Sequence Analysis and Comparison of TCTP Proteins from Human Protozoan Parasites

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Abstract

Purpose Translational controlled tumor protein (TCTP) is a functionally important protein in most eukaryotes because it participates in a wide variety of processes, the most representative being proliferation, differentiation, histamine release, cell death, protein synthesis and response to stress conditions. In the present work, we analyze the sequence, structure and phylogeny of TCTP orthologs in a group of human parasitic protozoan species.

Methods The complete sequences of TCTP orthologs in protozoan parasites were identified with the NCBI BLAST tool in the database of the EuPathDB Bioinformatics Resource Center. The sequences were aligned and important regions of the protein were identified, and later phylogenetic trees and 3D models were built with different bioinformatic tools.

Results Our results show evolutionarily and structurally conserved sites that could be exploited to create new therapeutic strategies given the increase in the number of strains resistant to current drugs.

Conclusion TCTP orthologs in protozoan parasites have been little studied but have been shown to be important in parasite growth, proliferation, reproduction, and response to changes in the environment. For all this, TCTP can be considered as a possible therapeutic target.

Keywords Histamine releasing factor · Phylogenetic analysis · Flexible loop · Dominant negative mutant

Introduction

Translational controlled tumor protein (TCTP), also called fortilin, P23 or histamine releasing factor (HRF), is a small multifunctional protein that is ubiquitous in eukaryotes [1]. This protein participates in a wide variety of key regulatory processes, such as control of proliferation and growth, pluripotency and differentiation, regulation of cell death, protein synthesis and degradation, the response to stress conditions and autophagy, microtubule stabilization, and histamine release, among others [2].

Particularly in human parasites, little is currently known about the functions and processes that involve TCTP orthologs, but some studies have shown that they collaborate in parasite growth, proliferation, reproduction and response to stress conditions, which is why this protein has been suggested as a possible therapeutic target [3–5]. Toxoplasma gondii has been reported to require its TCTP ortholog for rapid growth and to maintain its intracellular development [3]. Moreover, TCTP has been shown to act as an antioxidant and heat shock protein with chaperone activity in some parasites [6–8] and can also interact and sequester antiparasitic drugs, thus contributing to the development of resistant strains [9–11]. TCTP has been reported to be present in the plasma of Plasmodium falciparum-infected patients at concentrations between 2.4 and 6.9 µg/mL, indicating that these parasites secrete this protein [12]. In the same way, it has also been shown that other parasites also release this protein into the environment and it has been suggested that the TCTP protein secreted by the parasites could block the normal immune response by acting as a dominant negative mutant of human TCTP [4, 5, 13–15]. Notably, immunization of BALB/c mice with the purified recombinant TCTP protein from Plasmodium falciparum or Plasmodium yoelii reduced the parasitaemia generated during the early stages of Plasmodium yoelii or Plasmodium chabaudi infection and increased survival [16]. Likewise, a transient reduction in parasitemia was observed in OF1 mice infected with...
Trypanosoma brucei gambiense that were previously immunized with the parasite’s TCTP protein [13]. The production of anti-TCTP antibodies in the immunized mice in both assays indicates that the protein is capable of inducing an adaptive immune response [13, 16]. Furthermore, TCTP of some parasites has been shown to play a role in the development of allergic inflammatory responses in infected patients [14, 17], stimulating the release of histamine from basophils and IL-8 from eosinophils [12]. For all this, it is thought that TCTP orthologs in parasites could act in two different areas, one involved in the regulation of host cytokine signaling and the other in the maintenance of parasite homeostasis and its response to conditions of stress [15].

The proposal of the present work was to analyze, from different human parasitic protozoan species, the sequence, structure and phylogeny of TCTP orthologs to identify notable characteristics that could be exploited in the development of new therapeutic strategies.

