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Chapter 6

The Endomembrane System of *Giardia intestinalis*

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Abstract

*Giardia intestinalis* is a protozoan that colonizes the small intestine of virtually all mammals, adhering to the mucosal epithelial cells. It is a cosmopolitan parasite and agent of giardiasis, which can lead to human diarrheal diseases. The *Giardia* life cycle presents two forms—the trophozoite and the cyst—which are responsible for infection and transmission, respectively. This cell has been considered an excellent model for evolutionary studies, even though there are controversial hypotheses as to whether this parasite is an early eukaryote or not. *G. intestinalis* has a unique and very basic endomembrane system. The trophozoite gathers a very small pack of membrane-bounded structures: nuclei, endoplasmic reticulum (ER), peripheral vesicles (PV) and mitosomes. These organelles are involved in many functions from regulatory aspects in gene expression as well as membrane traffic events. Two functional nuclei are observed in the parasite; they are always located symmetrically in the anterior region of the trophozoite. The ER and PV commonly share and accumulate functions in the secretory pathway, they are responsible for endocytosis and digestion processes. The mitosome is a mitochondria-related organelle that does not produce ATP and lacks several mitochondrial characteristics. During the parasite differentiation into cyst, different types of vesicles appear into the cell body: the encystation specific vesicles (ESVs) and the encystation carbohydrate-positive vesicles (ECVs). These vesicles work together to form the parasite’s cyst wall in order to ensure that the cell reaches the cyst stage. Interestingly, *Giardia* does not present a morphologically recognized Golgi apparatus. It has been claimed that during the encystation process, the ESVs could represent a Golgi-like structure, because this organelle presents some characteristics of that high eukaryotic Golgi apparatus. In this book chapter, we highlight the *G. intestinalis* endomembrane system, emphasizing their morphology, proteins involved in its organization as well as their functional role.

Keywords: parasite, morphology, giardiasis, ultrastructure
1. Introduction

1.1. Giardia and giardiasis

*Giardia* was observed for the first time by Antony Van Leeuwenhoek in 1681, but it was Lambl who described the cell morphological characteristics in detail and named it *Cercomonas intestinalis*. Subsequently, Blanchard changed the nomenclature in 1888 to *Giardia lamblia* [1–3]. The parasite is also known as *Giardia intestinalis*, *Giardia duodenalis*, *Giardia enterica* and *Lamblia intestinalis*. Currently, the preferred name is *G. intestinalis*.

The trophozoite of *G. intestinalis* inhabits the small intestine and causes the disease, whereas the cyst is protected by a cyst wall, can survive in adverse environmental conditions and thus is responsible for parasite transmission. Giardiasis starts when the cysts are ingested via food or contaminated water and reach the small intestine. The trophozoites emerge from the cyst wall and colonize the intestinal epithelium [4]. The emerged trophozoites adhere and spread out by binary divisions and form a monolayer over the intestinal mucosa provoking local inflammation and reduction in nutrient uptake. The parasites may reach the final portions of the intestine, becoming a cyst again, and they are liberated with the feces. The cysts can then infect new hosts [4]. Diarrhea is the main symptom of *G. intestinalis* infection, and giardiasis occurs in humans and several animals throughout the world. Giardial transmission between different species is frequent, and this characterizes giardiasis as a zoonotic disease [5]. The infection rates of giardiasis are associated with sanitary conditions since low rates are observed when sanitary conditions are implemented [6]. Giardiasis mainly affects children and is considered a cosmopolitan disease [7]. Several factors such as geographic area, group of analysis, sensitivity of the diagnostic methods and health care accessibility influence the prevalence rates reported [8]. The disease treatment is based in nitroimidazole-derived drugs (metronidazole, tinidazole and ornidazole), since metronidazole is the most widely used drug [9].

2. Endomembrane system

The endomembrane system of higher eukaryotes comprises of a number of structures, such as the endoplasmic reticulum, nucleus, Golgi, lysosomes, peroxisomes, autophagosomes and vesicles involved in different traffic pathways. Many theories have addressed the evolutionary origin of eukaryotic membranes; the most acceptable one is the invagination of plasma membrane, which is based on the similarity between the endoplasmic reticulum (ER) lumen to the environment [10, 11].

