**On the Evolution of Hexose Transporters in Kinetoplastid Potozoans**

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**Abstract**

Glucose, an almost universally used energy and carbon source, is processed through several well-known metabolic pathways, primarily glycolysis. Glucose uptake is considered to be the first step in glycolysis. In kinetoplastids, a protozoan group that includes relevant human pathogens, the importance of glucose uptake in different phases of the life cycles is well established, and hexose transporters have been proposed as targets for therapeutic drugs. However, little is known about the evolutionary history of these hexose transporters. Hexose transporters contain an intracellular N- and C-termini, and 12 transmembrane spans connected by alternate intracellular and extracellular loops. In the present work we tested the hypothesis that the evolutionary rate of the transmembrane span is different from that of the whole sequence and that it is possible to define evolutionary units inside the sequence. The phylogeny of whole molecules was compared to that of their transmembrane spans and the loops connecting the transmembrane spans. We show that the evolutionary units in these proteins primarily consist of clustered rather than individual transmembrane spans. These analyses demonstrate that there are evolutionary constraints on the organization of these proteins; more specifically, the order of the transmembrane spans along the protein is highly conserved. Finally, we defined a signature sequence for the identification of kinetoplastid hexose transporters.

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**Introduction**

The order Kinetoplastidae consists of flagellated protozoans that have a peculiar mitochondrial DNA-containing structure called kinetoplast. This group includes species of parasitic protozoa of the genera Trypanosoma and Leishmania, which cause severe human disease. Two species of the genus Trypanosoma, T. brucei and T. cruzi, are the causative agents of sleeping sickness and Chagas’ disease, respectively. Species of the Leishmania subgenus Leishmania and Viannia are the causative agents of a group of diseases known together as leishmaniasis. Together, these parasites affect approximately 25 million people in endemic areas all over the world, with an estimated population of more than 350 million people at risk of acquiring these infections. Unfortunately, the drugs used to treat human infections by these parasites are unsatisfactory; their low therapeutic efficiency, high toxicity, and the appearance of resistant strains constitute serious drawbacks that remain to be overcome [1].

Kinetoplastid protozoa usually have a complex life cycle, alternating between one or more hosts and frequently moving between several territories with different nutrient compositions inside their hosts (i.e., different regions of the insect midgut). The ability of these cells to deal with these environmental changes is reflected by their flexible metabolism, which allows them to use glucose or amino acids (mainly proline) as their main carbon and energy source [2,3]. The cells usually consume amino acids only when they are subjected to glucose deprivation conditions [4,5], supporting the idea that glucose consumption is the default option and emphasizing the relevance of this carbohydrate for these organisms [6].

Transporters are essential proteins in most cells and are among the first molecules involved in the detection of their substrates in the extracellular medium [7]. In trypanosomatids, glucose uptake can be considered to be the first regulated step of glycolysis [8]. These findings led to the early study of glucose uptake pathways in pathogenic trypanosomatids and to molecular studies of hexose transporters in T. brucei, T. cruzi and Leishmania spp. parasites [9].

The relevance of glucose metabolism has been particularly well demonstrated in these trypanosomatids, and hexose transporters and several stages of glycolysis have been proposed as drug targets [10,11]. More recently, with the advance of the T. brucei, T. cruzi and L. major (TriTryp) genome projects, additional hexose transporter genes belonging to other pathogenic and non-pathogenic kinetoplastids have been annotated [12], and some of them have been experimentally validated [8]. All of the glucose transporters described to date in kinetoplastids are related to solute
carrier family 2, also known as facilitated glucose transporter member 1 (SLC2A1) or GLUT1, belonging to the Major Facilitator Superfamily (2.A.1, MFS). Although we have a considerable amount of information about the GLUT1 family, little is known about the evolution of these peculiar proteins [13].

GLUT1 is a glucose transporter family that is broadly distributed across Eukarya and Bacteria [14]. The structure of these facilitative hexose permeases is supported exclusively by twelve transmembrane spans, which are connected by extracellular and intracellular loops [15,16]. Because the transport activity of these proteins relies on their transmembrane regions, we hypothesize here that the connecting loops have fewer constraints with regard to amino acid substitution during evolution. Following this rationale, we hypothesize that the transmembrane regions of hexose transporters constitute evolutionary modules with more constrained variation patterns than the extracellular and intracellular loops. In the present work we used the kinetoplastid hexose transporter sequences available in the TriTryp database [17] to analyze the evolutionary history of these proteins in species belonging to the genera Trypanosoma and Leishmania, with particular focus on the transmembrane regions. The results presented herein show for the first time that clusters of consecutive transmembrane spans constitute evolutionary modules.