Materials and Methods

Database Screening

The orthologues of the human TCTP protein in protozoan parasites were found using the NCBI BLAST tool (with predetermined search parameters) in the database of the EuPathDB Bioinformatics Resource Center [18]. The complete sequences of the TCTP orthologs were compiled and included the following species: Homo sapiens (P13693), Cryptosporidium parvum (CPATCC_001190), Cryptosporidium hominis (Chro.30228), Toxoplasma gondii (TGME49_251680), Sarcocystis neurona (SN3_51680), Cyclospora cayetanensis (cyC_00965), Acanthamoeba castellanii (ACA1_069360 and ACA1_030760), Entamoeba histolytica (EH1_021360), Naegleria fowleri (FDP41_001128, NF0012290, FDP41_001927 and NF0009160), Giardia duodenalis (GL50803_6242 and DHA2_6242), Plasmodium falciparum (PF3D7_0511000), Trypanosoma brucei (Tb927.8.6750 and Tb927.8.6760), Trypanosoma cruzi (TcCLB.506207.50), Leishmania major (TcCLB.506207.50), Leishmania donovani (LmjF.24.1510 and LmjF.24.1500), Leishmania infantum (LINF_240020500 and LINF_240020600), Leishmania braziliensis (LbrM.24.1350), Leishmania mexicana (LmxM.24.1500a and LmxM.24.1500), and Trichomonas vaginalis (TVAG_180840).

Sequence Analysis, Alignments, Phylogenetic Analysis, and Protein Modeling

The sequences of the DDP4 proteins from all the organisms studied were analyzed using InterPro [19]. All the sequences obtained were aligned with the MEGA11 software [20] using the MUSCLE algorithm and then manually edited after visual inspection. Conservation calculations were performed with CLC Genomics Workbench 21 (QIAGEN Digital Insights). The aligned sequences were used to construct the phylogenetic trees using maximum likelihood and minimum evolution methods. The 3D models of the TCTP proteins were predicted with SWISS-MODEL [21], and illustrations were made using UCSF Chimera software [22].

Results

Sequence Analysis

After obtaining the complete sequences of the TCTP orthologs identified in the protozoan parasites, we performed an alignment (Supplementary Fig. 1) that showed an average identity of 30.9% and an overall similarity of 49.08% with respect to the human protein (Table 1). There was an overall identity of 38.19% among all proteins. The orthologist ACA1_069360 from A. castellanii was the one that had the greatest identity and similarity with the human protein. Protein sizes were around 151 and 229 amino acids (T. vaginalis and N. fowleri proteins, respectively) and the two protein fingerprints (TCTP1 and TCTP2) characteristic of this protein in all species were identified (Fig. 1). The TCTP1 fingerprint had 55.62% identity, while the TCTP2 fingerprint had 64.95%. Considering the positions of our alignment, the most conserved residues were M107 (96%), E123 (93%), D127 (89%), V186 (89%), K202 (93%), Y214 (89%), K234 (93%), F255 (100%), G260 (96%), P284 (93%) and D291 (96%), and L293 (89%).

Phylogenetic Analysis

The sequence alignment of TCTP orthologs was used to build phylogenetic trees using two methods to have different perspectives, a character-based method such as maximum likelihood and a distance-based method such as minimum evolution (Fig. 2). Both methods constructed similar phylogenetic trees, placing the N. fowleri orthologs as the most ancestral proteins, while the orthologues of organisms in the Kinetoplastea class were the most evolutionarily advanced. Both trees separated TCTP orthologs from G. duodenalis and T. vaginalis, although both species belong to the Metamonada phylum. The T. vaginalis ortholog was closer to those of N. fowleri, while the G. duodenalis orthologs to those of the Kinetoplastea class. The orthologs of the species of the subphylum Apicomplexa and of the phylum Amoebazoa were placed in the middle of the proteins of G. duodenalis and T. vaginalis. The trees had differences when placing the human TCTP protein, the algorithm of
maximum likelihood placed it evolutionarily close to the phylum Amoebozoa, particularly of *A. castellanii* orthologue ACA1_069360, while the algorithm of minimum evolution placed it close to *T. vaginalis* orthologue.

### Structural Analysis

We constructed 3D models of one of the TCTP orthologs in each organism using the human protein as a point of comparison (Fig. 3). First, we realized that the number and arrangement of β-sheets and α-helices is maintained in all species, only with variations in the size of these secondary structures. The tertiary structure was also similar in all the predicted proteins, the main difference being the size of the bridge between the fifth and sixth β sheet (flexible loop/TCTP1), which tends to be larger in the parasites studied compared to human protein.

