Chapter 7
Roles of the Translationally Controlled Tumor Protein (TCTP) in Plant Development

Léo Betsch, Julie Savarin, Mohammed Bendahmane, and Judit Szecsi

Abstract The Translationally Controlled Tumor Protein (TCTP) is a conserved protein which expression was associated with several biochemical and cellular functions. Loss-of-function mutants are lethal both in animals and in plants, making the identification of its exact role difficult. Recent data using the model plant *Arabidopsis thaliana* provided the first viable adult knockout for TCTP and helped addressing the biological role of TCTP during organ development and the functional conservation between plants and animals. This chapter summarizes our up to date knowledge about the role of TCTP in plants and discuss about conserved functions and mechanisms between plants and animals.

7.1 Introduction

In plants as in animals, the growth of an organism and the determination of its final size require the tight regulation of multiple internal developmental processes that affect organ growth and allow the ultimate differentiation into functional organs and tissues. The rising of an individual requires the fine-tuning and coordination of cell proliferation, cell growth, cell differentiation, and cell death. The mechanisms and regulatory networks that control these developmental processes in plants remain largely unknown (Anastasiou and Lenhard 2007; Bögre et al. 2008; Pan 2007; Busov et al. 2008; Krizek 2009; Johnson and Lenhard 2011; Van Hautegem et al. 2015). Current findings begin to explain how the enormous variety in organ sizes and shapes appeared during evolution. They also highlighted that plants and animals share various common growth regulatory pathways during development and organ morphogenesis (Van Hautegem et al. 2015; Cook and Tyers 2007; Arya and White 2015; Niklas 2015; Rexin et al. 2015). However, there exist also major differences between plant and animal development. For example, while organs are

Authors "Léo Betsch" and "Julie Savarin" have contributed equally

L. Betsch • J. Savarin • M. Bendahmane (✉) • J. Szecsi (✉)
Laboratoire Reproduction et Développement des Plantes, Univ Lyon, ENS de Lyon, Université Claude Bernard Lyon 1, CNRS, INRA, 69342 Lyon, France
e-mail: mohammed.bendahmane@ens-lyon.fr; judit.szecsi@ens-lyon.fr

A. Telerman, R. Amson (eds.), *TCTP/tpt1 - Remodeling Signaling from Stem Cell to Disease*, Results and Problems in Cell Differentiation 64,
DOI 10.1007/978-3-319-67591-6_7

produced during embryogenesis in animals, plants have the capacity to generate organs during their whole life, thus constantly influencing their body size and shape. Identifying how growth regulatory pathways are shared among animal and plant species remains a daunting task.

Developmental processes largely depend on both genetic factors and environmental inputs in animals and plants. Molecular integrators, such as hormones and other factors, are stimulated by environmental signals to control development at the cellular and tissue levels (Lau and Deng 2010; Leivar and Monte 2014; Nibau et al. 2006; Peleg and Blumwald 2011). Integration of the environmental signals is achieved by a number of growth-promoting and growth-restricting factors. Many genes with growth-promoting and growth-restricting functions that act on cell division or on cell expansion have been identified in plants and in animals (Bögre et al. 2008; Pan 2007; Busov et al. 2008; Krizek 2009; Niklas 2015; Rexin et al. 2015; Penzo-Méndez and Stanger 2015; Lloyd 2013; Crickmore and Mann 2008; Chen et al. 2013). However, these genes act in independent genetic pathways, making it difficult to develop an integrated and comprehensive model of organ size control.

A common pathway controlling animal as well as plant organ growth has been proposed to involve the Translationally Controlled Tumor Protein (TCTP). In mammals, TCTP is associated with many cancers and was shown to have an antagonist role to the tumor suppressor p53 (Chen et al. 2013; Amson et al. 2012; Rho et al. 2011). TCTP is conserved among all eukaryotes and has been proposed to have diverse roles in developmental and defense processes, including several cellular functions such as cell proliferation, expansion, and death (Bommer and Thiele 2004; Brioudes et al. 2010; Bommer 2012).

In this chapter, we will present and discuss the up-to-date knowledge on the multiple roles of TCTP in growth and in response to various signals and stresses in plants, and how gained knowledge help understanding the TCTP's central role in plant and animal development.

7.2 Features of Plant TCTP Genes

Since the early 1990s, homologs of *TCTP* have been identified in many plant species, such as the model plant *Arabidopsis thaliana,* alfalfa, pea, *Pharbitis nil*, grape vine, oil palm, *Jatropha curcas*, cassava, cabbage, rice, strawberry, tobacco, rubber tree (Pay et al. 1992; Woo and Hawes 1997; Cao et al. 2010; Sage-Ono et al. 1998; Kang et al. 2003; Szécsi et al. 2006; Lopez and Franco 2006; Vincent et al. 2007; Nakkaew et al. 2010; Masura et al. 2011; Qin et al. 2011; Li et al. 2013; Santa Brígida et al. 2014; Tao et al. 2015; Wang et al. 2015; Zhang et al. 2013). In Eukaryotes, *TCTP* is generally present as a single gene copy in the genome, but many species carry more than one gene (Gutierrez-Galeano et al. 2014; Hinojosa-Moya et al. 2013). Mammals seem to have many *TCTP* gene copies in their genome, but only one is likely functional (Thiele et al. 2000; Chen et al. 2007). Plant species harbor one and up to five *TCTP* gene copies (Gutierrez-Galeano et al. 2014; Hinojosa-Moya et al. 2013; Pavy et al. 2005), but many of these gene copies

are likely nonfunctional pseudogenes (Brioudes et al. 2010; Berkowitz et al. 2008). The role of these various *TCTP* pseudogenes and transcripts variants remain unknown, but might point toward a specialization of *TCTP* function.

Globally, the genomic structure of plant *TCTP* genes is very similar. *TCTP* gene is generally composed of five exons with conserved length and four introns with variable length (Zhang et al. 2013). In *Arabidopsis thaliana AtTCTP*, intron 3 is absent leading to fusion of the third and fourth exons (Zhang et al. 2013).

As in animals, 5′ and 3′ untranslated regions (UTRs) of variable sequence length are also present in plant *TCTPs*. These UTRs have been shown to be associated with *TCTP* mRNA stability and also to play a role in the regulation of its translation (Bommer and Thiele 2004; Brioudes et al. 2010). Like for animal *TCTPs, AtTCTP* 5′UTR contains a 5′TOP element (Terminal Oligo Pyrimidine) (Brioudes et al. 2010). 5′TOP elements are common in translationally controlled proteins (Meyuhas and Kahan 2015). However, conversely to animal *TCTPs, AtTCTP* 5′TOP is not GC-rich, suggesting a less complex secondary structure of the *AtTCTP* mRNA (Brioudes et al. 2010). *AtTCTP* 3′UTR contains classical AU-rich mRNA destabilizing elements found in short-lived mRNAs in animals and in plants (Ohme-Takagi et al. 1993; Barreau et al. 2005; Narsai et al. 2007).

