Chapter 3
Structure-Function Relationship of TCTP

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Abstract The translationally controlled tumor protein (TCTP) is a small, multifunctional protein found in most, if not all, eukaryotic lineages, involved in a myriad of key regulatory processes. Among these, the control of proliferation and inhibition of cell death, as well as differentiation, are the most important, and it is probable that other responses are derived from the ability of TCTP to influence them in both unicellular and multicellular organisms. In the latter, an additional function for TCTP stems from its capacity to be secreted via a nonclassical pathway and function in a non-cell autonomous (paracrine) manner, thus affecting the responses of neighboring or distant cells to developmental or environmental stimuli (as in the case of serum TCTP/histamine-releasing factor in mammals and phloem TCTP in *Arabidopsis*). The additional ability to traverse membranes without a requirement for transmembrane receptors adds to its functional flexibility. The long-distance transport of TCTP mRNA and protein in plants via the vascular system supports the notion that an important aspect of TCTP function is its ability to influence the response of neighboring and distant cells to endogenous and exogenous signals in a supracellular manner. The predicted tridimensional structure of TCTPs indicates a high degree of conservation, more than its amino acid sequence similarity could suggest. However, subtle differences in structure could lead to different activities, as evidenced by TCTPs secreted by *Plasmodium* spp. Similar structural variations in animal and plant TCTPs, likely the result of convergent evolution, could lead to deviations from the canonical function of this group of proteins, which could have an impact from a biomedical and agricultural perspectives.

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3.1 Introduction

There are multiple mechanisms through which cells regulate proliferation and differentiation. Some genes are specific to certain taxa, but the function of others is quite conserved among phylogenetically distant groups. These genes hint to a core mechanism controlling such fundamental processes; although, it is expected that unicellular organisms should have a simpler machinery underlying cell division and differentiation, recent evidence indicates that, at least in some eukaryotic lineages, co-option of components of a preexisting machinery, such as the retinoblastoma pathway, gave rise to multicellularity (Hanschen et al. 2016). Similarly, the evolution of multicellularity in animals required the emergence of novel genes but also the co-option of preexisting ones (Suga et al. 2013). Furthermore, basic gene modules have been adapted for novel functions during evolution, to which modified versions of these genes have been added, as in the evolution of the plant vascular system (Martínez-Navarro et al. 2013).

In eukaryotes, the translationally controlled tumor protein, or TCTP, is a central regulator of cell division, differentiation, and a host of other essential processes, being present in most extant eukaryote taxa analyzed to date. The messenger RNA for TCTP was initially identified in an erythroleukemia cell line and, as its name implies, accumulated to high levels without the corresponding accumulation of its encoded protein (Bommer and Thiele 2004; Amson et al. 2013). Translational regulation may occur with TCTP mRNAs from different taxa, but this has not been determined experimentally in most cases. High levels of accumulation of this transcript have been observed in several species (mostly animals), which is proportionally correlated with proliferation. Moreover, the repression of this gene is linked to tumor reversion (Tuynder et al. 2004). Indeed, increased accumulation of TCTP has been observed in different types of cancer, correlating with poor prognosis (Chan et al. 2012; Xiao et al. 2016). However, multitude of studies indicate that TCTP is involved in several other phenomena (Amson et al. 2013) and thus supports the notion that these proteins function as adapters within core modules involved in regulating a variety of processes. These include cell proliferation and differentiation, as well as others that may be termed idiosyncratic, since these are taxon, developmental, or tissue specific. For example, some regulate development of reproductive structures in plants, as well as plant regeneration and lateral roots. Still others may be involved in certain types of molecular mimicry in some parasites. Thus, the study of these proteins may yield significant insight on a wealth of phenomena, some of which could appear unrelated but are connected by the involvement of TCTP, as will be mentioned below.

3.2 Conserved Functions of TCTP Across Kingdoms

Much work has been done recently to elucidate the function of TCTP. As mentioned before, the mRNA of a human TCTP was first isolated from an erythroleukemia line. Such abundant RNA was not associated to any protein, and therefore it was thought to be regulated at the translational level. Abundant transcripts for TCTP were isolated from other organisms, mostly from developing tissues, which suggested that TCTP is involved in promoting development and/or cell proliferation. Several lines of evidence indicate that the primary function of TCTP is the regulation of proliferation. Indeed, human TCTP binding to microtubules is regulated by the polo kinase (Plk), which is essential for the control of polar spindle dynamics; overexpression of a TCTP mutant lacking the Plk phosphorylation site resulted in multinucleate cells (Yarm 2002). Thus, phosphorylated TCTP binds less efficiently to and stabilizes microtubules, leading to cell division arrest. Furthermore, phosphorylated mouse TCTP (and probably several other TCTPs from diverse organisms) promotes depolymerization of polar, but not kinetochore microtubules during oocyte meiosis (Jeon et al. 2016). Therefore, the primary function of all TCTPs may be promoting cytokinesis, although whether this occurs mostly in germline or in all somatic cells (which seems more likely) remains to be determined. However, it has been suggested that TCTP, based on structural similarities with the Mss family of chaperones (for they which have also been termed Mss4), is a guanine nucleotide exchange factor (GEF), which are involved in many processes, such as the polymerization of microtubules (Thaw et al. 2001). Furthermore, it has been demonstrated that TCTP inhibits the dissociation of GDP from the eukaryotic translation initiation factor eEF1A (Cans et al. 2003), implicating it in the regulation of protein synthesis. This binding is evolutionarily conserved, since the human TCTP can bind eEF1A from fission yeast and chlorophytes in vitro (Wu et al. 2015). The notion of TCTP as a second messenger involved in growth regulation and responses to external stimuli is supported by the fact that it is a calcium-binding protein, and this has been confirmed in several systems (Bommer and Thiele 2004).

