Review Article

Biosynthesis of Galactofuranose in Kinetoplastids: Novel Therapeutic Targets for Treating Leishmaniasis and Chagas’ Disease

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Cell surface proteins of parasites play a role in pathogenesis by modulating mammalian cell recognition and cell adhesion during infection. β-Galactofuranose (Galf) is an important component of glycoproteins and glycolipids found on the cell surface of Leishmania spp. and Trypanosoma cruzi. β-Galf-containing glycans have been shown to be important in parasite-cell interaction and protection against oxidative stress. Here, we discuss the role of β-Galf in pathogenesis and recent studies on the Galf-biosynthetic enzymes: UDP-galactose 4′-epimerase (GalE), UDP-galactopyranose mutase (UGM), and UDP-galactofuranosyl transferase (GalfT). The central role in Galf formation, its unique chemical mechanism, and the absence of a homologous enzyme in humans identify UGM as the most attractive drug target in the β-Galf-biosynthetic pathway in protozoan parasites.

1. Galactofuranose

β-Galactofuranose (β-Galf) is the five-member ring isomer of galactose (Figure 1). This rare sugar was initially found in several human bacterial pathogens including Mycobacterium tuberculosis, Escherichia coli, Salmonella typhimurium, and Klebsiella pneumoniae [1–4]. In M. tuberculosis, β-Galf is found in the arabinogalactan layer where it links the peptido-glycan and mycolic acid layers [1]. In E. coli and K. pneumoniae, it is present in the O antigen, while in S. typhimurium it is found in the T antigen [2–4]. In all of these organisms, the enzyme UDP-galactopyranose mutase (UGM) serves as the sole biosynthetic source of β-Galf as it is responsible for converting UDP-Galp to UDP-Galf (Figures 2 and 3) [5–10]. UDP-Galf serves as the precursor molecule of β-Galf, which is attached to the various components of the cell surface by galactofuranosyl transferases (GalfTs) (Figure 2) [11, 12]. UGMs and GalfTs are not found in humans, therefore, they have been examined as potential drug targets.

Deletion of the genes coding for UGM or GalfTs has shown that these proteins are essential in M. tuberculosis, highlighting the importance for Galf in bacteria [13]. Studies have also been conducted to identify inhibitors for M. tuberculosis UGM [14–17]. These studies showed that specific inhibitors of M. tuberculosis UGM were able to prevent mycobacterium growth and, therefore, validated Galf biosynthesis as a drug target against mycobacteria [14].

β-Galf has also been shown to be present in fungi [18–21]. In the human pathogen Aspergillus fumigatus, it is found in four components of the cell wall: galactomannan, glycoprotein oligosaccharides, glycophosphoinositol (GPI) anchored lipophosphogalactomannan (LPGM), and sphingolipids [18, 22]. Deletion of the UGM and the Galf transporter genes in Aspergillus resulted in attenuated virulence, increased temperature sensitivity, and thinner cell walls [23, 24]. Galf is also present in protozoan parasites and is a virulence factor [25]. In Leishmania spp., it is present in the lipophosphoglycan (LPG) and in glycosinositolphospholipids (GIPs). In T. cruzi, Galf is found in the GIPLs and glycoprotein oligosaccharides [26, 27]. This paper focuses on current knowledge on the biosynthetic pathway of β-Galf.
and its role in the pathogenesis of *T. cruzi* and *Leishmania* spp.

1.1. Overview of *T. cruzi* and *Leishmania* spp. *T. cruzi* is the causative agent of Chagas’ disease, which often develops severe cardiac complications in patients with the chronic form of the disease [28]. In the *T. cruzi* life cycle, the parasite undergoes three developmental stages as it is transmitted from the insect vector (triatomine bug) to mammals: trypomastigote (vector feces and mammalian bloodstream), epimastigote (vector midgut), and amastigote (mammalian smooth muscle) [29]. *Leishmania* spp. are the causative agents of leishmaniasis, which can manifest in three forms—visceral, cutaneous, or mucocutaneous—depending on the species [30]. In the *Leishmania* spp. lifecycle, there are two stages: the amastigote (mammalian host macrophages) and the promastigote stage (vector (sand fly) midgut) [30].