AtTCTP mRNA expression was shown to be strong and ubiquitous in the model plant *A. thaliana* (Brioudes et al. 2010; Szécsi et al. 2006; Berkowitz et al. 2008). The promoter region of *AtTCTP* is located in a short 0.3 kb intergenic region between *TCTP* and a neighboring gene on the complementary strand. Within this 0.3 kb intergenic region, typical core promoter elements were found at -16 bp (Y-patch) and -34 bp (TATA box) upstream of the transcription start. This 0.3 kb promoter was shown as sufficient to insure a strong and constitutive mRNA expression using a reporter gene (Han et al. 2015).

At the protein level, the relative high degree of conservation between TCTP proteins across kingdoms is reminiscent of its important role in development and survival of eukaryotes (Thayanithy 2005). For example, *Arabidopsis* AtTCTP protein shares 53.6%, 56%, and 62% amino acid similarity with human, *Drosophila* and yeast counterparts, respectively, and about 30% amino acid identity with human hTCTP (Fig. 7.1) (Hinojosa-Moya et al. 2013; Thayanithy 2005). Within the plant phylum, the majority of TCTP proteins are composed of 167 or 168 highly conserved amino acids that share 70–95% identity (Gutierrez-Galeano et al. 2014) (Fig. 7.1).

Sequence comparison showed that numerous domains in TCTP proteins are conserved in all eukaryotes (Thayanithy 2005; Hinojosa-Moya et al. 2008). Almost all identified TCTPs contain two TCTP signatures that are highly conserved and a basic domain for tubulin and calcium-binding (Figs. 7.1 and 7.2). The conserved putative GTPase interaction surface located in the central pocket indicates that TCTP proteins share GTPase binding property and GTPase activity regulating function (Cao et al. 2010; Li et al. 2013; Santa Brígida et al. 2014; Gachet et al. 1999) (Figs. 7.1 and 7.2). The N-terminal of TCTP contains a conserved MCL/Bcl-xL binding domain known to promote suppression of apoptosis in mammals (Yang et al. 2005). Like for animal TCTPs, the MCL/Bcl-xL

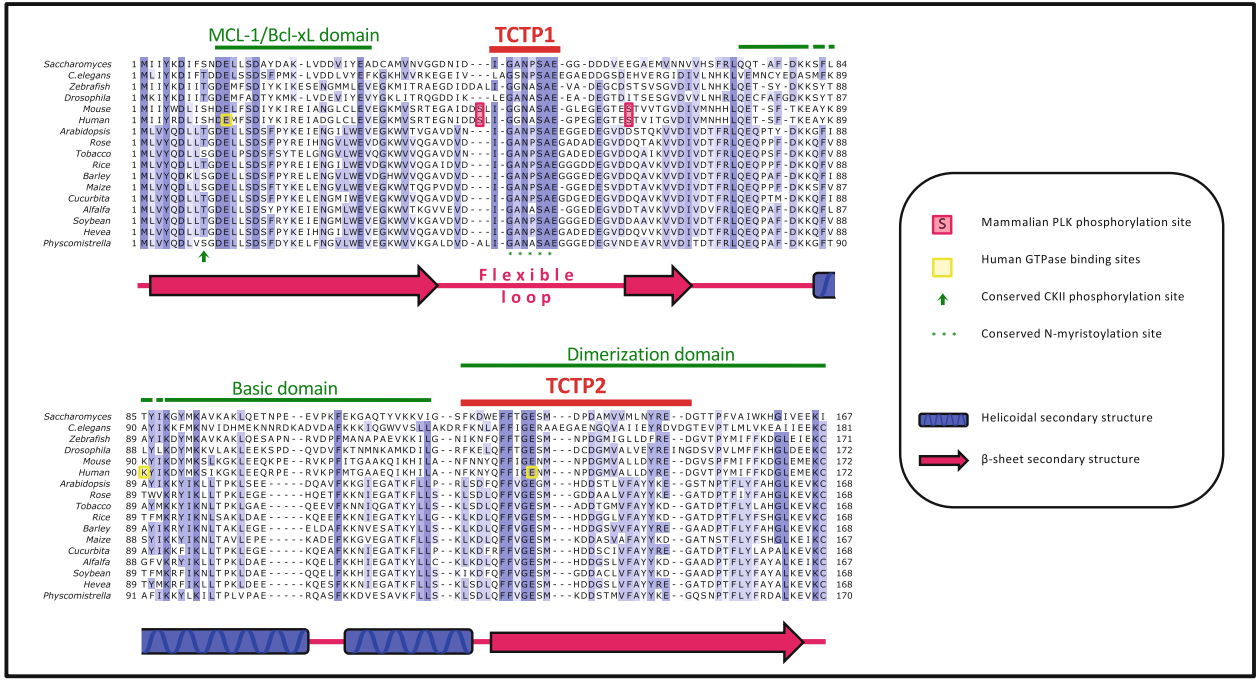

Fig. 7.1 Conservation of TCTP protein across kingdom. *Arabidopsis* AtTCTP protein shares 53.6%, 56%, and 62% amino acid similarity with human, drosophila, and yeast counterparts, respectively. Conserved TCTP signatures and binding domains are represented above amino acid sequences and secondary structure of AtTCTP at the bottom. Sequence alignments were performed using MuscleWS (Edgar 2004) software and edited with Jalview2.0 (Waterhouse et al. 2009). High conserved residues are *colored in blue* following BLOSUM 62 scoring matrix. TCTP sequences were retrieved from UniProtKB: P35691 (*Saccharomyces cerevisiae*), Q93573 (*Caenorhabditis elegans*), Q9DGK4 (Zebrafish), Q9VGS2 (*Drosophila melanogaster*), P63028 (*Mus musculus*), P13693 (human), P31265 (*Arabidopsis thaliana*), KX951492 (Rose), Q9XHL7 (Tobacco, *Nicotiana tabacum*), P35681 (Rice, *Oryza sativa*), Q9M5G3 (Barley, *Hordeum vulgare*), Q8H6A5 (Maize, *Zea mays*), Q2PS27 (*Cucurbita maxima*), P28014 (Alfalfa, *Medicago sativa*), Q9ZSW9 (*Hevea brasiliensis*), A9RT49 (*Physcomitrella patens*)