As a general regulator of growth in eukaryotes, it has been assumed that TCTP is also at the helm of pathways involved in such general processes, for example, the target of rapamycin (TOR) pathway. This is central in the control of cell growth in response to nutrients as well as to internal signals in extant eukaryotes (Albert and Hall 2015; Dobrenel et al. 2016). One of the inducers of TOR complex activity is the small G-protein Ras enriched in brain (Rheb) through their interaction in the lysosomal membrane (Heard et al. 2014). This implies that the regulation of this pathway necessitates a guanine nucleotide exchange factor (GEF); indeed, *Drosophila* TCTP binds Rheb, and such interaction is necessary for the regulation of growth and cell size (Hsu et al. 2007), although this has been disputed (Wang et al. 2008). Support that at least in *Drosophila* TCTP functions as a bona fide GEF comes from the fact that Rheb and TCTP interaction controls organ growth, which is in turn regulated by members of the large family of 14-3-3 general transcription factors (Le et al. 2016). It remains to be established how general is this interaction, but it must be considered

that analysis of genome databases yielded no Rheb homologs in plants or apicomplexans, such as *Plasmodium*. Insulin is another general regulator of growth in animals and other eukaryotes, which acts via, among several others, the TOR pathway (Albert and Hall 2015). TCTP appears to mediate insulin signaling, since this induces phosphorylation of the former in an embryonic kidney cell line, although not in HeLa cells (Maeng et al. 2015).

The complementation of TCTP mutants between evolutionarily distant species supports the notion that some functions of TCTP are conserved among kingdoms, as evidenced by wild-type phenotype rescue by expression of an *Arabidopsis* TCTP in a *Drosophila* mutant, and vice versa (Brioudes et al. 2010). Null mutations in TCTP are lethal during early embryonic development in *Drosophila*, underscoring its essential role in viability; hypomorphic mutations basically lead to a decrease in cell number and size, which in turn affects organ size (Hsu et al. 2007). Null alleles of *Arabidopsis* TCTP are also lethal during early stages of development, again supporting the hypothesis that the function of TCTP is essential for survival and it is required throughout the whole life cycle of an organism, but more importantly during phases that require sustained cell division (Brioudes et al. 2010; Toscano-Morales et al. 2015).

TCTP is known to inhibit programmed cell death during development in some animal models as well as in plants, in response to pathogen infection (Susini et al. 2008; Hoepflinger et al. 2013).

It is possible that these taxon-specific functions are derived from the aforementioned activities. Therefore, TCTP activity in the function or development of specialized structures in a wide variety of taxa (such as axons or pollen tubes) could have originated from their ability to interact with G proteins or with the outer mitochondrial membrane, as well as by stabilizing or destabilizing pro- or antiapoptotic factors.

3.3 Taxon-Specific Functions of TCTP

A *TCTP* mRNA was first isolated from a human erythroleukemia cell line, and the gene and its expression pattern analyzed in rabbit (Bommer and Thiele 2004). It was realized first that at least in some species, this gene was subject to translational regulation.

An interesting feature of TCTP is that its mRNA is capable of inducing protein kinase R. This kinase is induced by double-stranded RNA (dsRNA) and phosphorylates the translation elongation factor eEIF2, resulting in the inhibition of protein synthesis (Bommer et al. 2002). This indicates that (a) some TCTP mRNAs may have a considerable secondary structure, suggesting that these may be subjected to translational regulation; (b) the mRNA itself has a function other than being translated; and (c) that it may participate in the interferon pathway. Human TCTP has also been found to induce histamine release from basophils (and hence its other term histamine-releasing factor or HRF), and thus it is involved in the onset of

inflammation and allergic processes. Indeed, a dimerized form of TCTP is the active factor responsible for triggering inflammation and allergies (Kim et al. 2009), but it is not known whether this dimerized form is found only in pathological conditions or can be found carrying out normal functions in healthy individuals. This underscores an important point regarding TCTP localization. It is evident that TCTP/HRF is probably expressed in most cell types, but in the case of blood mononuclear cells, it is not clear whether there are two separate pools or, alternatively, the majority is secreted. Additionally, the possibility that other cell types secrete this protein is supported by the fact that a factor required for its export is expressed in tumor cells (and, incidentally, suggests a cell-to-cell signaling function during normal and abnormal proliferation) (Amzallag et al. 2004). In mice, TCTP is expressed during early stages of pancreas differentiation, where it is required for islet β-cell proliferation, and, in later stages, during adaptation to insulin resistance (Tsai et al. 2014).

Additional roles, at least at the biochemical level, indicate that TCTP binds to microtubules, which is regulated by phosphorylation. Such activity may regulate a host of functions, such as cytokinesis, vesicle trafficking, or organelle movement within the cell (Amson et al. 2013). All observations carried out in human cell lines point to an essential role in cell proliferation as well as Ca^{2+}-dependent inhibition of apoptosis (Amson et al. 2013). TCTP also appears to be a moonlighting protein regarding its cytokine function, although it may be related to its ability to interact with receptors in the surface of certain cell types; however, as will be mentioned below, it appears that this protein does not require transmembrane receptors. Earlier work in other species (such as *Oryctolagus*) indicated that the TCTP gene responds to heavy metal accumulation; similar results have been reported in earthworm. This suggests that TCTP has also a role in the response to abiotic stress, but its significance in this regard is not completely clear (Bommer and Thiele 2004; Amson et al. 2013). Importantly, a decrease in TCTP levels correlates with tumor reversion in breast cancer, which supports a role of this protein in inducing cell proliferation (Tuynder et al. 2004). Other roles of TCTP in vertebrates implicating the apoptotic machinery and more specifically its interaction with the P53 pathway and Bcl-xL have already been described extensively (Liu et al. 2005; Thébault et al. 2016). Its function in *Drosophila* has been reviewed in detail in this work by Kwang W. Choi.