Current treatments are limited due to toxic side effects and cost, therefore new drugs are needed [31–33]. Lifecycle progression of both *T. cruzi* and *Leishmania* spp. is associated with changes in the carbohydrate composition on the cell surface. These changes are important for mediating host-pathogen interactions Galf levels and Galf-containing glycan are shown to be modulated throughout the parasite life cycles and are important for pathogenesis [26, 34–36]. As Galf biosynthesis has been shown to be an attractive drug target for other pathogens, enzymes involved in this pathway may also prove to be ideal drug targets for the treatment of Chagas’ disease and leishmaniasis.

2. Biosynthesis of Galf in Kinetoplastids

The biosynthesis of Galf begins with the uptake and metabolism of galactose (Gal). Gal is an epimer of glucose that differs only by the orientation of the hydroxyl group at the carbon 4 position. Gal is a component of lactose in milk, is present in grains and beets, and can be utilized for energy after conversion to glucose (Glc). Gal is also a major component of glycans, present in proteins and lipids in most organisms, ranging from bacteria to mammals. The metabolism of Gal occurs via the Isselbacher or Leloir pathways (Figure 2). In the Leloir pathway, Gal is converted to UDP-Gal by the enzyme UDP-glucuronosyltransferase (UGM) (Figures 2(c) and 3) [7]. UDP-Gal is the substrate for several UDP-galactofuranosyl transferases, which decorate many glycoproteins and glycolipids on the cell surface of *T. cruzi* and *L. major*.

2.1. *Galactofuranose-Containing Proteins and Lipids*. Galf is found in many major components of the glycocalyx of *Leishmania* spp. and *T. cruzi*. In *Leishmania* spp., and Galf is found in the lipopolysaccharide (LPS) and in glycoconjugates. While in *T. cruzi*, Galf is found in the GPI and glycoprotein oligosaccharides (Figure 4) [26, 27]. In this section, we will describe the structure and role in pathogenesis of known Galf-containing glycoconjugates.

2.1.1. Lipopolysaccharide (LPS) from *Leishmania*. LPS from *Leishmania* spp. has four components: a phosphoinositol lipid, a core oligosaccharide, phosphoglycan (PG) repeat units, and a cap (Figure 4(a)). β-Galf is found in the core structure where it plays a role in connecting the PG repeat units to the phospholipid [35, 46]. LPS has been found to be important for adhesion to the sandfly midgut, resistance to the human complement C3b, protection from oxidative stress, and prevention from phagosomal transient fusion [47–50].
2.1.2. **Glycoinositolphospholipids (GIPLs)**. GIPLs are free glycosylated phospholipids found in many kinetoplastids. Those found in *Leishmania* spp. and *T. cruzi* are considered unique due to the presence of β-Galf (Figures 4(b) and 4(c)) [26, 51–54]. GIPL structure is species and strain dependent and varies in expression levels throughout the life stages of the parasite [55–58]. GIPLs from *Leishmania* spp. are thought to be precursor molecules for the synthesis of the LPG core structure [59]. *L. major* GIPL-1 has been shown to be involved in parasite-host interactions and is thought to play an important role in establishing infection [57, 60].