Materials and Methods

Sequence retrieval and domain identification

All available amino acid sequences annotated as hexose/glucose transporters were recovered from the TriTryp database version 3.2 (http://tritrypdb.org/tritrypdb) [17]. The species and accession numbers of the sequences used are listed in Table 1. Only sequences corresponding to a single allelic copy per species were chosen to be included in the present analysis. The initial search for constructing the starting-up database was performed as follow. Due to the presence of two haplotypes (Esmeraldo and non-Esmeraldo) in the available genome data from the T. cruzi CL Brener strain, only one representative gene was analyzed; T. cruzi Esmeraldo if it exists, otherwise T. cruzi non-Esmeraldo if it exists, otherwise T. cruzi unassigned genes. In the case of T. brucei, non-redundant genes were also analyzed considering the representative gene corresponding to T. brucei strain TREU927 if it exists, otherwise T. brucei gambiens. Sequences from other Trypanosoma spp. and Leishmania spp. were included if their identity were less than 98%. The obtained sequences were curated initially on the basis of their similarities to glucose transporters by using the online version of BLASTp at the NCBI (http://www.ncbi.nlm.nih.gov/BLAST/). BLASTp was run under default parameters using the non-redundant protein sequence database. The sequences were further analyzed for the position of the 12 transmembrane spans with SOSUI v1.11 [18], TMHMM v2.0 [19], TMPRED v1.0 (http://www.ch.embnet.org/software/TMPRED_form.html) and HMMTOP v2.0 (http://www.enzim.hu/hmmtop/). The predicted transmembrane regions were recovered as independent sequences for further analysis. Assemblies and analysis of the amino acid sequence data were carried out using the software package Vector NTI v. 10.3.0 (Invitrogen, California – USA).

Phylogenetic and other bioinformatic analyses

Phylogenetic analyses were performed using Molecular Evolutionary Genetics Analysis (MEGA) v5.05 [20,21,22]. Briefly, the evolutionary history was inferred with the maximum likelihood method with a JTT matrix-based model. The bootstrap consensus tree inferred from 500 replicates was taken to represent the evolutionary history of the sequences analyzed. Branches corresponding to partitions reproduced in fewer than 50% of bootstrap replicates were collapsed. Initial tree(s) for the heuristic search were obtained automatically as follows. When the number of common sites was lower than 100 or less than one-fourth of the total number of sites, the maximum parsimony method was used; otherwise, the BIONJ method with the MCL distance matrix was used. The trees were drawn to scale, with branch lengths measured in the number of substitutions per site. All positions containing gaps and missing data were eliminated. The average evolutionary divergence over all sequence pairs was also calculated using the JTT matrix-based model involving all amino acid sequences in each case. Similarity analyses based on the consensus sequence were conducted using the ClustalW algorithm [23]. For the identification of possible specific signatures, all sequences were scanned using Multiple Em for Motif Elicitation (MEME) v4.6.1 [24].

Results

Our search for all amino acid sequences annotated as hexose or glucose transporters in the TriTryp database returned 57 sequences (Table 1). To eliminate redundancies all allelic copies (>98% identity), truncated sequences and pseudogenes were discarded. Of the remaining 18 sequences distributed among 7 species of the genera Trypanosoma and Leishmania, the functions of 10 had been experimentally verified, while the functions of the other 8 had been inferred from sequence data [9,25,26,27,28,29,30,31].