3.3.1 Fungi

TCTP is found in the genome of extant fungi, although its function in these taxa has seldom been explored with detail. However, while TCTP inhibits apoptosis through interaction with P53 in human and mouse cell lines, in *Saccharomyces cerevisiae* (yeast) reports have shown to promote it by interacting with the external mitochondrial membrane in response to oxidative stress (Rinnerthaler et al. 2006). Furthermore, it is capable of interacting with stress granules where it modulates proteasome

activity, which could indirectly regulate cell death (Rinnerthaler et al. 2013). It has been proposed that the function of the yeast TCTP, and possibly in other organisms, is to protect proteins in granules after heat shock. Evidently this must be a highly regulated process, but how are pro- and antiapoptotic activities of TCTP balanced, if they do occur in yeast, as well as how general is this phenomenon, remains to be elucidated. An example of taxon-specific functions of TCTP can be found in *Aspergillus nidulans*, a polymorphic fungus, in which this protein is involved in branching as well as in sexual differentiation (Oh et al. 2013). Its localization is either nuclear or cytoplasmic, depending on the growth phase, similar to what has been found in human cell lines, yeast, or *Arabidopsis* (Ma and Zhu 2012; Rinnerthaler et al. 2013; Toscano-Morales et al. 2015). Interestingly, a human pathogenic fungus that causes eumycetoma, *Madurella mycetomatis*, secretes a TCTP homolog, which could be involved in the development of tumors as a result of infection with this pathogen (van de Sande et al. 2006). Similarly, mycelia of the human pathogen *Paracoccidioides* spp. secrete TCTP, which could have a role in infection and/or colonization of its host (Weber et al. 2012). The human opportunistic pathogen *Candida albicans* also secretes TCTP via exosomes; thus, secretion of this protein by pathogenic fungi could be a general strategy to suppress the host's defense response (Vargas et al. 2015). However, the role of TCTP may be more general, since a free-living fungus, yeast, also secretes a TCTP form through exosomes (Oliveira et al. 2010).

3.3.2 Plants

TCTP-like mRNAs were detected in plants early on. Indeed, a TCTP mRNA was found to increase its levels after dark treatment of *Pharbitis*, a plant in which flower induction is dependent on day length, suggesting a role in circadian rhythms (Sage-Ono et al. 1998). Another remarkable feature of this and other emerging plant sequences was the similarity to animal TCTP sequences. While to date the structure of a plant TCTP has not yet been resolved, given the sequence conservation and structural similarity between TCTPs from evolutionarily diverse organisms such as fission yeast, human, and *Plasmodium*, it can be confidently assumed that the structure of plant TCTPs is similar. This notion is supported by the fact that the *Arabidopsis* and *Drosophila* functions are, at least in part, exchangeable. Indeed, the expression of the *Drosophila* TCTP can rescue an *Arabidopsis* TCTP mutant and vice versa (Brioudes et al. 2010). There are not many studies on plant TCTP function, although in *Arabidopsis* its knockout causes early lethality; silenced plants also harbor defective pollen; furthermore, it controls cell cycle duration (Berkowitz et al. 2008; Brioudes et al. 2010). It could be assumed that TCTP genes could have overlapping or completely redundant functions in organisms harboring more than one copy; however, this may not always be the case, as will be detailed below. For instance, *Arabidopsis* itself harbors two TCTP genes, termed *AtTCTP1* and *AtTCTP2* (accession numbers At3g16640 and At3g05540, respectively). The data

regarding TCTP function corresponds to *AtTCTP1*, while *AtTCTP2* was initially considered a pseudogene (Berkowitz et al. 2008). However, work in our group demonstrated that the latter is not a pseudogene, and the loss of function is also lethal, although at later stages in development (Toscano-Morales et al. 2015). Thus, the wild-type *AtTCTP1* allele cannot compensate for the loss of the *AtTCTP*2 allele and vice versa, suggesting that these genes may have nonoverlapping functions. Developmental arrest in *AtTCTP1* null mutants occurs at early embryonic stages, while in *AtTCTP2* this occurs during the early rosette stage (Toscano-Morales et al. 2015). Additionally, while *AtTCTP2* expressed in *Agrobacterium rhizogenes* is capable of regenerating whole tobacco plants, *AtTCTP1* is not (Toscano-Morales et al. 2015). Furthermore, *AtTCTP2* mRNA is more difficult to detect than the *AtTCTP1* mRNA, not only because of lower expression levels but probably also because of more intricate secondary structure. All this evidence reinforces the notion that these genes may have at least partially different functions.

Despite their little overlap in activity, AtTCTP1 and AtTCTP2 differ mostly in a 13-amino-acid deletion in AtTCTP2 relative to AtTCTP1 in positions 35 to 47, plus a few substitutions distributed along the entire sequence. Insertion of this sequence in AtTCTP2 results in a marked decrease in its ability to induce plant regeneration, while the deletion of this sequence in AtTCTP1 leads to an in increase in its ability to induce regeneration (Toscano-Morales et al. 2015). Furthermore, AtTCTP2 localizes to nuclei in roots and AtTCTP1 in cytoplasm in this same plant organ, but the localization of the corresponding modified proteins is exchanged. Also, the predicted structure of the modified AtTCTP2 resembles more than that of AtTCTP1 and vice versa. The predicted structural modification is located in the putative G-protein-binding pocket, a modification predicted to be harbored by proteins from diverse taxa (see below). These results also highlight the ability of TCTP to shuttle between nucleus and cytoplasm, conceivably in response to signaling molecules, a phenomenon also observed in TCTPs from animals. Indeed, the TCTP localization pattern oscillates between nucleus and cytoplasm in a time-dependent manner in a human cell line (Ma and Zhu 2012). The mechanism for TCTP import to and export from the nucleus is not known, given the probable absence of a clear nuclear localization signal in TCTP. Although a recent report in which a role for TCTP in potyvirus infection in plants predicts that the tomato TCTP harbors a nuclear export signal (NES) (Bruckner et al. 2017) requires to be experimentally tested, it should be noted that this putative NES does not coincide with the region that blocks AtTCTP2 entry into the nucleus (i.e., the 13 amino acids present in AtTCTP1 but not in AtTCTP2). Recently, a role in regulating cell death in response to pathogens has been observed for TCTP in tobacco, as well as in the response to ethylene; it is well established that both phenomena are related in plants (Hoepflinger et al. 2013). Interestingly, overexpression of TCTP in tobacco decreased cell death induced in leaf disks by different effectors, among them BAX (a protein that induces cell death in mammals and other organisms). This supports the notion that protection against cell death is mediated in animals and plants via similar mechanisms involving TCTP. Furthermore, this activity likely requires calcium binding. TCTP in the plant-parasitic nematode *Meloidogyne enterolobii* has been recruited to block