GIPLs from *T. cruzi* include a class of phospholipids previously identified as lipopeptidophosphoglycans (LPPGs) [61–63]. The LPPGs were originally considered a separate class from the GIPLs due to the presence of contaminating amino acids during their purification; these amino acids have since been identified as part of the NETNES [27, 64]. The importance of GIPLs in *T. cruzi* is revealed by studies that show that it plays a role in antigenicity, both with rabbit and human sera [36, 53]. The antigenicity is thought to be primarily due to the terminal β-Galf residues either from the GIPLs or the O-linked mucins, as removal of β-Galf results in decreased levels of antigenicity [36, 53, 65]. It has also been shown that GIPLs play a role in attachment of the parasite to the luminal midgut of the vector *Rhodnius prolixus* [55]. *T. cruzi* modulates this interaction by altering GIPL expression levels during its life cycle, as epimastigotes have much higher expression of GIPLs than trypomastigotes [55, 65, 66].

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**Figure 2**: Biosynthetic pathways of Galf. (a) In the Leloir pathway, Galf is transported to the cytoplasm where it is converted to galactose-1-phosphate by galactokinase (GK). Galactose-1-phosphate uridyl transferase (GalPUT) and UDP-Glc 4′ epimerase (GalE) are involved in the synthesis of UDP-galactose. (b) Alternatively, galactose can be directly converted to UDP-galactose by the Isselbacher pathway by UDP-sugar pyrophosphorylase (USP). (c) UDP-Galactose is then converted to UDP-Galf by UDP-galactopyranose mutase (UGM), and UDP-Galf is subsequently added to the glycocalyx by Galactofuranosyl transferases (GalfT).

**Figure 3**: Reaction catalyzed by UDP-Galactopyranose mutase (UGM).
2.1.3. N-Linked Glycans. β-Gal is found in mannose N-linked oligosaccharides in several species of trypanosomatid flagellates including *T. cruzi*, *Leptomonas samueli*, *Herpetomonas samuellipessoai*, *Crithidia fasciculate*, and *Crithidia harmosa* [36, 67–70]. The glycan structures have been solved for *L. samueli*, *C. fasciculate*, and *C. harmosa* and are shown to be species dependent [67, 69]. β-Gal units are found as terminal sugars linked to mannose residues in high mannose type N-linked glycans [67, 69]. The role of N-linked glycans has currently not been significantly explored for *T. cruzi*.
2.1.4. *T. cruzi* O-Linked Glycans and Mucins. *T. cruzi* mucins are a family of GPI-linked glycoproteins with high levels of O-linked glycosylation [71]. Several studies have been conducted to determine the composition of the oligosaccharides bound to Thr and Ser residues in these glycoproteins [72–76]. In *T. cruzi*, the O-glycans are not linked to N-acetylgalactosamine as in mammals and other organisms; instead, they are linked to N-acetylgalcosamnine [77]. It has been demonstrated that these glycans vary highly among *T. cruzi* strains, and β-Galf is a component of the glycan structures of *T. cruzi* strains G, Tulahuen, and Dm28c; however, β-Galf is not found in *T. cruzi* strains CL-Brener and Y (Figure 4(e)) [72–74, 78, 79]. These mucins play an important role in parasite-host interaction by both protecting against host defense mechanisms and ensuring targeting of specific cells and tissues [71, 77].

### 3. Galactofuranose Is a Virulence Factor in Kinetoplastids

It has been shown that incubation of *L. major* or *T. cruzi* with Galf-specific antibodies blocks parasite binding to macrophages or mammalian cells, resulting in a 50–80% decrease in infection rates [60, 66, 80, 81]. It was further shown that the antibody specifically bound to the β-Galf present in GIPLs of *T. cruzi* and GIPL-1 of *L. major* [60, 66]. This suggests that β-Galf and the GIPLs of *T. cruzi* and GIPL-1 of *L. major* play a role in cell adhesion and infection. Furthermore, it was shown that macrophages incubated with p-nitrophenol-β-Galf were infected 80% less by *L. major*, while macrophages incubated with p-nitrophenol-β-Galp saw no decrease in infectivity [60]. Together, these results confirm that β-Galf plays an important role in parasite-host interaction and suggest that β-Galf biosynthetic enzymes are potential drug targets.