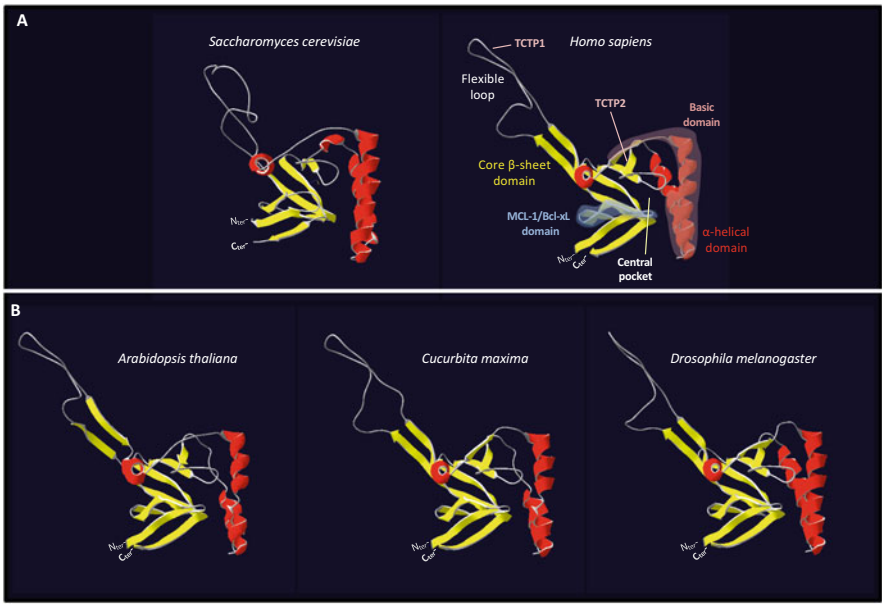

Fig. 7.2 Tridimensional structure of TCTP. (**a**) Computer graphic representation of three-dimensional structure of yeast and human TCTPs using PDB 1H6Q and 2hR9, respectively (Thaw et al. 2001; Susini et al. 2008). Ribbon representation of the alpha-carbon backbone of one TCTP molecule is shown. The N and C termini as well as the position of the various TCTP functional domains are shown on human TCTP structure. (**b**) Structure-based modeling of *Arabidopsis*, *Cucurbita*, and *Drosophila* TCTPs. 3D-structure models were developed using SWISS-MODEL (Biasini et al. 2014) server. Swiss-PDBViewer (Guex and Peitsch 1997) was used to visualized 3D structures. Note that the TCTP core domain is strongly conserved between species. The major alterations between the different TCTP structures lie in the flexible loops and in the length of the second alpha helix

domain of tobacco TCTP was demonstrated to be implicated in cell death suppression (Gupta et al. 2013). Moreover, plant and non-plant TCTPs contain conserved posttranslational modification sites such as the Casein Kinase II (CKII) phosphorylation site and the N-myristoylation site (Brioudes et al. 2010; Thayanithy 2005; Bruckner et al. 2016) (Fig. 7.1). These similarities suggest that plant and non-plant TCTPs likely harbor similar activities and may act in similar regulatory pathways. Despite the high degree of sequence homology between all eukaryotic TCTPs, there are slight differences suggesting some divergent functions of TCTP in plants and animals. For example, the Polo Like Kinase (PLK) phosphorylation site, previously shown to be functional in mouse (Yarm 2002), is conserved only in mammalian TCTPs and is absent in plant TCTPs (Fig. 7.1). The biological significance of these differences remains unclear, but its discovery may help unravel plant specific function(s) (Thayanithy 2005).

In agreement with the conserved TCTP primary and secondary structures, the predicted tri-dimensional structure of plant TCTP is very similar to yeast and

human structures (Hinojosa-Moya et al. 2008; Feng et al. 2007; Thaw et al. 2001) (Fig. 7.2). Three distinct structural domains are found in TCTP: a core β-sheet domain, an α-helical domain, and a flexible loop structure. Major differences between plant and animal TCTPs are observed in the flexible loop, while the alpha-hairpin, which includes the basic domain known to be the interface for many interactions in animals, is well conserved (Bommer 2012; Gutierrez-Galeano et al. 2014; Berkowitz et al. 2008; Hinojosa-Moya et al. 2008). In plants, the predictive structures of TCTP support the phylogenetic evidence that they fall into two sub-clades, AtTCTP1-like and CmTCTP-like (*Cucurbita max*.), that differ in the structure of the central "pocket" region and in the flexible loop, suggesting different functions. It should be noted that in plant species harboring a single *TCTP* gene, the sequence is usually *AtTCTP1*-like (Gutierrez-Galeano et al. 2014).

Considering the high degree of amino-acids conservation and the high similarity of predictive tri-dimensional structure among phyla, it is tempting to suggest that plant and animal TCTPs share many of their roles. In agreement with this hypothesis, Brioudes et al. (2010) demonstrated in vivo that *Drosophila dTCTP* could complement cell proliferation defects associated with *AtTCTP* loss-of-function in *Arabidopsis* and vice versa.

In animals, TCTP was reported to interact with several proteins such as the tumor suppressor p53, BAX (Bcl2 Associated X protein), or MDM2 (Mouse Double Minute 2) (Amson et al. 2012). Interestingly, to date no orthologous proteins for these TCTP interactors could be found in plant genomes. It will be very interesting to know if nevertheless these interactions described in animals exist or not in plants. However, it has been reported that plant TCTP is able to interact with mammalian Bax protein (Hoepflinger et al. 2013). One could imagine that despite the obvious absence of primary amino acid similarities of TCTP interacting proteins, other functionally conserved proteins can fulfill their role and secure TCTP signaling in plants. Such information might give precious indications about evolution of TCTP function and interactors across kingdoms.

7.3 TCTP Is Essential for Plant Development

TCTP was demonstrated to have a major role in development and in organ size control in plants as in animals. Final organ shape and size are the result of coordinated cell proliferation, cell expansion, and cell death processes. These three processes have to be tightly controlled and coordinated in order to obtain organs and organisms of species-specific size and shape (Day and Lawrence 2000). As in animals, many reports proposed plant *TCTP* as good candidate to control cell proliferation and cell death. Compared to animals, the role of plant *TCTP* in development is much less understood. All reports in the literature show that plant *TCTP* is essential for the correct development and for the determination of final plant size. Like in animals, knockout of plant *TCTP* leads to embryo lethality (Brioudes et al. 2010). The fact that *TCTP* knockouts are lethal hampered the