Table 1. Description of the main characteristics of the used sequences.

| AN   | Species     | Length | TMS | NTP/CTR | NTL | CTL |
|------|-------------|--------|-----|---------|-----|-----|
| LbrM.33.0290 | L. braziliensis | 617    | 12  | I/I     | 94  | 27  |
| LbrM.35.6490 | L. braziliensis | 531    | 12  | I/I     | 20  | 24  |
| LinJ.36.6550 | L. infantum   | 567    | 12  | I/I     | 46  | 32  |
| LinJ.36.6560 | L. infantum   | 653    | 12  | I/I     | 135 | 32  |
| LmjF.33.0290 | L. major      | 594    | 12  | I/I     | 73  | 24  |
| LmjF.36.6280 | L. major      | 568    | 12  | I/I     | 46  | 32  |
| LmjF.36.6290 | L. major      | 561    | 12  | I/I     | 45  | 26  |
| LmjF.36.6300 | L. major      | 653    | 12  | I/I     | 135 | 32  |
| LmM.32.0290 | L. mexicana   | 627    | 12  | I/I     | 107 | 24  |
| LmM.36.6280 | L. mexicana   | 566    | 12  | I/I     | 48  | 32  |
| LmM.36.6290 | L. mexicana   | 567    | 12  | I/I     | 49  | 32  |
| LmM.36.6300 | L. mexicana   | 610    | 12  | I/I     | 88  | 32  |
| Tb427.04.2290 | T. brucei     | 552    | 12  | I/I     | 51  | 07  |
| Tb427.10.8450 | T. brucei     | 527    | 12  | I/I     | 43  | 30  |
| Tb427.10.8530 | T. brucei     | 529    | 12  | I/I     | 41  | 31  |
| Tc001.104705306355.10 | T. cruzi | 544    | 12  | I/I     | 34  | 47  |
| Tcl3000.10.7320 | T. congolense | 525    | 12  | I/I     | 40  | 29  |
| TcY486_00402140 | T. vivax   | 558    | 12  | I/I     | 48  | 09  |
| Ecoli_P02920 (Lac Y) | E. coli | 417    | 12  | I/I     | 07  | 19  |
The analyzed genes fall into three syntenic orthologous groups. The first group comprises the genes LinJ.36.6550 (and its paralog LinJ.36.6560), LmjF.36.6290 (and its paralogs LmjF.36.6290-LmjF.36.6300, called lmtg1-3), LmxM.36.6290 (and its paralogs LmxM.36.6290-LmxM.36.6300), TcIL3000.10.7320 and Tb427.10.8540 (and its paralog Tb427.10.8530, called THT1). This group of genes has expanded into 10 tandem duplications. Lila shadows indicates the syntenic genes and all the sequences are represented by their systematic ID. The synteny analyses and scheme was made at the TriTrypDB (http://tritrypdb.org/tritrypdb).

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Figure 1. Hexose transporters synteny analysis. The genomic contexts of the Trypanosoma spp and Leishmania spp hexose transporters were analyzed. The figure represent one syntenic orthologous group (highlighted in green) comprising the genes LinJ.36.6550 (and its paralog LinJ.36.6560), LmjF.36.6280 (and its paralogs LmjF.36.6290-LmjF.36.6300, called lmtg1-3), LmxM.36.6280 (and its paralogs LmxM.36.6290-LmxM.36.6300), TcIL3000.10.7320 and Tb427.10.8540 (and its paralog Tb427.10.8530, called THT1). This group of genes has expanded into 10 tandem duplications. Lila shadows indicates the syntenic genes and all the sequences are represented by their systematic ID. The synteny analyses and scheme was made at the TriTrypDB (http://tritrypdb.org/tritrypdb).
amino acid position were completely lost: the mean global identity values diminished from 71.9% for TMSJ to 20.4% for S-TMSJ. When the same analysis was performed on the connecting loops, the identity values decreased for both the LJ and S-LJ sequences (36.5 and 12.2%, respectively) (Figure 4B), indicating a small contribution of the order of the L regions to global identity (see values in Figure 3C). This result strongly indicates that, in addition to the fact that individual or clusters of transmembrane regions act as evolutionary modules, their order inside the molecule is critical for functional hexose transporters. To estimate the evolutionary divergence between TMSs in a single sequence and between TMSs at the same location in different sequences, the TMSs were grouped by constructing a matrix \( M_{i,j} \), where \( i \) represents a sequential array of TMSs from the same molecule (TMS-1, ..., TMS-12) and \( j \) represents TMS-i for each of the 18 sequences under analysis (TMS-1,1, ..., TMS-1,18) (Table S1). The whole matrix divergence was calculated to be 7.7 arbitrary units. This value was similar to those obtained within each row and among rows and to that calculated among columns. Interestingly, the mean divergence within each column was 1.45; the column corresponding to TMS-1 was the only one with a high divergence value (8.46). Interestingly, the N- and C- termini were the most
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divergent regions along the whole molecule. These data indicate
that the TMSs corresponding to the same positions in different
proteins are the most conserved evolutionary units of kinetoplastid
hexose transporters. In addition, although it is likely that these
proteins evolved by internal TMS duplications, no traces of this
process remain detectable in the sequences under analysis. This
conclusion is supported by our analysis of internal amino acid
repeats in these proteins using four different algorithms, none of
which found evidence of TMS duplications.