#### 3.1. UDP-Glucose 4'-Epimerase (GalE)

In *T. cruzi*, GalE is the first protein required for Galf biosynthesis [82]. GalE is classified as a short-chain dehydrogenase/reductase (SDR) with a conserved Tyr-X-X-X-Lys motif and a characteristic Rossmann fold structure for NAD(P)+ binding [38, 83]. GalE is a homodimer that consists of two domains, an N-terminal domain with the Rossmann fold and a C-terminal domain that binds the substrate, UDP-Glc [84, 85]. The catalytic site is located in the cleft between the two domains [84, 85]. The mechanism is shown to be conserved across species and involves the deprotonation of the Glc O4′ hydroxyl and hydride transfer from the C4 carbon of Gal to NAD+[84, 85]. The intermediate 4-keto sugar rotates in the active site and NADH transfers back the hydride to the opposite face forming UDP-Gal [84, 85].

Mutant strains of *T. brucei* and *T. cruzi* with deletion of the *gale* gene have not been obtained suggesting that Gal metabolism is essential for parasite survival [45, 82, 86, 87]. Conditional null mutants were created in *T. brucei* using tetracycline-regulated expression [45, 86]. Studies with this strain showed that removal of tetracycline from the trypomastigote parasite led to cell death and decreased Gal surface-expression levels by 30% [45, 86]. These studies showed that, upon Gal starvation, Gal was eliminated from *T. brucei* variant surface glycoprotein (VSG) and from poly-N-acetyllactosamine-containing glycoproteins causing cell growth to cease and differentiation to a stumpy-like form, ultimately leading to cell death [87].

Single *gale* knockout mutants of *T. cruzi* epimastigotes were also constructed [82]. These cell strains showed several phenotypic differences including shortened flagella and agglutination, which is thought to be the result of a lack of surface mucins [82]. Interestingly, these cell strains show a preference for expressing high levels of Galp-containing GIPLs over Galp mucins, whose expression levels were reduced 6–9-fold, suggesting levels of Galp is preferentially maintained in the glycoalyx over Galp [82].

Studies have been undertaken to identify novel inhibitors that specifically target the GalE of *T. brucei* [89, 90]. Using high-throughput screens and computer modeling experiments, inhibitors that showed preference to *T. brucei* GalE over human GalE were identified [89, 90]. However, when these compounds were tested *in vitro* with *T. brucei* and either mammalian CHO cells or liver (MRC5) cells, these compounds either were cytotoxic to both the parasite and mammalian cells or the compound was ineffective against *T. brucei* [89, 90]. These studies suggest that, while GalE remains a potential drug target, there will be many difficulties in designing specific inhibitors for the treatment of these diseases without unwanted side effects.

#### 3.2. UDP-Galactopyranose Mutase (UGM)

UGM is a flavo-dependent enzyme that catalyzes the conversion of UDP-Galp to UDP-Galf. UGM was first identified in *Escherichia coli* K-12 in 1996, and since then it has been identified in several other pathogenic microorganisms including *M. tuberculosis*, *L. major*, *T. cruzi*, and *A. fumigatus* [5–8]. Interestingly, while *T. cruzi* produces UGM the related *T. brucei* does not, and as a result, *T. brucei* does not produce Galp [70]. UGM has been found to be the sole biosynthetic source of Galp and since it is not found in mammals is considered an ideal drug target.

Deletion of the UGM gene in *L. major* shows that this enzyme plays an important role in pathogenesis [25]. In the absence of UGM, *L. major* mutants were completely depleted of Galf, lacked LPG PG repeats, and contained truncated forms of GIPLs [25]. Furthermore, mice infection by *L. major* lacking Galf was significantly attenuated [25]. As previously mentioned, deletion of UGM also showed that Galp is a virulence factor in *A. fumigatus* and *Aspergillus nidulans* [23, 95]. These studies show the importance of UGM and validate this enzyme as a drug target in protozoan and other eukaryotic human pathogens.