programmed cell death in response to pathogens, thus effectively favoring colonization of its host; thus, it is likely that plant and TCTPs from other taxa display an antiapoptotic activity (Zhuo et al. 2016). Another interesting feature of some TCTPs is that they have been found in the phloem translocation stream of certain species (Lin et al. 2009; Rodríguez-Medina et al. 2011). This suggests that in vascular plants, TCTP may function in a non-cell autonomous manner, although the nature of such function is still a matter of speculation. Conversely, this protein could be involved in the reorganization of its cytoskeletal system; given the enucleate nature of the phloem sieve tube, its longevity, and its role in long-distance transport of nutrients and chemical signals, it is evident that it requires structural reinforcement, an activity that could be partially provided by this protein, although this is also speculative. The extracellular proteome of different species was searched for TCTP, with no matches found. Thus, in contrast to certain vertebrate TCTPs, the corresponding plant proteins are probably not secreted in normal conditions. However, AtTCTP1 has been observed in cell wall-rich fractions in *Arabidopsis*, implying that it could be secreted in some cell types (Jamet et al. 2008). Additionally, the tomato TCTP has been found in the xylem proteome in response to *Fusarium* effectors (Gawehns et al. 2015). More recently, AtTCTP1 has been found in the pollen tube secretome; mutants in this gene show defects in fertilization, indicating an important role in this regard (Hafidh et al. 2016). Thus, it has been suggested that TCTP has an important role in pollen tube guidance, although its precise function in this case is not clear. Interestingly, in this same work, proteins that are secreted via a nonclassical pathway were also detected in the pollen secretome, i.e., proteins lacking a discernible signal peptide, suggesting that this secretion pathway is more conspicuous than previously thought. Additionally, nonclassical secretion pathways in plants are not known, although TCTP export could occur via exosomes, which have been observed in soybean protoplasts (Tanchak and Fowke, 1987).

In the few cases analyzed in plants, TCTP displays dual intracellular localization, while AtTCTP1 localizes to nuclei in mesophyll and accumulates mostly in cytoplasm in roots; the opposite has been observed in AtTCTP2 (Toscano-Morales et al. 2015). How general is this dual localization in plants and other organisms remains to be determined.

On the other hand, it is necessary to study whether the function of TCTP in other plant species, particularly nonvascular plants and chlorophytes, is similar. It must be mentioned that in the five chlorophyte genomes sequenced to date, a TCTP gene homolog is found in only one of this, *Coccomyxa subellipsoidea*, although erroneous annotation or incomplete coverage (i.e., if these sequences were found close to centromeres) could explain this observation (Gutiérrez-Galeano et al. 2014).

3.3.3 Blood-Borne and Other Vertebrate Parasites

In a previous work, we scoured for TCTP sequences in extant taxa genomic databases, and, as expected, most harbored at least one gene (Hinojosa-Moya et al. 2008). Interestingly, it had been reported that several evolutionarily distant organisms secrete a form of TCTP; these organisms have in common that they either colonize or feed on blood from vertebrates. These include apicomplexa, arthropods, and filarial parasites (Chmelar et al. 2008; Hewitson et al. 2008; Silverman et al. 2008; Weir et al. 2010). Secretomes of other parasites, such as *Trypanosoma* spp., also include TCTP homologs, although in most cases their function is far from clear (Bayer-Santos et al. 2013). In the particular case of *Plasmodium falciparum*, it has been observed that in some cases a very high concentration of TCTP is found in sera of infected individuals (approximately 7 μg/ml). *E. coli*-expressed *P. falciparum* TCTP has been shown to induce histamine release from mast cells, thus possessing a cytokine activity (although its efficacy is much lower than the purified human homolog, likely because of expression efficiency in this heterologous system, and/or missing possible posttranslational modifications; MacDonald et al. 2001). Thus, its function, at least in vitro, appears to be similar to its human counterpart. Additionally, as implied by its ability to induce secretion of histamine when applied exogenously, it also functions in a non-cell autonomous manner. Since the host TCTP induces inflammation, as a response to microbial infection, it would not be clear the role of the *Plasmodium* TCTP in the pathogenic process if this were its sole function. We have previously analyzed the reported structure of *P. knowlesi* and *P. falciparum* and compared them with the structure of human and *S. pombe* TCTPs (Hinojosa-Moya et al. 2008). It must be considered that the structure of protein in solution, particularly in its physiological milieu, is quite dynamic, and thus in its crystalized form may represent only a possible conformation. Nonetheless, the aforementioned analysis suggested that, while the predicted structure of TCTPs from diverse clades is strikingly similar, the *Plasmodium* protein showed a structural alteration relative to *S. pombe*, in that an alpha helix was present in the former, instead of a beta sheet close to the N end. Interestingly, the predicted secondary structure of other members of the *Plasmodium* genus suggested the presence of this helix in the same position. This region is part of the potential G-protein-binding pocket that includes the conserved glutamic acid in position 12 (in *Drosophila*) (Hsu et al. 2007). Thus, while the evidence that the ability of TCTP to bind G proteins may be lacking, it is evident that this region is essential for this protein to sustain cell proliferation. In the case of *Plasmodium*, its target is unlikely to be Rheb, since this gene ortholog has not been found in the extant genomes of this genus (Ruiz-Medrano and Xoconostle-Cázares, unpublished observations).