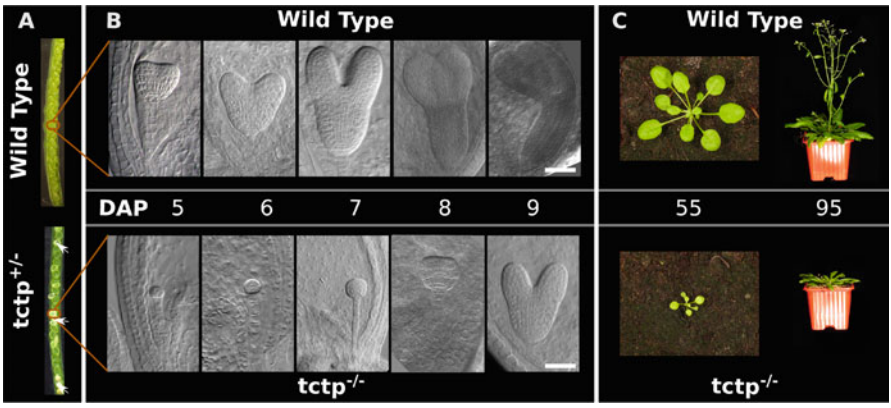

Fig. 7.3 Developmental phenotype associated with TCTP loss of function in *Arabidopsis thaliana*. (**a**) Fruit of *Arabidopsis* plants wild-type or heterozygous for *tctp* mutation (*tctp*+/−). In *tctp*+/− fruit, 25% of the seeds are homozygous for the *tctp* mutation (*tctp*−/−) leading to a white seed phenotype (*white arrows*). (**b**) Wild-type and *tctp*−/− embryos. *tctp*−/− embryos exhibit retarded growth compared to the wild-type. Six days after pollination **(DAP),** wild-type embryos are at heart stage while *tctp*−/− are still at the globular stage. Such delay in development is maintained in the subsequent developmental stages. Scale bar 100 μm. (**c**) Supplementing *tctp*−/− embryos with nutrient in vivo [embryo rescue, for detailed protocol see Brioudes et al. (2010)] allows them to continue their development and became adult plants full knockout for *TCTP* (*tctp*−/−). Note that *tctp*−/− plants are delayed in development compared to the wild-type

studies to address in detail *TCTP* function. To overcome this difficulty, *TCTP* knockdown, by mean of RNA interference approach, was used to explore TCTP roles during development. Although such approach led to significant reduction of *TCTP* expression, full obliteration of *TCTP* expression couldn't be achieved, thus making it difficult to address in detail TCTP function (Brioudes et al. 2010; Cao et al. 2010; Tao et al. 2015; Zhang et al. 2013; Berkowitz et al. 2008; Hsu et al. 2007; Hu et al. 2015).

Brioudes et al. (2010) used an embryo-rescue approach in *Arabidopsis thaliana* to generate the first *tctp*−/− full knockout adult organism in eukaryote (Fig. 7.3c). The authors supplemented *Arabidopsis tctp*−/− knockout embryos with nutrients *in vitro* that allowed their development to adult plants. However, the generated *tctp*−/− knockout plants were delayed in their development and showed severe growth defects, including small organs and plant size, late flowering, and sterility (Fig. 7.3). Nevertheless, the obtained *tctp*−/− knockout plants were very useful and helped dissect the multiple roles of *TCTP* in plant development (Brioudes et al. 2010).

Like in animals, TCTP knockout plants die early during embryo development (Brioudes et al. 2010) and the TCTP down-regulation delayed development and resulted in reduced organ size (Brioudes et al. 2010; Berkowitz et al. 2008). Even though it is generally accepted that *TCTP* is essential for organ and plant development, there are some discrepancies in observations and hypothesis, and a number of conclusions are still under debate. Brioudes et al. (2010) and Berkowitz et al. (2008)

showed a clear negative effect of *TCTP* downregulation on plant development and growth in *A. thaliana*. However, these studies do not agree on the causes of these phenotypes. Berkowitz et al. (2008) proposed that *tctp* lethality was associated with male gametophytic defects leading to failed fertilization and suggested a role of *TCTP* as a general stimulator of cell expansion. Conversely, Brioudes et al. (2010) demonstrated that fertilization took place in *tctp*−/− knockouts, and the lethality was a result of retarded growth of the developing embryos (Fig. 7.3). The fact that Brioudes et al. (2010) were able to rescue the *tctp*−/− knockout embryos to generate the first full knockout adult organism for *tctp* supports the conclusion that the *tctp* lethality is not associated with male gametophytic defect. In agreement with Brioudes et al. (2010), very recently Hafidh et al. (2016) showed that pollen competitiveness between *tctp* and wild type pollen is not different and confirmed that the fertilization between *tctp* pollen and a *tctp* ovule could occur. They also confirmed that the lethality is due to a delay in embryo growth in the early stages of development and thus in agreement with Brioudes et al. (2010) (Fig. 7.3b). Moreover, the authors demonstrated that like animal TCTPs, plant TCTP, even though lacking signal secretion peptide, can be secreted to plant apoplastic spaces *via* exosomes (Hafidh et al. 2016; Amzallag et al. 2004). This feature of TCTP might contribute to the signaling between pollen tube and pistil during fertilization and thus affect pollen tube guidance, ovule targeting, and seed development (Hafidh et al. 2016). Therefore, the data by Brioudes et al. (2010), recently confirmed by Hafidh et al. (2016), support the conclusion that the lethality of *tctp* loss-of-function mutants is a result of a retarded embryo growth that leads to embryo abortion in the developing siliques.

In *Arabidopsis*, the characterization of *tctp*−/− knockout (obtained via embryo rescue), *RNAi-TCTP*, and *TCTP* overexpressing lines through detailed kinematic analysis of leaf growth allowed to demonstrate that AtTCTP controls cell proliferation but not cell expansion (Brioudes et al. 2010). Similar data were recently reported for tobacco, cabbage, and tomato (Cao et al. 2010; Tao et al. 2015; Gupta et al. 2013; Bruckner et al. 2017). In these plants, *TCTP* downregulation leads to delayed plant development and smaller organs compared to wild type. Moreover, flowers were smaller and root growth was reduced (Tao et al. 2015; Bruckner et al. 2017). The authors suggest that at least part of these phenotypes can be explained by a reduction of cell proliferation activity in TCTP-RNAi lines as *TCTP* plays a positive role in plant growth regulation. In agreement with the role of *TCTP* in the control of cell proliferation, *Arabidopsis* AtTCTP protein was shown to accumulate in highly dividing cells (Brioudes et al. 2010). In *Pisum sativum*, mRNA was localized predominantly in dividing cells of root caps and in other rapidly growing tissues as young leaves and stems (Woo and Hawes 1997; Kang et al. 2003). Accordingly, TCTP protein accumulation was correlated with the accumulation of other cell proliferation proteins in the skin of young potato tubers, an actively dividing tissue (Barel and Ginzberg 2008).

To the best of our knowledge, only two studies showed the direct implication of *TCTP* in the control of cell proliferation. In a first study, Brioudes et al. (2010) used synchronized tobacco (*Nicotiana tabacum*) BY-2 cells knockdown for *NtTCTP* to

demonstrate that *TCTP* regulates cell cycle progression (Brioudes et al. 2010). In this study, they showed a 4 h delay of cell cycle progression, and such delay affected more specifically G1/S transition (Brioudes et al. 2010). Recently, report by Tao et al. (2015) confirmed these results. Moreover, measurements of leaf size and cell number in *Arabidopsis* and tobacco plants knockdown for *TCTP* showed that delayed leaf growth and smaller leaf size were due to a decrease in the cell number but not in cell size. However, the precise molecular pathway by which TCTP controls cell proliferation in plants is still unknown. Tao et al. (2015) suggested that TCTP could prevent the polyubiquitination of NTHK1 (a Type 2 ethylene receptor) to control cell cycle.