The presence of conserved regions in the hexose transporters
studied could prove valuable for identifying critical regions related
to the protein activity. All of the sequences were analyzed using the
Multiple Em for Motif Elicitation (MEME) algorithm (http://
meme.nbcr.net/). This analysis identified the motif QLTGINA
(which we refer to as the “GINA” motif), which was primarily
present in TMS-6 and TMS-7 (Figure S2).

Discussion

The kinetoplastid hexose transporters have low but significant
identity to members of the mammalian GLUT1 family [35]. For
those hexose transporters that have been cloned and have had
their activity demonstrated, it is predicted that the proteins contain
12 transmembrane spans [25,26,27,31,36,37,38,39,40,41]. How-
ever, this should not be taken as a rigid rule. As the genome
projects for more trypanosomatids progress, new sequences are
being annotated as putative transporters, some of which have
10 or 11 transmembrane regions predicted by validated
bioinformatic tools [12]. In the present study, we found 57 hexose
transporters annotated for seven pathogenic and non-pathogenic
kinetoplastid species (listed in Table 1). After curating the obtained
sequences, we arrived at a total of 18 sequences, all them bearing
12 transmembrane spans. Because glucose transporters are
essential for most living cells, new ones will likely be found in
other trypanosomatid genomes. In this study, we detected a
signature for kinetoplastid hexose transporters, the “GINA” motif
(QLTGINA), which could be useful for detecting putative hexose
transporters in newly sequenced kinetoplastids.

The probable structure of the kinetoplastid hexose transporters
was classically based on that of the mammalian GLUT1 family [35].
For those hexose transporters that have been cloned and have had
their activity demonstrated, it is predicted that the proteins contain
12 transmembrane helices based on the hydrophathy plot for GLUT1 [13] which was first described by Mueckler et al. [42]. One of the best studied members of this
group is the E. coli LacY protein, the structure of which was
resolved in detail by crystallographic studies [33,34]. This protein
consists of 12 transmembrane regions, which act as the structural
support for the protein’s transport activity. In the LacY
crystallography model, it was established that the spans are not
arranged in space in sequential order (i.e., helix 1 is surrounded by
helices 4 and 5 instead of helix 2). LacY is organized into two
groups of six helices each (1 to VI and VII to XII), and both groups
are connected by a long loop between helices VI and VII. These
groups of N- and C-terminal TMSs display two-fold symmetry.
In addition, the N- and C-terminal halves present some weak
similarities, suggesting gene duplication or fusion. Based on the
known structure of LacY, we modeled the T. cruzi hexose
transporter, which is a well characterized and representative
member of the others analyzed in the present study. Interestingly,
the model presented reliable adjusting parameters, with an e-value
of 1.9 x 10^-27 (Figure S3). Based on their structural similarity, we
expected that evolutionary modules would correspond to neigh-
boring TMSs, but this was not the case. This finding could be explained by the fact that, differently from what was predicted for
human GLUT1, it was not expected that trypanosomatid hexose
transporters interact with other proteins: the only human GLUT1
known interactor (beside itself [43]) is GLUT1CBP [44], which
is absent in trypanosomatids.

The N-terminus, TMS-1, L-1 and the C-terminus were
Generally the most divergent regions of GLUT1 proteins. In fact,
the large extracellular loop between helices 1 and 2, present in all
sequences, is one of the factors that diminished the quality of the
LacY-based models. This result is not surprising because this
feature, while common in the GLUT1 family, is absent in LacY
[13]. When these regions were excluded, the resulting models
showed that trypanosomatid transporters had similar architect-
ture to that of LacY (Figure S3). As discussed for Lac Y, two
domains were present, constituted by helices 2 to 6 (corresponding
to the N-terminal half of the molecule), and constituted by helices
7 to 12 (corresponding to the C-terminal half of the molecule).
Based on the model, both halves seem to be linked by a long
intracellular loop and surround a predicted cavity that opens to the
cytosolic side of the membrane. It is also assumed that both the
N- and C-terminals are intracellular.