The extra alpha helix in the *P. knowlesi* and *P. falciparum* TCTPs causes a distortion in its potential G-protein-binding pocket (Hinojosa-Moya et al. 2008). This alteration in the putative G-protein-binding pocket results in this displaying a more "open" conformation in the parasite TCTP relative to the *S. pombe* and human proteins. We hypothesized that this structural alteration could lead to functional

differences with the host TCTP. This could be relevant, considering the high amount that *Plasmodium* secretes into the host's bloodstream. We therefore tested this hypothesis by comparing the effect of recombinant human and *P. falciparum* TCTPs (HsTCTP and PfTCTP, respectively) on mouse spleen B cell proliferation. As mentioned earlier, human TCTP induced the proliferation of these cells (Kang et al. 2001). Interestingly, PfTCTP induced B cell proliferation at much lower levels than those of HsTCTP (Calderón-Pérez et al. 2014). Furthermore, when these proteins were incubated with isolated B cells, PfTCTP was incorporated much more efficiently than HsTCTP; additionally, the intracellular distribution of fluorescently labeled proteins appeared different, although more work is needed in this direction. In all, these results suggest that PfTCTP and HsTCTP have different activities, or at least these do not overlap completely. It remains to be determined whether there is an intracellular pool of PfTCTP, and if so, what is its function in the parasite life cycle, although some data indicates that there is indeed intracellular *Plasmodium* TCTP that localizes to cytoplasm and food vacuolar membrane (Bhisutthibhan et al. 1999). *Plasmodium* TCTP has received attention because it has been proposed as a target of the antimalarial drug artemisinin; more recently, it has been shown that artemisinin binds to various proteins, including TCTP; such interactions are activated by the heme group from the host's ingested blood (Wang et al. 2015). Importantly, most of the target proteins are required for parasite survival. That *Plasmodium* TCTP could be a therapeutic target for treatment of malaria is supported by the fact that immunization of mice with this protein leads to increased resistance (Taylor et al. 2015). It is tempting to speculate that a fragment encompassing the region that is structurally different from the host TCTP could be used for more effective immunization. Furthermore, a similar structural variation of certain vertebrate parasites TCTPs has been predicted.

TCTP is almost ubiquitous in eukaryotes, and some hematophagous arthropods and certain parasites (blood-borne ones as well), secrete a TCTP homolog. It is possible that these have a role in facilitating infection or suppressing the host immune response, although this has not been established with detail. To explore whether the aforementioned structural variation of the PfTCTP was also observed with these proteins, we have obtained predictive structures of TCTPs from representative human parasites, using the Protein Homology/analogY Recognition Engine V 2.0 (http://www.sbg.bio.ic.ac.uk/phyre2; Kelley et al. 2015). These are shown in Figs. 3.1, 3.2 and 3.3. To assess the precision of this analysis, the human TCTP isoform 2 structure was also predicted (as mentioned before, the structure of this protein has been solved; Fig. 3.1a). The structural similarity between all these proteins is striking; however, subtle variations can be observed. *P. berghei*, *Trypanosoma cruzi*, and *Toxoplasma gondii* TCTPs display a potential G-protein-binding pocket in a more open conformation relative to the human TCTP isoform 2 (Fig. 3.1b–d). In addition, the clamp that is central to this domain is perpendicular to the central alpha helices (1 and 2) in parasite TCTPs, but not in the human TCTP. Furthermore, the predicted *Cryptosporidium hominis*, *Theileria annulata*, and *Schistosoma mansoni* TCTPs show similar structural variations relative to human isoform 2; however, *Ixodes scapularis* TCTP resembles more the latter, harboring a

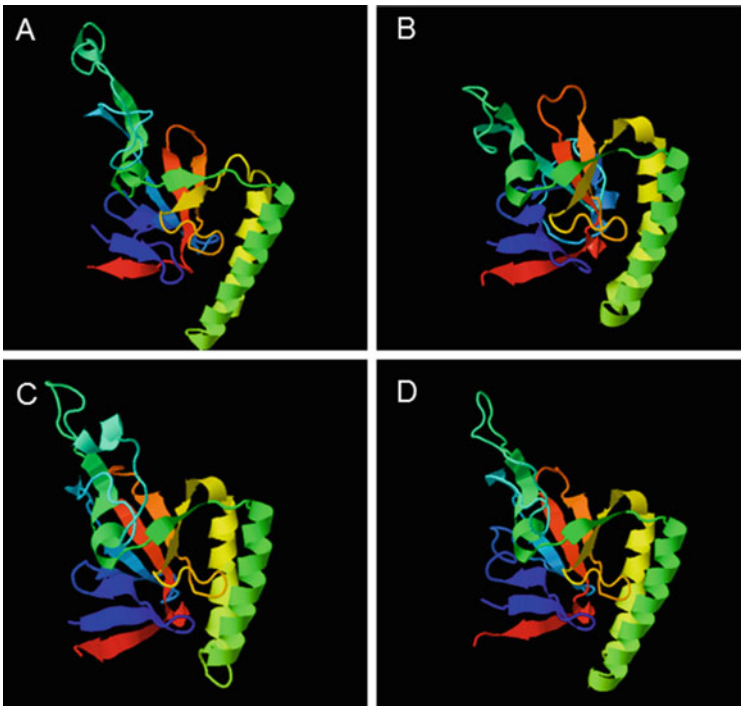

Fig. 3.1 Predictive structures of TCTP obtained with the Protein Homology/analogY Recognition Engine V 2.0 (http://www.sbg.bio.ic.ac.uk/phyre2; Kelley et al. 2015) from the following organisms: (**a**) *Homo sapiens* TCTP (isoform 2, GenBank accession number NP_003286.1); (**b**) *Plasmodium berghei* TCTP (GenBank accession number CXI61325.1); (**c**) *Trypanosoma cruzi* TCTP (GenBank accession number XP_806523.1); and (**d**) *Toxoplasma gondii* TCTP (GenBank accession number CEL78687.1)

clamp that is not completely perpendicular to the aforementioned alpha helices (Fig. 3.2a–d). Different structural isoforms of TCTP may be present in some organisms, including human. Indeed, in TCTP isoform 1 the clamp is perpendicular to the main helices, suggesting additional or different functions of this isoform relative to the more thoroughly studied isoform 2 (Fig. 3.3a). Human TCTP isoform 3 shows a similar structural variation, with a disordered lower part of the clamp (Fig. 3.3b). It must be mentioned that isoform 1 is 197 aa in length, isoform 2 is 172 aa, and isoform 3 is much shorter, 136 aa, further supporting different activities for these proteins. However, there is some confusion regarding the function of these proteins, since in several studies they are mentioned interchangeably. On the other hand, *Leishmania* TCTP structure lacks the lower part of the clamp and appears less organized overall (Fig. 3.3c). TCTP from *Giardia lamblia* (causal agent of giardiasis) may have a similar structure to parasite TCTPs, although it is not known whether it is secreted (Fig. 3.3d).