Although *Giardia* belongs to the eukaryotic group, it lacks some of the typical organelles found in eukaryotes; therefore, this parasite is an interesting model to study cell evolution. Mitochondria and peroxisomes are not present in this parasite, as found in morphological and biochemical studies. In addition, Golgi complex and vesicles of the endocytic pathway are incipient. On the other hand, *Giardia* trophozoites exhibit membrane structures that incorporate the cationic, membrane potential-sensitive fluorophore rhodamine 123 and reduce a tetrazolium fluorogen. Based on this observation, the existence of membrane-associated sites with some similarities to
mitochondria has been suggested; an aerobic flagellate presenting mitochondria was proposed to possibly be the ancestor of G. intestinalis [12].

The membrane system of G. intestinalis comprises a unique set of vesicles named peripheral vesicles and a much diffused endoplasmic reticulum network. Moreover, this cell possesses two nuclei with a very similar nuclear membrane complex as observed in higher eukaryote cells (Figure 1a). During the differentiation of trophozoite to cysts, two types of membrane-bounded vesicles appear, the ESVs and ECVs, and both act to build the cyst wall, which is a constitutive and important structure of cyst (Figure 1b). Deeper in the encystation process, we face a paradigm: is there a Golgi-like structure in Giardia? Some authors claimed that during the encystation process, the ESVs assume some Golgi characteristics [13].

Below, we will discuss each of the membrane-bounded structures that compose the endomembrane system of G. intestinalis (Figure 1).

3. Peripheral vesicles

G. intestinalis belongs to the Giardiinae family, and it has a unique organellar system formed by numerous small vacuoles named peripheral vesicles (PVs) (Figures 2–4, 5c, 9a). The PVs are oval, elongated and are 100–200 nm in size (Figure 2c); they are located in the cell periphery, right below the plasma membrane (Figure 2) [14, 15]. The PVs have a fundamental role in the endocytosis process as well as during the digestion and retrograde transport of the parasite [16, 17]. A number of cytochemical studies indicated resident enzymes, such as acid phosphatases, sulfur-binding proteins (SH) and glucose-6-phosphatase in the PVs. The localization of these proteins pointed that the PVs present compatible functions to those initial or late
endosomes [17]. The accumulation of gold-labeled macromolecules such as albumin, peroxidase, transferrin and low-density lipoprotein in PVs [15] reinforced this idea. Moreover, the cytochemical localization of acid phosphatase, a classical lysosomal marker, in these vesicles Kattenbach and colleagues [15] led to the suggestion that *G. intestinalis* presents an endosomal-lysosomal system that later on during evolution was subdivided into compartments such as early or late endosomes and lysosomes [17]. Besides the degradation function played by the PVs, to date, it is the only known organelle involved in the *Giardia* endocytic pathway that is capable of accumulating fluid phase and membrane-bound molecules [18].

Figure 2. Peripheral vesicles of *G. intestinalis*. Transmission electron microscopy (TEM) of vegetative non-encysting (a and b) and encysting (c) parasite. The peripheral vesicles (PV, arrows) are right below the plasma membrane (a–c) and present similar size, shape and location in both forms (a–c). Artificially colored (b). N, nucleus; A, axoneme; F, flagellum; ESV, encystation-specific vesicle.
demonstrated that these vesicles periodically open to the cell exterior either via a channel or by fusion with the plasma membrane and take up soluble material before closing again (Figure 4) [19]. The uptake of soluble material from the environment into PV is not selective, which is in contrast to further retrograde transport that allows only certain, yet undefined, substances to rapidly cross over into the proximal ER [19]. It has been demonstrated that three protein complexes are associated with the endocytic machinery in *Giardia*, showing a discrete localization in the cortical area of trophozoites by fluorescence microscopy [20, 21]. These protein complexes are the clathrin heavy chain (GlCHC), subunits of the AP2 heterotetramer (GlAP2) and Giardia dynamin-related protein (GiDRP) [20, 21]. Recently, a detailed protein interactome of GlCHC revealed all of the conserved factors in addition to a novel protein, a putative clathrin light chain [22]. However, there are no clathrin coated-vesicles in *Giardia*. It was claimed that the giardial clathrin is organized into static cores surrounded by dynamic interaction partners, which are most likely involved in the regulation of fusion between the plasma...
membrane and the PVs in a “kiss-and-flush”-like mechanism [22]. These factors are key components of the clathrin-dependent endocytic machinery in higher eukaryotes and protozoa alike.