The role of TCTP in controlling cell proliferation and mitotic growth is conserved between plants and animals. Brioudes et al. (2010) demonstrated that *Drosophila dTCTP* could fully complement cell proliferation defects associated with *TCTP* loss-of-function phenotypes in *Arabidopsis* and *vice versa*. However, this study also showed that loss-of-function of *Drosophila dTCTP* also leads to defects in cell expansion, although such defect is not observed in *tctp*−/− knockout plants. In agreement with these data, *AtTCTP* could not complement the cell expansion defect in *Drosophila* mutants. These interspecies complementation experiments highlighted the conserved role of TCTP in controlling cell proliferation and demonstrated that conversely to plant *TCTP*, *Drosophila TCTP* also controls cell expansion.

In animals, TCTP was shown to have an anti-apoptotic role (Susini et al. 2008). This role was also investigated in plants. As for animals, cell death process occurs in plants with genetically and environmentally defined temporal and spatial patterns and is absolutely required for normal plant development (Greenberg 1996). Lliso et al. (2007) showed that TCTP protein accumulation decreased during postharvest aging process in citrus fruits and suggested an anti-apoptotic activity for TCTP in relation with microtubule stabilization. In agreement with these data, Hoepflinger et al. (2013) reported that constitutive expression of *AtTCTP* prevents the apoptotic effect of programmed cell death (PCD)-inducing agent tunicamycin on tobacco leaf disc. The authors then proposed that, as in animals, plant TCTP could act as a cytosolic Ca^{2+} sequester to protect cells against Ca^{2+}-dependent PCD (Graidist et al. 2007).

Cell death process is also induced during an incompatible interaction between plants and pathogens in order to limit pathogen spread and disease development. This process, also termed hypersensitive response (HR), is used as a model to study cell death in plants (Morel and Dangl 1997). In tobacco, it was demonstrated that the downregulation of *NtTCTP* promotes HR and the constitutive transient expression of *NtTCTP* decreases the HR rate, thus another argument to support the anti-apoptotic activity of TCTP in plants (Gupta et al. 2013). In this study, the authors also demonstrated that TCTP inhibits the Reactive Oxygen Species (ROS) production and the MAPK (Mitogen Activating Protein Kinase) cascade observed in HR. Taking together, these published work show that like in animals, plant TCTPs very likely have an anti-apoptotic role. However, the mechanism by which

TCTP prevents PCD is still unknown as counterparts of TCTP interacting mammalian proteins are missing in plants.

7.4 Role of TCTP in Plant Signaling

As discussed above, *TCTP* is absolutely required for plant development and organ size determination. In *Arabidopsis* and tobacco, the downregulation of *TCTP* leads to severe developmental defects that are at least in part due to perturbation of cell proliferation, but many other processes are affected. A number of published work associates TCTP to other cellular functions and signaling molecules/pathways. In the next paragraph, we will provide the up-to-date information on the putative links between TCTP and these cellular functions and signaling molecules/pathways.

7.4.1 Is TCTP a Component of the TOR Pathway?

Hsu et al. (2007) reported that *Drosophila dTCTP* controls organ growth by positively regulating the TARGET OF RAPAMYCIN (TOR) pathway. TOR kinase is part of a signaling complex that controls cell proliferation and growth in animals and in plants, in response to environmental conditions, growth factors (*e.g.*, insulin), nutrients, energy, or stress (Robaglia et al. 2004; Deprost et al. 2007; Wullschleger et al. 2006; Oldham et al. 2000; Zhang et al. 2000). In mammals, the TOR pathway (mTOR) controls cell growth by acting as a central regulator of protein synthesis and ribosome biogenesis at the transcriptional and translational levels. This is performed by integrating signals from mitogens and nutrients to downsream signaling pathways (Wullschleger et al. 2006). mTOR activity is positively controlled by the small Ras GTPase, Rheb, that binds directly to mTOR kinase domain in order to activate the mTOR complex in a GTP-dependent manner (Wullschleger et al. 2006). The Tuberous Sclerosis Complex (TSC) negatively regulates TOR pathway by inactivating Rheb through a GTPase-activating protein (GAP) activity.

Based on epistatic analysis, Hsu et al. (2007) showed that in *Drosophila melanogaster*, *dTCTP* acts in parallel to *TSC*, but upstream of *dRheb*. Using GST pull-down and in vivo GDP release assays, they demonstrated that dTCTP binds to nucleotide-free dRheb and specifically displays Guanine nucleotide exchange factor (GEF) activity on it. In this model, dTCTP directly associates with dRheb and is required for its activation in vivo, which in turn positively controls TOR activity; thus, TCTP may have an opposite function to TSC. Mouse TCTP was also reported to function as GEF upstream of S6K (Chen et al. 2007) and human TCTP was demonstrated to activate the mTOR pathway in vivo (Dong et al. 2009). In plants, TOR is highly conserved and its expression positively correlates with growth (Deprost et al. 2007; Wullschleger et al. 2006). Homologous members and substrates of the mammalian mTORC1 complex have been identified in plants, such as

TOR, LST8, S6 kinase, and RAPTOR (Menand et al. 2004; Mahfouz 2006), but the presence of TORC2 components has yet to be proven. In plants, the TOR pathway is conserved and has been shown to be important for plant growth, development, flowering, senescence, and life span by modulating transcription, translation, autophagy, and primary and secondary metabolism (Deprost et al. 2007; Ahn et al. 2011; Ren et al. 2011, 2012; Moreau et al. 2012; Xiong and Sheen 2012; Xiong et al. 2013; Caldana et al. 2013).

There are only indirect indications about the putative link between TCTP and TOR pathway in plants. BiFC (Bi-Fluorscent Complementation) and GST pull-down experiments showed that *Arabidopsis* TCTP is able to bind plant Rab GTPases and also *Drosophila* Rheb, and similarly, *Drosophila* TCTP can bind *Arabidopsis* Rab (Brioudes et al. 2010). However, no data were reported regarding a putative GEF activity of plant TCTP. Similarly, no genetic studies are available to confirm that TCTP acts as a regulator of the TOR pathway. However, knockout or knockdown of *TCTP* or *TOR* in plants exhibit similar phenotypes. For both genes, knockouts are lethal and knockdown display prolonged reduction in cell proliferation and reduced growth (Brioudes et al. 2010; Deprost et al. 2007). Another indication of the putative link between TCTP and TOR in plants is the fact that transcript level of EBP1, a TOR downstream component, is significantly decreased in *TOR* and in *TCTP* knockdown plants, suggesting a common pathway (Berkowitz et al. 2008; Deprost et al. 2007).

