTP and SIAH-1. Proc Natl Acad Sci USA 99(23):14976–14981

Walczak M, Martens S (2013) Dissecting the role of the Atg12-Atg5-Atg16 complex during autophagosome formation. Autophagy 9(3):424–425. Epub 2013/01/17

Yang Y, Yang F, Xiong Z, Yan Y, Wang X, Nishino M et al (2005) An N-terminal region of translationally controlled tumor protein is required for its antiapoptotic activity. Oncogene 24 (30):4778–4788

Yarm FR (2002) Plk phosphorylation regulates the microtubule-stabilizing protein TCTP. Mol Cell Biol 22(17):6209–6221

Zhang D, Li F, Weidner D, Mnjoyan ZH, Fujise K (2002) Physical and functional interaction between myeloid cell leukemia 1 protein (MCL1) and Fortilin. The potential role of MCL1 as a fortilin chaperone. J Biol Chem 277(40):37430–37438. Epub 2002/08/01

Zhang J, de Toledo SM, Pandey BN, Guo G, Pain D, Li H et al (2012) Role of the translationally controlled tumor protein in DNA damage sensing and repair. Proc Natl Acad Sci USA 109(16): E926–E933. Epub 2012/03/28

Zhang F, Liu B, Wang Z, Yu XJ, Ni QX, Yang WT et al (2013) A novel regulatory mechanism of Pim-3 kinase stability and its involvement in pancreatic cancer progression. Mol Cancer Res MCR 11(12):1508–1520. Epub 2013/10/30