**Table 1** Identity and similarity of TCTP orthologues in protozoan parasites compared to human protein

| Species                                   | UniProtKBa | Sizeb | Ic   | Sd   |
|-------------------------------------------|------------|-------|------|------|
| Cryptosporidium parvum                   | CPATCC_001190 | 172   | 30.51| 50.85|
| Cryptosporidium hominis                   | Chro.30228 | 172   | 30.51| 50.85|
| Toxoplasma gondii                        | TGME49_251680 | 171   | 35.03| 56.50|
| Sarcocystis neurona                      | SN3_51680 | 171   | 32.77| 54.80|
| Cyclospora cayetanensis                  | cye_00965 | 171   | 31.07| 50.85|
| Acanthamoeba castellani                  | ACA1_069360 | 165   | 39.88| 57.80|
| Leishmania braziliensis                  | LINF_240020600 | 170   | 31.84| 52.85|
| Leishmania donovani                      | ACA1_030760 | 191   | 35.75| 52.85|
| Entamoeba histolytica                    | EHL_021360 | 170   | 36.42| 57.23|
| Naegleria fowleri                        | FDP41_001128 | 229   | 21.19| 33.05|
| Plasmodium falciparum                    | NF0012290 | 244   | 19.92| 31.08|
| Trypanosoma brucei                       | Tb927.8.6750 | 170   | 32.96| 53.63|
| *Giardia duodenalis*                     | GL50803_6242 | 151   | 28.74| 43.68|
| *Trichomonas vaginalis*                  | DHA2_6242 | 151   | 28.74| 43.68|
| *Plasmodium falciparum*                  | PF3D7_0511000 | 171   | 33.14| 55.43|
| Trypanosoma cruzi                        | Tb927.8.6760 | 170   | 31.43| 55.43|
| Trypanosoma brucei                       | TcCLB_506207.50 | 170   | 30.43| 51.09|
| Leishmania major                         | LmjF.24.1510 | 170   | 33.70| 51.63|
| Leishmania infantum                      | LmjF.24.1500 | 170   | 33.70| 51.63|
| Leishmania donovani                      | LdbPK_241560.1 | 170   | 33.15| 51.63|
| Leishmania braziliensis                  | LbrM.24.1350 | 170   | 31.84| 52.51|
| Leishmania mexicana                      | LmxM.24.1500a | 170   | 33.15| 50.54|
| Average                                  | 177.70      | 30.90 | 49.08|

*a* Access number in the UniProt Knowledgebase

*b* Number of amino acids

*c* Identity values expressed in percentage (%)

*d* Similarity values expressed in percentage (%)

**Discussion**

Given the functional relevance of TCTP in eukaryotes and its possible use as a therapeutic target against protozoan parasites, we carried out an analysis of this protein from several aspects. A moderate identity (38.19%) was found when aligning the sequences of all the orthologues studied and the TCTP1 and TCPT2 fingerprints were identified in all of them. Among the most conserved residues that we found in the protozoan parasites studied was E123 (corresponding to residue 12 of human TCTP), which previous reports showed that it is an important residue for the binding of TCTP to RHEB (RAS homologue enrichment in brain) GTPase to activate TOR (Target of rapamycin) [23]. In contrast, residues S46 and S64 of human TCTP (residues 163 and 181 of our alignment), which are subject to phosphorylation by PLK, are not conserved in parasites and are only found in mammalian TCTPs [24, 25]. Interestingly, the V186 residue of our alignment that was highly conserved in parasites, in humans (residue 69) is changed by a glycine that participates in the binding of TCTP with the PIM-3 (Provirus integrating site Moloney murine leukemia virus 3) kinase [26]. The conservation of K202 (residue 85 of human TCTP), induces the release of histamine, which is more efficiently incorporated into B cells than its human counterpart [29], induces the release of histamine, but could block the activation of B cells by not being able to interact with G proteins and, therefore, the parasite protects itself, to some extent, from the host’s immune system [15].