It should be noted that in animals, the putative GEF activity of TCTP also remains a matter of debate, and the molecular function of TCTP as an upstream activator of Rheb has been questioned. Rehmann et al. (2008) addressed the putative interaction between TCTP and Rheb and compared the Rheb activation and S6K or S6 phosphorylation status in presence of TCTP and in mammalian cells knockdown for TCTP. Conversely to Hsu et al. (2007), they didn't observe any difference on Rheb and its downstream targets (Rehmann et al. 2008). Similarly, overexpression of *hTCTP* had no significant effect on the phosphorylation state of S6, a substrate of S6K, in stressed human cell lines (Wang et al. 2008). Furthermore, NMR spectroscopy failed to confirm any interaction between TCTP and Rheb (Rehmann et al. 2008). These data do not support the idea that TCTP is an upstream activator of mammalian TOR signaling. It is probable that TCTP acts on Rheb but not as a GEF. Cans et al. (2003) reported that human TCTP was able to interact with a GTP-binding protein (eEF1A) and its GEF (eEF1B) and to act as a guanine nucleotide dissociation inhibitor (GDI). The atomic structure of *Schizosaccharomyces pombe* and human TCTP proteins revealed that TCTP is structurally related to the Mss4/Dss4 protein family (Thaw et al. 2001; Susini et al. 2008). In human, Mss4 has been shown to bind to several exocytic but not endocytic Rab GTPases in vivo and in vivo, and analysis of its catalytic activity towards them confirmed its function as a relatively inefficient GEF, thus supporting the idea that it would most likely function as a guanine nucleotide-free chaperone (GFC) (Nuoffer et al. 1997; Wixler et al. 2011). Moreover, Gnanasekar et al. (2009) identified heat shock protein function and chaperone-like activities of human TCTP and a TCTP homolog from *Schistosoma mansoni*. Given that TCTP is structurally

similar to the Mss4/Dss4 family (Thaw et al. 2001) and that it can interact with many cellular proteins involved in cell growth or survival control, it was tempting to propose animal TCTP as a protein chaperone. Although it is still not clear whether TCTP is a GEF, a GDI, or a GFC, the studies above revealed TCTP as a regulator of GTPases activities and associated it with the control of translation. Whether TCTP acts as a GEF or not on Rheb proteins remains to be clarified. There are reported studies that defend both hypotheses. Clearly, more studies are required in order to decipher the relationship between TCTP and TOR pathway in animals as in plants.

7.4.2 Role of TCTP in Hormone Signaling

Very little information exists on the putative roles of *TCTP* in hormonal signaling in plants (Fig. 7.4). Only few studies investigated changes in *TCTP* expression in response to treatment with phytohormones, such as auxin, abscisic acid (ABA), ethylene, or methyl jasmonate (MeJA) (Cao et al. 2010; Li et al. 2013; Kim et al. 2012). Most of the published work simply provided hypothesis based on observations, and sometimes results are contradictory.

In plants, auxin is an essential hormone involved in a wide variety of functions such as cell division, organogenesis, senescence, apical dominance, gravitropism, root growth, etc. (Vanneste and Friml 2009). Berkowitz et al. (2008) showed that *Arabidopsis* TCTP-RNAi plants were less sensitive to increasing concentrations of exogenous auxin compared to the wild-type and proposed an implication of TCTP in the auxin signaling pathway. These data are surprising since auxin signaling mutants often show severe and aberrant phenotypes that are different from that observed in TCTP-RNAi (Estelle and Somerville 1987; Křeček et al. 2009). In cabbage, TCTP-RNAi plants grow slower and accumulate low auxin contents compared to the wild-type (Cao et al. 2010). The authors suggested that such decrease of endogenous auxin content could be responsible of the observed delayed growth. However, this remains highly hypothetical as no direct proof has been provided by the authors to support such hypothesis. Clearly, more studies are required to confirm the putative role of TCTP in auxin signaling pathway.

Several studies reported interaction of TCTP with the abscisic acid (ABA) signaling pathway. ABA is a plant hormone known to be implicated in seed germination and response to drought. It has been suggested in *Arabidopsis* that AtTCTP interacts with ABA signaling pathway to control stomatal closure mechanism in response to drought (Kim et al. 2012). Stomata are differentiated leaf cells that tightly control gas and water exchanges between plant leaves and environment. During the night or in drought condition, plants synthesize ABA to control stomatal closure, avoiding water evaporation (Venkatachalam et al. 2007). Kim et al. (2012) reported that overexpression of *Arabidopsis AtTCTP* confers drought tolerance by rapid ABA-mediated stomatal closure. The authors also proposed that this rapid ABA-mediated stomatal closure is mediated by the interaction of *AtTCTP* with

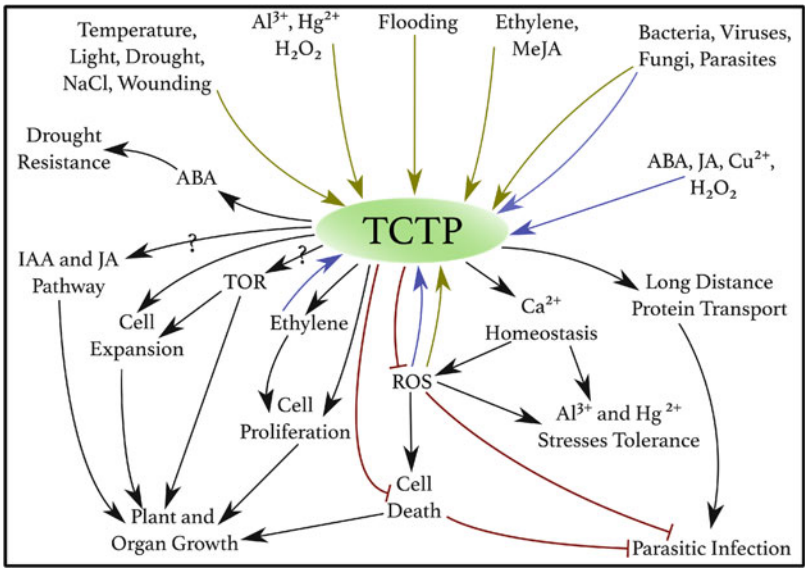

Fig. 7.4 Schematic representation of the multiple stimuli affecting *TCTP* expression (*green arrows*) or TCTP protein accumulation (*blue arrows*) and of the various putative biological processes associated with TCTP function (*red* and *black arrows*) in plants

microtubules during water stress leading to microtubules depolymerization, stomata closure, and drought resistance. Moreover, this interaction between TCTP and tubulin is increased by calcium, a microtubule depolymerization factor. As the expression domain of *TCTP* is increased following ABA-treatments and because putative ABA-responsive elements were identified in the *AtTCTP* promoter, it is possible that there is a feedback loop between ABA and *TCTP* expression that regulates stomatal closure in leaves. Unfortunately, the data by Kim et al. (2012) are based on *TCTP* overexpression experiments and on in vivo data only, and direct link between ABA and TCTP for stomatal closure is not shown. To date, no other study links stomatal behavior in response to ABA and *TCTP*.

In cabbage, knockdown of *TCTP* is associated with higher levels of ABA (Cao et al. 2010) and thus an inverse response to that reported by Kim et al. (2012). In rice, OsTCTP protein accumulation is induced in response to ABA, while in cabbage no difference in *TCTP* expression was observed under ABA stress (Cao et al. 2010; Wang et al. 2015). In Orchardgrass (*Dactylis glomerata*), *TCTP* has been demonstrated to be one of the most stable genes in response to ABA (Huang et al. 2014). All these data suggest that there is a link between the ABA pathway and TCTP, but the inconsistency of the results is evident and therefore more studies are required to consolidate these observations.