Although the reaction catalyzed by UGM does not involve a net redox change for the conversion of UDP-Galp to UDP-Galf, the reaction requires the flavin cofactor to be in the reduced form [96, 97]. Structural and mechanistic studies of the prokaryotic UGM have led to two proposals for the ring contraction mechanism (Figure 5). One mechanism
Table 1: UDP-galactopyranose mutases.

| Species               | Amino acids | % identitya | Oligomeric state | Reference |
|-----------------------|-------------|-------------|------------------|-----------|
| *E. coli*             | 367         | 100         | Dimer            | [91]      |
| *M. tuberculosis*     | 399         | 44          | Dimer            | [92]      |
| *L. major*            | 491         | 15          | Monomer          | b         |
| *T. cruzi*            | 480         | 15          | Monomer          | b         |
| *A. fumigatus*        | 510         | 14          | Tetramer         | [93]      |

aIdentity to the *E. coli* enzyme.
bOppenheimer and Sobrado unpublished results.

Figure 5: Proposed chemical mechanism for UGMs. Nucleophilic attack by the reduced flavin (1) leads to a flavin-galactose adduct (2). This step can either occur via an Sn1 or Sn2 reaction. Alternatively, the flavin can transfer one electron to a galactose oxocarbenium ion, forming a sugar and flavin radical that can also form the flavin-galactose adduct. Formation of a flavin iminium ion leads to sugar ring opening (4). Sugar ring contraction occurs by attack of the C4 hydroxyl to the C1-carbon (5). The final step is the bond formation to UDP (6).

depicts the reduced flavin acting as a nucleophile, attacking the anomeric carbon (C1) of Gal to form a flavin N5-C1 Gal adduct [98]. This adduct has been isolated and characterized in the prokaryotic UGM from *K. pneumoniae* [98, 99]. The other proposed mechanism involves a single-electron transfer from the reduced flavin to Gal, which then forms the sugar-flavin adduct [100].

Several structures have been solved for prokaryotic UGMs, in both oxidized and reduced states with and without substrate bound, providing excellent groundwork for the development of specific inhibitors [92, 99, 101]. The structure of prokaryotic UGMs show that it is a homodimer and a mixed α/β class protein with 3 domains: an FAD-binding domain with a typical Rossmann fold, a 5-helix bundle, and a 6-stranded antiparallel β-sheet [91, 101]. The structures of the reduced protein with substrate bound show that Gal is properly positioned for interaction with the flavin [99, 101].

Much less is known about the mechanism and structure of eukaryotic UGMs. These enzymes share low sequence identity, and the presence of inserts in the primary structure predicts significant structural differences (Figure 6). In fact, comparison of the oligomeric states between prokaryotic and eukaryotic UGMs indicates that quaternary structures vary among species (Table 1) [93]. Furthermore, our group, as well as others, has demonstrated that known inhibitors of eukaryotic UGM are not effective or have decreased potency against *L. major*, *A. fumigatus*, and *T. cruzi* UGMs [7] (Qi and Sobrado unpublished results). Therefore, mechanistic and structural work is urgently needed on the eukaryotic enzymes.