Regarding our phylogenetic analysis, the clusters generated are largely in agreement with the proposed phylogeny of eukaryotes (Fig. 2) [30, 31]. The phylogenetic trees
Fig. 1 Partial alignment of the sequences of TCTP orthologs identified in protozoan parasites. Consensus was obtained on all available sequences. TCTP1 and TCTP2 fingerprints are identified by red boxes. The calcium (orange) and microtubule (green) binding regions are underlined. Letters with a red background indicate conserved residues. The predicted secondary structure corresponds to human TCTP. β-sheets are represented as arrows, while α-helices are represented as a spiral line.
identified the TCTP orthologs in the amoeboid-flagellate *N. fowleri* as the most ancestral proteins. *N. fowleri* belongs to the *Heterolobosea* clade that diverged from other eukaryotic lineages over a billion years ago [32]. Meanwhile, the phylum *Metamonada* has also been identified as one of the oldest, and particularly the flagellated protozoan *G. duodenalis* has been recognized as one of the closest to ancestral eukaryotes, although there is still much debate as to the evidence supporting this claim [33–36]. *N. fowleri*, *T. vaginalis* and *G. duodenalis* belong to the *Excavata* sub-kingdom. The members of the *Apicomplexa* subphylum belonging to the SAR supergroup (which includes *Stramenopiles*, *Alveolata* and *Rhizaria*) and also the members of the *Amoebozoa* phylum are considered evolutionarily more advanced that the members of the *Excavata* sub-kingdom [30, 31]. The evolutionary position of the *Kinetoplastea* class is not yet well established, but since parasitic kinetoplastids have arisen from non-pathogenic free-living ancestors, multiple processes must have occurred before this step could be taken [37].

Structural analysis of TCTP orthologs predicted a highly conserved secondary and tertiary structure (Fig. 3). Furthermore, an increase in flexible loop size was observed in most TCTP orthologs compared to human protein. Although we do not know the functional reason for this change, it is known that the flexible loop is critical to promote cytokine release and the limitation of the flexibility of this region by disulfide bonds is required [38]. Notably, this area has also served as a binding site for potential TCTP inhibitors (Brompheniramine, Sertraline, ZINC19364226, ZINC19361042, ZINC03831041, ZINC12657067, ZINC12657071, ZINC12863423, ZINC08918508) [39]. This opens up the option of creating new therapeutic strategies against protozoan parasites taking TCTP as a target, which would also
take advantage of the differences in this region compared to human protein. *P. falciparum* TCTP has been suggested to be a potential target for artemisinin, one of the most effective antimalarial drugs, and some residues involved in binding have been described. The C14 residue (position 115 of our alignment) of *P. falciparum* TCTP and other species of the subphylum *Apicomplexa* has been proposed as one of the possible artemisinin alkylation sites and could serve as an electron donor during endoperoxide activation [40, 41]. However, in species of the *Kinetoplastea* class, this cysteine

Fig. 3 Comparison of predicted three-dimensional structures of TCTP orthologs in protozoan parasites. Structures are represented as ribbons and chains. Note the high level of structural similarity exhibited between these representative TCTPs. The flexible loop, which is the region with the most notable differences between TCTP orthologs studied, is indicated by a red arrow.
is found in position 15 (116 of our alignment) and in the other species of protozoan parasites, this residue is replaced by hydrophobic amino acids (phenylalanine, valine, alanine or leucine) (Fig. 1) that have been shown to completely inhibit binding to artemisinin [40]. The F8A mutation (position 119 of our alignment) also significantly decreased the binding of the *Plasmodium* falciparum TCTP protein to artemisinin [40], which is important since in human and most other protozoan parasites, it is replaced by a leucine or isoleucine (Supplementary Fig. 1). D11A or F18A mutations (positions 122 and 129 of our alignment) had only a small effect on artemisinin binding [40]. Furthermore, the regions corresponding to residues 19–46 (130–154 in our alignment), 108–134 (229–255 in our alignment) and 140–163 (265–290 in our alignment) have been reported to be covalently modified by artemisinin radicals [42]. Another thing that has to be considered when designing TCTP inhibitor drugs is that it is a dynamic molecule and in a study where a series of putative compounds inhibiting human TCTP were found [43], the amino acids most involved in the interaction with the chemicals were K34, M35, V36, G69, V70, D71, I72 and P158 (residues K151, M152, V153, G195, V196, D197, I198, P283 in our alignment).