Ethylene is an important phytohormone for plant growth and development, and it is associated with fruit ripening. Tao et al. (2015) reported that tobacco NtTCTP protein accumulation increases in response to ethylene treatments. NtTCTP then

interacts with the ethylene receptor NTHK1, and such interaction is enhanced by ethylene and protects NTHK1 from degradation by the 26S proteasome and promotes seedling growth. Some studies also report a change in *TCTP* expression upon Jasmonic acid (JA) treatment. JA is a lipid-derived plant hormone that regulates a wide range of processes, such as biotic and abiotic plant stress responses (insects, pathogens, wounding…) and developmental processes (root growth, senescence…) (Abe et al. 2008; Devoto and Turner 2003; Browse 2005). In *Hevea brasiliensis, HbTCTP* expression is strongly reduced in response to MeJA treatment (Li et al. 2013). In cotton, overexpression of *TCTP* leads to important decrease of expression of genes in the JA pathway (Zhang et al. 2014). Conversely, Wang et al. (2015) reported that OsTCTP protein accumulation is not affected by MeJA in *Oryza sativa*. These results are contradictory, and further experiments are required to address more precisely the putative role of *TCTP* in JA signaling.

To summarize, we have little knowledge about the link between *TCTP* and phytohormone signaling, and clearly, more studies are needed to determine the role of *TCTP* in phytohormone signaling during plant growth and development.

7.4.3 Response to Abiotic and Biotic Stresses

Conversely to animals, plants have sessile lifestyle and they have to cope with and adapt to their environment. In order to grow, plants need light, water, and nutrients. The availability of those elements directly impact their development, morphology, and size. While some reports show that the expression of *Arabidopsis AtTCTP* and tomato *SlTCTP* mRNAs is highly stable in different growth conditions (Brioudes et al. 2010; Coker and Davies 2003), several other studies reported variations of *TCTP* mRNA expression and/or protein accumulation in response to environmental stresses (Fig. 7.4). In plants, *TCTP* expression was reported to vary in response to salt stress, high temperature, drought, and pathogen attacks (Fig. 7.4). In this section, we will provide and discuss the up-to-date knowledge on the putative roles of TCTP in response to environmental signals and stresses.

Different studies suggest that TCTP may have a role in tolerance to drought and heat stresses. In *Jatropha curcas* and in cabbage, the expression of *TCTP* was shown to be induced following heat shock (Cao et al. 2010; Qin et al. 2011). In *Hevea brasiliensis*, *HbTCTP1* transcripts were rapidly increased after drought treatment and then returned to normal level (Li et al. 2013). However, an inverse behavior was observed in grapevine, where *TCTP* expression was repressed under water deficit stress (Vincent et al. 2007). Kim et al. (2012) showed that in *Arabidopsis,* plants overexpressing *AtTCTP* were more tolerant to drought due to reduced water loss. As described above, AtTCTP interacts with microtubules in guard cells, which leads to microtubule depolymerization and rapid ABA-mediated stomatal closure and reduced water loss (Kim et al. 2012). The stomatal closure induced by ABA is one of the major adaptive responses to drought

stress (Zhang et al. 2006). The binding of plant TCTP to tubulins seems calcium dependent. Calcium is a known factor in microtubule depolymerization (Kim et al. 2012; O'Brien et al. 1997; Yu et al. 2001). It was reported that animal TCTP also associates transiently with microtubules during cell cycle and binds calcium (Gachet et al. 1999; Kim et al. 2000). Visibly, plant and animal TCTPs bind to and associate with microtubules and calcium to perform different roles, although more data are required to address how conserved these roles are between plants and animals and what are the underlying molecular mechanisms.

Altogether, it seems that heat shock and drought rapidly induce *TCTP* expression, and high level of TCTP might be required to resist such stress. However, the reported data remain as observation, and no data on the molecular and genetic mechanisms that might be involved are available.

In many plant species, *TCTP* mRNA accumulation was also found to be stimulated by a number of other abiotic stress signals such as aluminum, mercury, Cu^{2+}, H_2O_2, high salt, ethrel, wounding, and MeJA (Sage-Ono et al. 1998; Li et al. 2013; Santa Brígida et al. 2014; Wang et al. 2012, 2015; Ermolayev 2003) (Fig. 7.4). *TCTP* expression was shown to be induced by aluminum treatment in an aluminum-tolerant soybean cultivar, but not in an aluminum-sensitive cultivar, suggesting a putative role of TCTP in aluminum homeostasis maintanance (Ermolayev 2003). More recently, it was reported that rice *OsTCTP* expression was induced in response to H_2O_2 and to high levels of mercury in soil and that *OsTCTP* expression enhances tolerance to mercury in rice *via* a decrease of the Hg-induced reactive oxygen species (ROS) (Wang et al. 2012, 2015). In rubber tree (*Hevea brasiliensis),* transient changes in *HbTCTP1* transcript levels were also observed after diverse abiotic treatments as high salt, ethrel, and H_2O_2 (Li et al. 2013). Moreover, *TCTP* expression is reduced in this species during wounding and Tapping Panel Dryness (TPD) syndrome, which is the result of repeated wounding (Li et al. 2013; Venkatachalam et al. 2007). This *TCTP* down-regulation is preceded by ROS outburst that induces hypersensitive response (HR) indicating that programmed cell death due to repeated wounding might be the cause of TPD (Li et al. 2013).

Although these data remain as observations with no clear data to support the role of *TCTP* in response to stresses, many of these abiotic stresses are known to lead to the production of ROS. In animals as in plants, ROS are natural by-products of the normal metabolism and have important roles in cell signaling and homeostasis (Kardeh et al. 2014; Russell and Cotter 2015; Li and Yu 2015; del Rio 2015; Choudhury et al. 2013). ROS levels are known to increase dramatically in response to various environmental stresses, which can result in significant damage to cells and tissues (Møller et al. 2007; Xia et al. 2015). In animals, ROS also play a role in tissue protection and defense against cancer by controlling cell proliferation through apoptosis induction (Kardeh et al. 2014).

In plants, the majority of published data suggest that ROS either induce *TCTP* expression and promote stress tolerance and adaptation or inhibit *TCTP* expression in parallel with PCD induction. Some authors also suggested that TCTP could control the adaptive response to abiotic stresses *via* its Ca^{2+} bindings ability (Li et al. 2013; Gupta et al. 2013; Hoepflinger et al. 2013). However, part of the

data remains contradictory. To reconciliate these contradictory published data, we can imagine that despite the amino acid sequence conservation, TCTP proteins from different species may have different roles in response to abiotic stresses. Further investigations are required to address the discrepancies in the literature and more importantly to shed light to the molecular mechanisms underlying the role of TCTP in abiotic stress response.