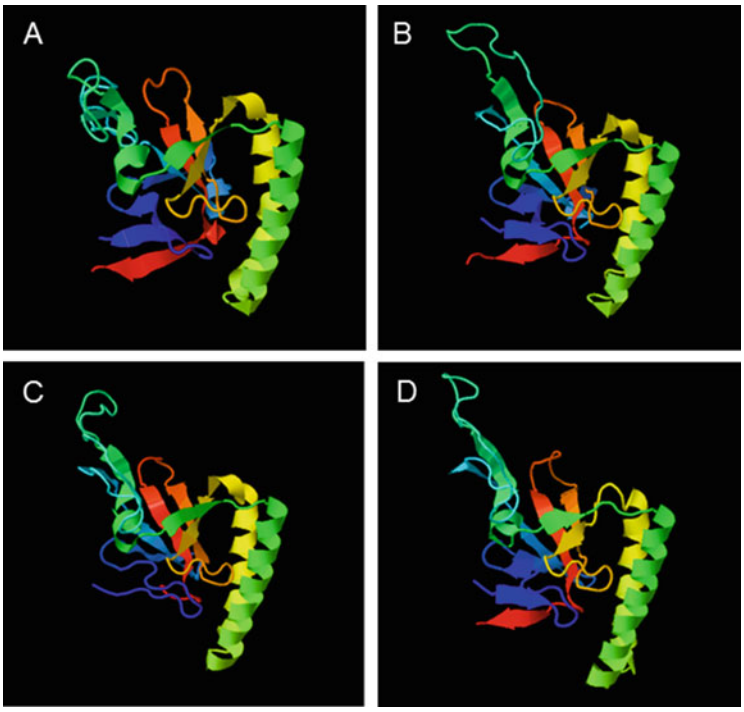

Fig. 3.2 Predictive structures of TCTP from the following organisms: (**a**) *Cryptosporidium hominis* TCTP (GenBank accession number XP_668673.1); (**b**) *Theileria annulata* TCTP; (GenBank accession number CAI73774.1); (**c**) *Schistosoma mansoni* TCTP (Swiss-Prot accession number: Q95WA2.1); and (**d**) *Ixodes scapularis* TCTP (GenBank accession number AAY66972.1)

These predictions suggest that in certain vertebrate parasites, a secreted form of TCTP may have a function that is different from the host TCTP; this could help to downregulate the immune response by mimicking and interfering with the host TCTP activity. Finally, this knowledge could be used to devise strategies for protection against blood-borne or blood-feeding parasites. Thus, it will be important to determine experimentally the tridimensional structure of these proteins. Recently, a role for the *P. berghei* TCTP/HRF has been established; this protein suppresses the secretion of interleukin-6, which is known to inhibit liver infection by the parasite (Mathieu et al. 2015). Furthermore, host infection with parasites in which its TCTP/HRF gene had been deleted protects against subsequent infection, which underscores the importance of TCTP for the infection process in malaria and, possibly, other diseases (Demarta-Gatsi et al. 2016).

There is evidence suggesting that the phylogeny of plant TCTPs cannot be resolved completely, in contrast to animals, in which the phylogeny derived from TCTP is in agreement with that obtained using other sequences (Hinojosa-Moya et al. 2008; Gutiérrez-Galeano et al. 2014). The reasons for this are probably

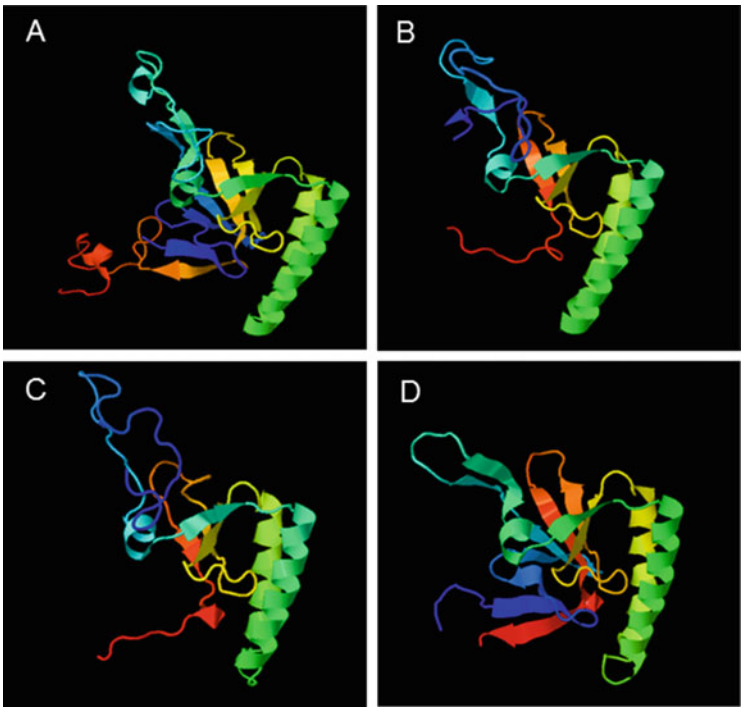

Fig. 3.3 Predictive structures of TCTP from the following organisms: (**a**) *Homo sapiens* TCTP (isoform 1, GenBank accession number NP_001273201.1); (**b**) *Homo sapiens* TCTP (isoform 3, GenBank accession number NP_001273202.1); (**c**) *Leishmania major* TCTP (GenBank accession number XP_001683667.1); and (**d**) *Giardia lamblia* TCTP (GenBank accession number EDO80348.1)

manifold and could include unequal substitution rates between clades and horizontal gene transfer. However, the predicted structure of some plant TCTPs suggests that these proteins can be classified in two large groups, one that is similar to *Arabidopsis* AtTCTP1 and the other to CmTCTP and AtTCTP2. Interestingly, AtTCTP1 predicted structure resembles that of *Schizosaccharomyces pombe* TCTP (SpTCTP), while CmTCTP/AtTCTP2 is more similar to the corresponding proteins from *P. falciparum* and *P. knowlesi* (PfTCTP and PkTCTP, respectively; Gutiérrez-Galeano et al. 2014). If these predictions based on its structure are correct, a more general classification of these proteins could be envisaged. Additionally, a broader function for members of each of these two groups could be proposed; indeed, it is possible that the proteins belonging to the SpTCTP/AtTCTP1 clade have a more direct role in cell division and proliferation, while members of the CmTCTP/AtTCTP2/PfTCTP group possibly function in diverse roles more related to differentiation. In the case of PfTCTP, this role would be more precisely to compete against the endogenous TCTP, thus helping suppress the immune response of the host. Also, the predicted structure of human TCTP isoform

1 is more similar to the *P. falciparum* TCTP and as such would be expected to have similar functional properties.