In conclusion, we can say that TCTP orthologues have important functions in protozoan parasites, they maintain a moderate identity between them, but their structure is quite conserved, evolutionarily they follow the proposed phylogeny of eukaryotes and the changes in the flexible loop could be used in the creation of new antiparasitic drugs.

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Declarations

Conflict of Interest The author declares no conflict of interest.

Ethical Statement This material is the original work of the author and has not been previously published elsewhere. Bioinformatic work does not require an ethical permit and the goal is to reduce work with animals.

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References

1. Xocoonostle-Cázares B, Ruiz-Medrano R (2017) Structure-function relationship of TCTP. In: Telerman A, Amson R (eds) TCTP/ tpt1—remodeling signaling from stem cell to disease. Springer International Publishing, Cham, pp 47–68

2. Bommer U-A, Telerman A (2020) Dysregulation of TCTP in biological processes and diseases. Cells 9:1632. https://doi.org/10.3390/cells9071632

3. Zheng J, Chen Y, Li Z et al (2018) Transitionally controlled tumor protein is required for the fast growth of *Toxoplasma gondii* and maintenance of its intracellular development. FASEB J 32:906–919. https://doi.org/10.1096/fj.201700994R

4. Meyvis Y, Houwhoofd W, Visser A et al (2009) Analysis of the translationally controlled tumour protein in the nematodes *Ostertagia ostertagi* and *Caenorhabditis elegans* suggests a pivotal role in egg production. Int J Parasitol 39:1205–1213. https://doi.org/10.1016/j.ijpara.2009.02.017

5. Gnanasekar M, Rao KVN, Chen L et al (2002) Molecular characterization of a calcium binding translationally controlled tumor protein homologue from the filarial parasites *Brugia malayi* and *Wuchereria bancrofti*. Mol Biochem Parasitol 121:107–118. https://doi.org/10.1016/S0166-6851(02)00027-0

6. Gnanasekar M, Dakshinamoorthy G, Ramaswamy K (2009) Transitionally controlled tumor protein is a novel heat shock protein with chaperone-like activity. Biochem Biophys Res Commun 386:333–337. https://doi.org/10.1016/j.bbrc.2009.06.028

7. Mak CH, Sun KW, Ko RC (2001) Identification of some heat-induced genes of *Trichinella spiralis*. Parasitology 123:293–300. https://doi.org/10.1074/jp.2001111820001008320

8. Gnanasekar M, Ramaswamy K (2007) Transitionally controlled tumor protein of *Brugia malayi* functions as an antioxidant protein. Parasitol Res 101:1533–1540. https://doi.org/10.1007/s00436-007-0671-z

9. Bhisutthibhan J, Pan X-Q, Hossler PA et al (1998) The *Plasmodium falciparum* translationally controlled tumor protein homolog and its reaction with the antimalarial drug artemisinin. J Biol Chem 273:16192–16198. https://doi.org/10.1074/jbc.273.26.16192

10. Bhisutthibhan J, Meshnick SR (2001) Immunoprecipitation of [3 H]dihydroartemisinin translationally controlled tumor protein (TCTP) adducts from *Plasmodium falciparum*-infected erythrocytes by using anti-TCTP antibodies. Antimicrob Agents Chemother 45:2397–2399. https://doi.org/10.1128/AAC.45.8.2397-2399.2001

11. Afonso A, Hunt P, Cheesman S et al (2006) Malaria parasites can develop stable resistance to artemisinin but lack mutations in candidate genes atp6 (encoding the sarcoplasmic and endoplasmic reticulum Ca 2+ ATPase), tctp, mdr1, and cg10. Antimicrob Agents Chemother 50:480–489. https://doi.org/10.1128/AAC.50.2.480-489.2006

12. MacDonald SM, Bhisutthibhan J, Shapiro TA et al (2001) Immune micromyelina in malaria: *Plasmodium falciparum* secretes a functional histamine-releasing factor homolog in vitro and in vivo. Proc Natl Acad Sci 98:10829–10832. https://doi.org/10.1073/pnas.201191498