The differences in the role of transmembrane regions of most
metabolite transporters, which are critical for their correct
insertion into the membrane, as well as for their conformation
and activity [7], led us to analyze if these TMSs should be more
constrained during evolution than the loops which seem to be
more prone to amino acid substitutions. Indeed, the only
predictable evolutionary constraint for the loops would be related
to the avoidance of highly immunogenic structures on the
parasite’s surface. The hexose transporters provide a very
interesting and biologically relevant model to test the hypothesis
that intramolecular evolutionary modules exist. Initially, we
hypothesized that the TMSs would act as individual modules.
However, the phylogenetic tree obtained with the TMSs showed a
more complex pattern, including a positional clustering of
consecutively ordered sequences (TMSs 1 and 2 or 11 and 12),
strongly supporting the idea that these modules could originate via
duplication. However, non-positional clustering (i.e., of TMSs that
are not necessarily contiguous) was also observed. This finding
could be explained by possible interactions between non-contig-
uous TMSs as reported for LacY.

The arrangement of the genes coding the trypanosomatids
hexose transporters in their respective genomes was also analyzed.
An interesting novelty is the fact that some trypanosomatids’
transporters are expanded into multiple tandem duplications, and
most of them are syntenic. This fact is contrasting with what is
found in the orthologs from other organisms, like the human or
crude GLUT1, both as single-copy genes located in the
chromosome 1 and 4, respectively, or Drosophila melanogaster
GLUT1, located in the chromosome 3 L, in all cases flanked by

Figure 3. Evolutionary trees of transmembrane spans and loops. Evolutionary tree using the TMSJ (A) or LJ (B) sequences. A maximum
likelihood method based on the JTT matrix-based model was used, with 500 bootstrap replicates. Trees with the highest log likelihood (~3067.0851
and ~4129.5431, respectively) are shown. Trees are drawn to scale, with branch lengths measured in the number of substitutions per site. In both
cases, sequences segregate into two main groups corresponding to the genera Trypanosoma and Leishmania. C: The mean distances for each group
of sequences analyzed (FL, TMS, TMSJ, S-TMSJ, NT, LJ and S-LJ) were calculated and are presented as similarity values.

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different pseudogenes. In synthesis, the genomic context is not conserved at all.

To summarize, as observed for the full-length sequences, phylogenetic analysis of the TMS, TMSJ and LJ sequences produced two major clusters that separated the sequences by genus. However, the phylogenetic trees constructed with the individual TMS sequences displayed the lowest mean distances, indicating that the TMSs are highly similar between proteins. This fact, together with the results obtained from the phylogenetic analysis, strongly supports the hypothesis that the loops are variable regions that are subject to the selective pressure of the immune system of the host. The TMSs, in contrast, are more constrained in terms of variation because they constitute the structural basis for the transport activity of the protein. The phylogenetic analysis of the pool of individual TMSs also showed their segregation in superclusters, some of which contain contiguous TMSs. This result indicates that the TMSs are positionally conserved and also suggests that the TMSs originated via intramolecular duplications. Nevertheless, the screening of the full-length sequences for internal repeats failed to detect consistently repeated sequences in the analyzed hexose transporters. The lack of data supporting duplications led us to conclude that the

Figure 4. Evolution of each transmembrane span individually. A: Evolutionary tree using the pool of individual TMS sequences. A maximum likelihood method based on the JTT matrix-based model was used, with 500 bootstrap replicates. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The tree with the highest log likelihood (−3119.4504) is shown. Two major superclusters are separated by a solid line in which numbers indicate the main positions for the grouped TMSs. Colored numbers indicate consecutive TMSs from each supercluster. Scale bar corresponds to distance expressed in amino acid substitutions per site. B: Similarity as a function of position was plotted to compare TMSJ against S-TMSJ, and LJ against S-LJ.

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ancestral trypanosomatid already had a hexose transporter with multiple TMSs. However, we cannot rule out the occurrence of these kinds of events, which were reported as frequent in the original formation of the modules constituting these molecules.