3.4 Non-cell Autonomous Functions of TCTP

All extant evidence indicates that TCTP is a multifunctional protein, with activities ranging from regulation and promotion of proliferation to intercellular signaling. It could be inferred, also, that this protein localizes to different subcellular compartments under different circumstances. Indeed, this has been observed in different systems. The isoform 2 of TCTP corresponds to the histamine releasing factor (HRF); thus, it is secreted into the bloodstream (MacDonald et al. 1995). As implied by its name, this protein induces secretion of histamine, as well as interleukins, from eosinophils and basophils (Amson et al. 2013). TCTP lacks a signal peptide, so it is secreted by an alternative mechanism. It has been shown that its secretion requires the TSAP6 protein that is also involved in exosome production (Amzallag et al. 2004; Lespagnol et al. 2008; Feng 2010). Secreted TCTP also promotes liver regeneration and, on the other hand, enhances colorectal cancer invasion, which further supports a role of this protein in non-cell autonomous regulation of cell growth (Hao et al. 2016; Xiao et al. 2016).

In the case of secreted TCTP, it is reasonable to assume that the target cell should have specific mechanisms to bind, in some cases internalize, and respond to a potential signaling cascade triggered by this protein. However, in a human lung carcinoma cell line, TCTP can be internalized via endocytosis and macropinocytosis processes that are dependent of the cytoskeleton (Kim et al. 2011, 2015). Indeed, the first ten amino acids of the N-terminus of TCTP act as a protein transduction domain (PTD) that enable this protein, or unrelated cargo fused to it, to enter cells independently of a putative specific transmembrane receptor (Kim et al. 2011). Although the precise mechanism through which PTDs are capable of entering cells is not completely known, extant evidence suggests that this process requires interaction of basic amino acids of the PTD with the membrane surface, after which endocytosis ensues, and thus it does not require interaction with a specific receptor. Moreover, lipid rafts and caveolin, but not clathrin, appear to be involved in the internalization of TCTP (Kim et al. 2011, 2015). How general is this process is not known, but given the high structural conservation of this protein family, it is likely that most, if not all, TCTPs harbor a structurally related PTD. On the other hand, with the exception of unicellular parasites that secrete TCTP into its human host bloodstream, it is not clear whether TCTP is also secreted in unicellular eukaryotes, and if so, what would be the function of such secretion. Extracellular TCTP in humans can undergo dimerization, which results from proteolytic processing by an extracellular protease (and which eliminates its N-end); this dimerized form, in contrast to in vitro synthesized TCTP, acts as a cytokine and inducing histamine secretion from mast cells and basophils and therefore has an important role in allergies; indeed, this dimerized form of TCTP is found in sera of individuals affected by allergies (Kim et al. 2009).

Interestingly, this dimerized form is bound by immunoglobulin E (IgE), which is in turn recognized by an IgE receptor, suggesting that only the dimerized form of TCTP requires a receptor, in this case, to trigger histamine release (Kashiwakura et al. 2012). While it has not been established that this dimerization occurs in other conditions or is involved in additional processes other than allergies in humans (and, conceivably, in vertebrates), it has been suggested that the *Brugia malayi* TCTP undergoes a similar modification, since this protein is also secreted into the serum of its host, suggesting that this form is also functionally relevant (Gnanasekar et al. 2002).

As mentioned in the present work, the secretion of TCTP, and thus its likely non-cell autonomous function, has been observed in several different systems, pointing to an important role in intercellular signaling. This function ranges from a cytokine-like one in the immune response to molecular mimicry by different parasitic protozoa. More recently, TCTP has been implicated in the regulation of axon development of the visual system of *Xenopus laevis* (Roque et al. 2016). An extracellular form TCTP is required to control this process, and this seems to be related to its ability to interact with the antiapoptotic Mcl1 protein. Thus, TCTP maintains viability of axons during development. The importance of TCTP in central nervous system function throughout different developmental stages is illustrated by the fact that lower levels of this protein are found in individuals with Down syndrome or afflicted with Alzheimer's disease (Kim et al. 2001). A fascinating analogy could be suggested with the pollen tube secretome in plants; it is possible that this protein is required for pollen tube survival during growth, rather than for its guidance (Hafidh et al. 2016). As mentioned before, the pollen tube secretome includes several other proteins that lack a signal peptide, indicating that these are secreted via unconventional pathways, possibly via exosomes. These vesicles have been observed in plants and are thought to have a role in defense signaling (Tanchak and Fowke 1987; An et al. 2006; Hafidh et al. 2016).