13. Bossard G, Rodrigues V, Tour E, Geiger A (2021) Mice immunization with *Trypanosoma brucei* gambiense translationally controlled tumor protein modulates immunoglobulin and cytokine production, as well as parasitaemia and mice survival after
chall`e with the parasite. Infect Genet Evol 87:104636. https://doi.org/10.1016/j.meegid.2020.104636
14. Rao KVN, Chen L, Gnanasekar M, Ramaswamy K (2002) Cloning and characterization of a calcium-binding, histamine-releasing protein from Schistosoma mansoni. J Biol Chem 277:31207–31213. https://doi.org/10.1074/jbc.M204114200
15. Hinojosa-Moya J, Xoconostle-Cázares B, Piedra-Ibarra E et al (2008) Phylogenetic and structural analysis of translationally controlled tumor proteins. J Mol Evol 66:472–483. https://doi.org/10.1007/s00239-008-0909-z
16. Taylor KJ, Van TTH, MacDonald SM et al (2015) Immunization of mice with Plasmodium TCTP delays establishment of Plasmodium infection. Parasite Immunol 37:23–31. https://doi.org/10.1111/pim.12158
17. Pelleau S, Diop S, Dia Badiane M et al (2012) Enhanced basophil reactivities during severe malaria and their relationship with the Plasmodium falciparum histamine-releasing factor translationally controlled tumor protein. Infect Immun 80:2963–2970. https://doi.org/10.1128/IAI.00072-12
18. Aurrecoechea C, Barreto A, Basenko EY et al (2017) EuPathDB: the eukaryotic pathogen genomics database resource. Nucleic Acids Res 45:D581–D591. https://doi.org/10.1093/nar/gkw1105
19. Blum M, Chang H-Y, Chuguransky S et al (2021) The InterPro and families database and domains database: 20 years on. Nucleic Acids Res 50:D344–D354. https://doi.org/10.1093/nar/gkaa977
20. Tamura K, Stecher G, Kumar S (2021) MEGA11: molecular evolutionary genetics analysis version 11. Mol Biol Evol 38:3022–3027. https://doi.org/10.1093/molbev/msab120
21. Biasini M, Bienert S, Waterhouse A et al (2014) SWISS-MODEL: modelling proteins tertiary and quaternary structure using evolutionary information. Nucleic Acids Res 42:W252–W258. https://doi.org/10.1093/nar/gku540
22. Pettersen EF, Goddard TD, Huang CC et al (2004) UCSF Chimera—a visualization system for exploratory research and analysis. J Comput Chem 25:1605–1612. https://doi.org/10.1002/jcc.20084
23. Kumar R, Maurya R, Saran S (2020) Investigating the role of translationally control tumor protein in growth, development and differentiation of Dictyostelium discoideum. Front Cell Dev Biol 8:1–13. https://doi.org/10.3389/fcell.2020.00742
24. Yarm FR (2002) Ptk phosphorylation regulates the microtubule-stabilizing protein TCTP. Mol Cell Biol 22:6209–6221. https://doi.org/10.1128/MCB.22.17.6209–6221.2002
25. Cucchi U, Gianellini LM, De Ponti A et al (2010) Phosphorylation of TCTP as a marker for polo-like kinase-1 activity in vivo. Anticancer Res 30:4973–4985
26. Zhang F, Liu B, Wang Z et al (2013) A novel regulatory mechanism of Pim-3 kinase stability and its involvement in pancreatic cancer progression. Mol Cancer Res 11:1508–1520. https://doi.org/10.1158/1541-7786.MCR-13-0389
27. Malard F, Assir N, Alami M et al (2018) Conformational ensemble and biological role of the TCTP intrinsically disordered region: influence of calcium and phosphorylation. J Mol Biol 430:1621–1639. https://doi.org/10.1016/j.jmb.2018.04.024
28. Hsu Y-C, Chern JJ, Cai Y et al (2007) Drosophila TCTP is essential for growth and proliferation through regulation of dRheb GTPase. Nature 445:785–788. https://doi.org/10.1038/nature05528