3.3. UDP-Galactofuranose Transferases. UDP-α-Galf is synthesized in the cytosol by UGM and is transported into the Golgi where it is attached to the LPG and GIPLs by galactofuranosyl transferases (GalfTs) [102]. Currently, all known linkages of Galf in *T. cruzi* and *Leishmania* spp. are in the β anomer conformation. The most extensively studied GalfT is LPG-1 from *L. major* and *L. donovani*. Studies on LPG-1 have revealed that it is localized to the Golgi apparatus, where it adds the β-Galf to the core LPG structure [102, 103]. LPG-1 is a metal glycosyltransferase with typical conserved motifs including a cytoplasmic tail, a transmembrane domain, and a DXD metal-binding motif [104]. LPG-1 has been shown to only be responsible for the addition of Galf to LPG and to not play a role in the addition of Galf in the GIPLs [103, 105]. Mutants with the deletion of *lpg-1* gene in both *L. major* and *L. donovani* show LPG-1 to be important for LPG formation. Due to the lack of LPG, the mutant strains with *lpg-1* gene deleted in *L. major* display
Figure 6: Multiple sequence alignment of UDP-galactopyranose mutases. Conserved amino acids found in the active site of bacterial UGM are marked with a star, and those involved in flavin binding are marked with arrowheads. Mt: *M. tuberculosis;* Ec: *E. coli;* Kp, *K. pneumoniae;* Tc: *T. cruzi;* Lm: *L. major;* Af: *A. fumigatus*. The program ClustalW was used to generate the alignment and Espript 2.2 to create the figure [94].
Figure 7: Alignment of *L. major* LPG-1 (XP001683753), *L. donovani* LPG-1 (ADG26596), *L. mexicana* LPG-1 (CAB6682), and ten putative *T. cruzi* GalTls. Putative *T. cruzi* GalTls were identified by BLAST search using *L. major* LPG-1 as the probe. The active site residues are shown in brackets, and the metal binding motif is represented with asterisks. The alignment was created as indicated in Figure 6.
attenuated virulence [103, 105]. These studies showed that LPG-1 could serve as a drug target in \textit{L. major}.

There are no published studies on the GalfTs from \textit{T. cruzi}. In order to identify GalfTs in \textit{T. cruzi}, a BLAST search was conducted using LPG-1 from \textit{L. major} as a template, and more than 30 putative proteins annotated as β-GalfTs in the \textit{T. cruzi} genome were identified [106, 107]. The top 10 putative GalfT sequences from the \textit{T. cruzi} BLAST search were aligned with the \textit{L. major} and \textit{L. donovani} LPG-1 showing high sequence identity between these sequences (Figure 7). These sequences all contain the proposed catalytic site and demonstrate redundancy of the genes [104]. Redundancy of GalfTs is common in many different species, as often different transferases are used for each linkage type based on anomericity, bond linkage, and the substrate acceptors for Galf [108]. Due to the high number of GalfTs within \textit{T. cruzi}, targeting GalfTs for drug design most likely would not be effective.

### 4. Concluding Remarks

To cause infection, protozoan parasites must recognize the mammalian host environment, bind and infect the target cells, and evade the immune system. Undoubtedly, the cell surface of these pathogens plays important roles in these processes. Current drugs are able to kill most of the parasites during treatment; however, these treatments do not eliminate all the parasites, presumably because they can “hide” in the intracellular forms. Modification of the cell surface sugar composition will alter the mechanism of infection. Enzymes involved in the biosynthesis of Galf have been shown to play a role in parasite growth and pathogenesis. GaEl is essential for growth in \textit{T. cruzi} and \textit{T. brucei}, while UGM, and LPG-1 are important virulence factors in \textit{L. major} [25, 82, 103]. Due to the presence of a GaEl homolog in humans, compounds that inhibit this enzyme have toxic side effects. Furthermore, this enzyme is not important for virulence in \textit{Leishmania} spp. UGM plays a central role in Galf biosynthesis and is the only source of UDP-Galf, which is the substrate for all the GalfT that attach Galf to the final sugar-acceptor molecules. Consequently, UGM emerges as an attractive drug candidate, as no homolog is found in humans [109]. The unique chemical structure of UGM suggests that specific inhibitors can be identified. Targeting UGM in \textit{T. cruzi} and \textit{L. major} will affect their virulence in humans and perhaps allow the immune system to effectively clear the parasite. Alternatively, inhibition of UGM will enhance the activity of other antiparasitic drugs. Such combination therapy might be necessary to combat these complex eukaryotic human pathogens.

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