An important aspect to consider is that TCTP has an essential role in regulating cell proliferation and viability through its interaction with multiple factors, such as microtubules and antiapoptotic proteins. These roles have been found mostly in multicellular organisms, but it is not clear whether the same applies to unicellular eukaryotes, more importantly in blood-borne parasites described in the previous sections. Additionally, it is not known whether free-living unicellular or colonial eukaryotes require secretion of TCTP for their viability. It will be of interest to determine if the extracellular functions of TCTP are essential for survival; extant data suggests that this is the case (see, e.g., Roque et al. 2016). *Plasmodium* TCTP has been localized intracellularly in different developmental stages in the parasite (Bhisutthibhan et al. 1999); the factors that regulate the "partition" of this protein between the cytoplasm, food vacuoles, and the extracellular space are not known; intriguingly, no TCTP has been observed in the nucleus of *Plasmodium,* although more work is needed in this direction. Additionally, TCTP from model multicellular organisms (fundamentally human, *Drosophila,* and *Arabidopsis*) is expressed in most tissues, but it remains to be determined if this protein has the potential to be secreted from all cell types. Since TSAP6, which is required for

TCTP export, is expressed in several different organs and tissues, including skin, cardiac muscle, lungs peripheral blood, and central nervous system (see https://www.ebi.ac.uk/gxa/home), it is then likely that TCTP is secreted in all these tissues. Secretion of TCTP occurs in normal as well as in pathological conditions, as evidenced by the role of the dysregulation of this protein in endothelial cells under serum starvation and in prostate and colorectal cancers (Sirois et al. 2011; Xiao et al. 2016). The mechanism through which TCTP could act in a paracrine manner (in normal and pathologic conditions) is likely through downregulation of apoptosis in cells that bind and internalize the extracellular form of this protein; a decrease in TCTP increases apoptosis, while extracellular TCTP induces an increase in colony formation in a metastatic cell line (Sirois et al. 2011). TCTP induces migration and invasion of colon cancer cells via activation of the CDC42 small GTPase, which is a central regulator of the cell cycle, and the mitogen activated protein kinase (MAPK) JNK; this same mechanism could be involved in liver cancer and metastasis (Chan et al. 2012; Xiao et al. 2016).

Monomeric TCTP appears not to require a transmembrane receptor to induce the aforementioned effects. Given the presence of a PTD, TCTP is probably internalized through caveolar endocytosis (lipid rafts) and released from the endoplasmic reticulum into the cytoplasm, where it conceivably interacts with target proteins (Kim et al. 2015).

TCTP has been found in the phloem sap proteome of several plant species. Given that these proteins reside in the enucleate sieve tubes (ST), which deliver fixed carbon from photosynthetic to heterotrophic tissues and where there is probably no protein synthesis (Lucas et al. 2013), it is possible that TCTP functions in the maintenance of the ST system and/or long-distance (and hence non-cell autonomous) signaling. The long-distance transport of TCTP mRNA and protein suggests that this is indeed the case (Toscano-Morales et al. 2014). An intriguing possibility is that TCTP that resides in the ST system could regulate the differentiation of the sieve elements (SE), which are the individual cells that form the STs. Indeed, since plant TCTPs inhibit programmed cell death induced by pathogen infection (similar to the animal counterparts; Hoepflinger et al. 2013), these proteins could arrest the process before plasma membrane disruption, which in xylem leads to cell death, so that SEs retain a functional plasma membrane. This evidently requires experimental testing; if true, ectopic expression of TCTP in the cells that give rise to xylem should inhibit mature xylem formation. Intriguingly, *TCTP* mRNA has been found also in the phloem long-distance translocation stream of lupin, and *AtTCTP1* is one of the more conspicuous mobile RNAs found both in heterografts between different *Arabidopsis* ecotypes, as well as between *Arabidopsis* and a parasitic plant, which illustrates its efficient long-distance mobility (Rodríguez-Medina et al. 2011; Kim et al. 2014; Thieme et al. 2015). *AtTCTP2* mRNA also moves long distance from a transgenic to a non-transgenic tobacco graft, where it possibly induces the formation of aerial roots (Toscano-Morales et al. 2014). The function of the long-distance transport of *TCTP* mRNA and protein is not known; the only instance of a possible function is precisely the induction of aerial roots, which are formed in response to stress (Toscano-Morales

et al. 2014). Mobile TCTP mRNA could be translated in systemic tissues or serve another function, such as a source of phosphate and nitrogen. The function of this protein in nonvascular plants, as well as in chlorophytes, has not been reported. In the latter case, the apparent absence of this gene in all chlorophyte genomes, except for one species, *Coccomyxa subellipsoidea*, needs to be evaluated (whether this results from incomplete coverage of these genomes, genuine absence of this gene, or very low similarity to extant TCTP sequences). In the case of nonvascular plants, a non-cell autonomous function has not been observed.

The secretion of TCTP by fungi, either free-living or pathogenic, suggests that this non-cell autonomous function is pivotal to maintain homeostasis; the function in this case is far from clear, but, on a speculative note, it constitutes an extracellular signal required for survival in hostile environments; further, it is possible that this secreted form is endocyted by neighboring cells, where conceivably an antiapoptotic program would be triggered.

It has become increasingly clear that TCTP bears key functions in both cell autonomous and non-cell autonomous manner in eukaryotes, ranging from vertebrates to plants and fungal pathogens.

3.5 Perspectives

Growing evidence indicates that TCTP is a central regulator of proliferation and cell survival through inhibition of apoptosis both in animals and plants. Also, a role in differentiation as well as in the modulation of the defense response in diverse taxa has been found. The knowledge of the precise mechanisms through which this protein (and conceivably its mRNA in some instances) regulates a plethora of seemingly disparate processes will be essential to understand those that are of interest from biomedical and agricultural perspectives. Thus, recent work indicates that it could constitute a therapeutic target in metastasis in different types of cancer, infectious diseases, and neurodegenerative disorders, as well as a tool for increasing plant productivity. Several questions remain to be answered regarding the diverse roles of this polyfacetic protein, such as whether the function of secreted and internalized TCTP is the same as non-secreted protein, the mechanisms regulating the secretion of this protein in different organisms (and, in particular, in several blood-borne parasites and fungal pathogens), and the non-cell autonomous function of TCTP in animals and plants. To understand the function of this protein, it will also be essential to determine whether the microtubule destabilization function and the inhibition of apoptosis are different aspects of the same activity of TCTP. It is evident that an integrated approach is required to help answering such questions, including those involving cell and molecular biology as well as massive analysis techniques. Finally, the therapeutic potential of this protein in diseases caused by the aforementioned pathogens, in cancer, and in developmental maladies (such as those pertaining to the central nervous system) cannot be overstated. From an evolutionary viewpoint, the multiple roles of this protein are a fascinating example

of structural conservation despite a high-sequence divergence in plants and, if confirmed, a case of convergent evolution of molecular mimicry in unrelated taxa that share a common strategy to downregulate the immune response to certain human parasites.

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