29. Calderón-Pérez B, Xoconostle-Cázares B, Lira-Carmona R et al (2014) The Plasmodium falciparum translationally controlled tumor protein (TCTP) is incorporated more efficiently into B cells than its human homologue. PLoS ONE 9:e85514. https://doi.org/10.1371/journal.pone.0085514
30. Adl SM, Simpson AGB, Farmer MA et al (2005) The new higher level classification of eukaryotes with emphasis on the taxonomy of protists. J Eukaryot Microbiol 52:399–451. https://doi.org/10.1111/j.1550-7408.2005.00053.x
31. Adl SM, Simpson AGB, Lane CE et al (2012) The revised classification of eukaryotes. J Eukaryot Microbiol 59:429–514. https://doi.org/10.1111/j.1550-7408.2012.00644.x
32. Fritz-Laylin LK, Prochnik SE, Ginger ML et al (2010) The genome of Naegleria gruberi illuminates early eukaryotic versatility. Cell 140:631–642. https://doi.org/10.1016/j.cell.2010.01.032
33. Lloyd D, Harris JC (2002) Giardia: highly evolved parasite or early branching eukaryote? Trends Microbiol 10:122–127. https://doi.org/10.1016/S0966-842X(02)02306-5
34. He D, Fiz-Palacios O, Fu C-J et al (2014) An alternative root for the eukaryote tree of life. Curr Biol 24:465–470. https://doi.org/10.1016/j.cub.2014.01.036
35. Lagunas-Rangel FA, Bermúdez-Cruz RM (2019) Epigenetics in the early divergent eukaryotic Giardia duodenalis: an update. Biochimie 156:123–128. https://doi.org/10.1016/j.biochi.2018.10.008
36. Lagunas-Rangel FA, Yee J, Bermúdez-Cruz RM (2021) An update on cell division of Giardia duodenalis trophozoites. Microbiol Res 250:126807. https://doi.org/10.1016/j.microbes.2021.126807
37. Cenci U, Moog D, Curtis BA et al (2016) Heme pathway evolution in kinetoplastid protists. BMC Evol Biol 16:109. https://doi.org/10.1186/s12862-016-0664-6
38. Lee H, Kim M-S, Lee J-S et al (2020) Flexible loop and helix 2 domains of TCTP are the functional domains of dimerizer TCTP. Sci Rep 10:197. https://doi.org/10.1038/s41598-019-57064-9
39. Kumar R, Maurya R, Saran S (2017) Identification of novel inhibitors of the translationally controlled tumor protein (TCTP): insights from molecular dynamics. Mol Biosyst 13:510–524. https://doi.org/10.1039/C6MB00850J
40. Li W, Zhou Y, Tang G, Xiao Y (2016) Characterization of the artemisinin binding site for translationally controlled tumor protein (TCTP) by bioorthogonal click chemistry. Bioconjug Chem 27:2828–2833. https://doi.org/10.1021/bc.6b00556
41. Chae J, Choi I, Kim C (2006) Homology modeling and molecular docking study of translationally controlled tumor protein and artemisinin. Arch Pharm Res 29:50–58. https://doi.org/10.1007/ BF02977468
42. Eichhorn T, Winter D, Büchele B et al (2013) Molecular interaction of artemisinin with translationally controlled tumor protein (TCTP) of Plasmodium falciparum. Biochem Pharmacol 85:38–45. https://doi.org/10.1016/j.bcp.2012.10.006
43. Fischer N, Seo E-J, Klinger A et al (2021) AMG900 as novel inhibitor of the translationally controlled tumor protein (TCTP): influence of calcium and phosphorylation. J Mol Biol 430:1621–1639. https://doi.org/10.1016/j.jmb.2018.04.024
44. Hsu Y-C, Chern JJ, Cai Y et al (2007) Drosophila TCTP is essential for growth and proliferation through regulation of dRheb GTPase. Nature 445:785–788. https://doi.org/10.1038/nature05528
45. Calderón-Pérez B, Xoconostle-Cázares B, Lira-Carmona R et al (2014) The Plasmodium falciparum translationally controlled tumor protein (TCTP) is incorporated more efficiently into B cells than its human homologue. PLoS ONE 9:e85514. https://doi.org/10.1371/journal.pone.0085514
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