**Supporting Information**

**Figure S1** Evolutionary tree using the pool of individual L sequences. A maximum likelihood method based on the JTT matrix-based model was used, with 500 bootstrap replicates. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site.

**Figure S2** All 18 sequences were analyzed using the Multiple Em for Motif Elicitation (MEME) algorithm (http://meme.nbcr.net/). This analysis identified the motif QLTGINA (or the ‘‘GINA’’ motif), which was primarily present in TMS-6 and TMS-7. A. Sequence logo of the GINA motif. B. Conservation of the GINA motif in the analyzed sequences. C. Position of the GINA motif in the sequences.

**Figure S3** The *T. cruzi* hexose transporter sequence was modeled based on the known structure of the Major Facilitator Superfamily (MFS) member LacY from *E. coli*. Wire models of both transporters (*T. cruzi*: blue; *E. coli* LacY: yellow) are shown, with the *T. cruzi* structure overlaid on the *E. coli* structure. Both molecules appear to be heart shaped when represented in a view parallel to the membrane. The red arrow indicates the direction of movement of the substrate (from the extracellular to the intracellular side).

**Table S1** The number of amino acid substitutions per site between sequences is shown. Analyses were conducted using the JTT matrix-based model [21]. The analysis involved 216 amino acid sequences. All ambiguous positions were removed for each sequence pair. A total of 34 positions were included in the final dataset. Evolutionary analyses were conducted using MEGA5 [22].

**Dataset S1** Dataset of sequences in FASTA format.

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**Author Contributions**

Conceived and designed the experiments: CAP AMS. Performed the experiments: CAP AMS. Analyzed the data: CAP AMS. Contributed reagents/materials/analysis tools: CAP AMS. Wrote the paper: CAP AMS. Conceived the initial hypothesis: CAP AMS. Designed and ran the bioinformatic work: CAP AMS. Data analysis, processed and interpreted the results: CAP AMS.
33. Abramson J, Smirnova I, Kasbo V, Verner G, Kaback HR, et al. (2003) Structure and mechanism of the lactose permease of Escherichia coli. Science 301: 610–615.
34. Guan L, Mirza O, Verner G, Iwata S, Kaback HR (2007) Structural determination of wild-type lactose permease. Proc Natl Acad Sci U S A 104: 15294–15298.
35. Landfear SM (2011) Nutrient transport and pathogenesis in selected parasitic protozoa. Eukaryot Cell 10: 483–493.
36. Barrett MP, Tetaud E, Seyfang A, Bringaud F, Baltz T (1995) Functional expression and characterization of the Trypanosoma brucei procyclic glucose transporter, THT2. Biochem J 312 (Pt 3): 687–694.
37. Bringaud F, Baltz T (1994) African trypanosome glucose transporter genes: organization and evolution of a multigene family. Mol Biol Evol 11: 220–230.
38. Tetaud E, Bringaud F, Chabas S, Barrett MP, Baltz T (1994) Characterization of glucose transport and cloning of a hexose transporter gene in Trypanosoma cruzi. Proc Natl Acad Sci U S A 91: 8278–8282.
39. Tetaud E, Chabas S, Giroud C, Barrett MP, Baltz T (1996) Hexose uptake in Trypanosoma cruzi: structure-activity relationship between substrate and transporter. Biochem J 317 (Pt 2): 353–359.
40. Burchmore RJ, Landfear SM (1998) Differential regulation of multiple glucose transporter genes in Leishmania mexicana. J Biol Chem 273: 29118–29126.
41. Krishna S, Woodrow CJ, Burchmore RJ, Saliba KJ, Kirk K (2000) Hexose transport in asexual stages of Plasmodium falciparum and kinetoplastidae. Parasitol Today 16: 516–521.
42. Mueckler M, Caruso C, Baldwin SA, Panico M, Bleich I, et al. (1985) Sequence and structure of a human glucose transporter. Science 229: 941–945.
43. Hebert DN, Carruthers A (1992) Glucose transporter oligomeric structure determines transporter function. Reversible redox-dependent interconversions of tetrameric and dimeric GLUT1. J Biol Chem 267: 23029–23038.
44. Bunn RC, Jensen MA, Reed BC (1999) Protein interactions with the glucose transporter binding protein GLUT1CBP that provide a link between GLUT1 and the cytoskeleton. Mol Biol Cell 10: 819–832.