As mentioned above, TCTP is an anti-apoptotic protein associated with plant hypersensitive response (HR) during incompatible interaction with many pathogens. HR is one of the best-characterized defense responses in plants that occurs during incompatible host–pathogen interaction. It is characterized by rapid, localized PCD to restrict the spread of pathogens and protect the plant. Because HR is one of the major defense mechanisms against pathogen attacks (Morel and Dangl 1997), TCTP is assumed to play a role in plants defense. Wide-genome as well as proteomics analysis show that both *TCTP* transcript and protein were differentially expressed and accumulated in response to attacks by viruses, bacteria, and fungi.

Analysis of proteomic changes in *Arabidopsis* infected by *Pseudomonas syringae* demonstrated that infection with an avirulent strain or induction of HR by bacteria correlates with *TCTP* downregulation, and conversely, in the case of established bacterial infection, *TCTP* expression is upregulated (Jones et al. 2006; Fabro et al. 2008). Successful infection by *Agrobacterium tumefaciens* that requires suppression of plant defense mechanism, also correlates with increased *TCTP* expression (Veena et al. 2003). In agreement with these reports, *NbTCTP* silencing in tobacco accelerates HR following infection by various bacteria, while *TCTP* overexpression diminished HR response to bacterial infection (Gupta et al. 2013). *NtTCTP* seems to negatively regulate HR cell death by acting on the MAPK-regulated cell death pathway. Moreover, expression of the BAX protein in *NtTCTP* downregulated plants accelerated the HR phenotype. BAX is a mammalian pro-apoptotic protein, which in mammals antagonizes TCTP effect. In this study, the authors clearly demonstrate the anti-apoptotic effect of plant TCTP (Gupta et al. 2013).

TCTP has been proposed to play a major role during plant infection by potyvirus. In a first study, *TCTP* was identified among the most strongly induced genes after potyvirus infection in tomato (Alfenas-Zerbini et al. 2009). In a more recent study, it was demonstrated that TCTP is an important host factor for an efficient infection by potyviruses in tomato and *Nicotiana benthamiana* plants. Plants silenced for *TCTP* exhibited reduced accumulation of PepYMV early during infection (Bruckner et al. 2017). Furthermore, TCTP was observed in both nuclei and cytoplasm of non-infected cells, while only in the cytoplasm of infected cells, which suggest that the virus may alter TCTP localization to promote viral infection. However, the mechanism by which TCTP promote successful infection by viruses is not yet clear. In animals, the highly structured *TCTP* mRNA was shown to activate the dsRNA-dependent protein kinase PKR (Bommer et al. 2002), thus suggesting antiviral responses. In plants, dsRNA binding is used by plant viruses to suppress RNA silencing (Merai et al. 2006). It is possible that viruses induce *TCTP* expression to deactivate dsRNA-induced plant defense response in order to allow efficient plant infection. Alternatively, TCTP could be associated with viral

movement and selective loading of various viral components at specific cell boundaries during virus infection (Zhu 2002; Voinnet et al. 1998; Itaya et al. 2002). In pumpkin, *CmTCTP* was shown to associate with phloem RNA binding proteins CmPP16-1 and CmPP16-2 (Aoki et al. 2005), and this complex was demonstrated to move selectively in pumpkin phloem. In *Ricinus communis,* TCTP protein was also found in the vascular system phloem sap that carries organic nutrients or photosynthate (Barnes et al. 2004). The authors suggest that TCTP might be involved in the selective transport and/or unload of macromolecules such as viral components by the phloem, for long-distance movement in the sieve tube.

The role of *TCTP* seems to be not solely restricted to response to bacteria and viruses. In *Arabidopsis*, infection with obligate biotroph fungi induces *TCTP* expression, and conversely *TCTP* expression is negatively regulated by the SA and JA-mediated host defense pathway (Fabro et al. 2008). Obligate biotroph fungi must establish compatible interactions with their hosts to survive, and TCTP could be necessary for a successful fungal infection (Fabro et al. 2008). However, it is still unclear how these parasites are able to avoid plant defense activation (Panstruga 2003).

Similar to animal parasitic nematodes, TCTP from two plant parasitic nematodes (*Meloidogyne incognita* and *M. enterolobii*) was found among the proteins secreted during host plant invasion and in agreement with such observation, nematode infection was promoted by overexpressing *Meloidogyne MeTCTP in planta* (Bellafiore et al. 2008; Zhuo et al. 2017). In *M. incognita*, TCTP is localized in the sub-ventral gland while in *M. enterolobii* it was found in the dorsal gland, indicating that the site of TCTP secretion might be species dependent. Similar to observations during bacterial infection, nematode TCTP could suppress BAX-induced programmed cell death. However, the authors did not show direct evidence of MeTCTP secretion into host organism and did not quantify the changes in host *TCTP* expression/accumulation upon nematode infection (Zhuo et al. 2017). All together these published data indicate that nematode TCTP might be a plant-parasitic effector excreted into the host plants to promote parasitism. However, how nematode TCTP accomplishes this role remains unclear. Analysis of other proteins secreted by *M. incognita* indicates that nematode infection can interfere with plant ROS signaling to suppress cell death. Analysis of *M. incognita* secretome demonstrated the presence of detoxification enzymes that may be able to degrade ROSs (Bellafiore et al. 2008). In cotton plant, Zhang et al. (2014) show that TCTP was downregulated upon aphid attack and that cotton *TCTP* overexpression in *Arabidopsis* leads to a reduction of the symptoms induced by the parasite.

The published data suggest that TCTP likely plays a role in response to various pathogens. It is possible that TCTP is acting to circumvent the plant defense in order to establish compatible pathogen infection probably through diverse processes, such as preventing cell death and/or allowing the selective transport of macromolecules.

7.5 Conclusion

In plants as in animals, TCTP is involved and likely plays major roles in many cellular processes (Fig. 7.4), such as cell proliferation and cell death control or response to abiotic and biotic stresses. The precise molecular mechanisms associated with many of these processes in plants are still unknown. In animals, TCTP is involved in diverse cancers and is thought to be one of the best therapeutic targets to fight against the disease (Acunzo et al. 2014). In plants, tumorogenesis occurs but rarely induces physiological disorder (Doonan and Sablowski 2010). It is clear in many published work that *TCTP* has conserved functions in plants and in animals. However, to the best of our knowledge, only one report addressed the TCTP functional conservation between plants and animals at the molecular level (Brioudes et al. 2010). Future directions must take into account animal and plant model organisms to investigate at the molecular, genetic and biochemical levels the mechanisms by which TCTP act in these various processes. Such work may help in understanding some development disorders associated with TCTP misexpression in mammals and in plants.

Acknowledgements This work was funded by the "Biologie et Amélioration des Plantes" Department of the French "Institut National de la Recherche Agronomique", by The "Ecole Normale Supérieure de Lyon", by the Claude Bernard University at Lyon (UCBL), and by the CIFRE program of the ANRT.

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