4. Endoplasmic reticulum

Although electron microscopy revealed similar structures to endoplasmic reticulum (ER), there is still a controversy concerning the real presence of this organelle in Giardia. The cloning and characterization of SRα, a receptor for signal recognition particle (SRP) as well as the use of binding immunoglobulin protein (BiP), a ER resident 70 kDa heat shock protein, allowed the
identification of an extensive membrane system in *G. intestinalis* [23]. So far, the presence of an ER has been demonstrated in the parasite; moreover, three genes for protein disulfide isomerase (PDI) in *Giardia* were cloned and characterized, and its products were localized into ER [24]. Electron microscopy cytochemistry for glucose-6-phosphate, a resident ER enzyme, allowed the observation of an extensive reticular system in this parasite [17]. The ER presents a complex, bilaterally symmetrical organization that is distributed throughout the cell body (Figure 3). The presence of this archetypical eukaryotic organelle in *Giardia* has been called into question [16]. The ER in giardia trophozoites is composed by little tinny cisternae (Figure 3c), while during the encystation process, there is an increase in the ER cisternae number [17].

Although *G. intestinalis* has a conventional ER concerning the secretory trafficking, some elements are missing entirely, such as the post-translational modification machinery. The calnexin-calreticulin machinery, which acts in the quality control of N-glycosylated secreted proteins, is absent [25]. An extensive genomic and biochemical analyses demonstrated that the parasite lacks several nucleotide sugar transporters [26]. Thus, Asn-linked glycosylation in the giardial ER is limited to the addition of GlcNAc1–2 to proteins. A coordinated work among conserved machinery for translocation [27], and chaperones and members of the PDI family [28] support the co-translational import and folding of secreted proteins. Giardial PDIs play a major role in assisting the folding of the cyst wall proteins (CWP) [29].

It was proposed that the *Giardia*’s reticulum would be a tubule-vesicular network with ER functions as well as endosomes and lysosomes activities by connections with the peripheral vesicles (Figure 4) [19]. Based on that, the ER of *G. intestinalis* possesses different functions (e.g., protein synthesis, endocytic activities and extracellular material degradation), since it is a pluripotent compartment [19].

5. Nuclear envelope

One of the most intriguing features of *G. intestinalis* trophozoite is the presence of two nuclei with mirror symmetry (Figures 1, 2a and b, 5a). The nuclei are spherical or oval and symmetrically placed in the anterior portion of the cell (Figures 1, 2a and b, 8). Both nuclei are equivalent; they have the same amount of chromosomes, 2n = 10, and show a great homology when the nucleotide sequences are compared [30].

An inner and an outer membrane compose the nuclear envelope of higher eukaryote cells. The outer membrane is continuous with the ER membrane, which presents ribosomes engaged in protein synthesis. The inner nuclear membrane contains, in addition to the trilaminar membrane, filamentous proteins that form the nuclear lamina, which provides structural support for this membrane. The nuclear envelope of all eukaryotes is perforated by elaborated structures known as nuclear pore complexes [31].

The *Giardia*’s nuclear envelope displays different profiles, such as blebs in the outer nuclear membrane envelope. This structure could correspond to the formation of vesicles from the endoplasmic reticulum that forms the outer nuclear membrane (Figure 5) [32]. Close proximity
areas exist between the two nuclear membranes that become parallel but are distinct from the diaphragms found in nuclear envelopes of the eukaryotic cells [33]. Interestingly, the parasite pore complex distribution and clustering is different in each nucleus. *Giardia* nuclei are not identical; they seem to be either in different phases of chromosome condensation or they have different metabolic activity. Dividing nuclei displayed very few pore complexes, which is a characteristic of low metabolic activity and/or low nucleus-cytoplasm transport. The pore complexes in *G. intestinalis* are very uniform in size and shape, and they contain annular substructures (Figure 5b) that are similar to those of higher eukaryotic cells [33].

The parasite mitosis is not similar to other organisms, presenting different characteristics: (1) the nuclear envelope does not fragment completely during mitosis, leaving open places on the
nuclei poles. This type of division is named semi-open mitosis, because only the nuclear poles are open. The spindle microtubules penetrate into the nuclei by these open poles. (2) Each nucleus moves to the central portion of the parasite, and one of them is located in the dorsal region and another in the ventral region and (3) the spindle is observed in the telophase [34]. Moreover, the parasite does not synchronize the nuclei division, and thus it is possible to find cells with three or four nuclei [35]. During the encystation process, the parasite mitosis still occurs; this is similar to what happens in the trophozoite vegetative form [36]. The nuclear division starts in the initial stages of encystation process through a semi-open mitosis. Bridges that originate by the nuclear membrane fusion connect the parental daughter nuclei. This interconnection between the nuclei remains intact while the parasite is in the cyst form; this is a characteristic of this stage in the Giardia life cycle [36].

Encysting cells show intranuclear inclusions that are morphologically similar to the ESVs and the ER membranes (Figure 5c and d), which may be a result of nuclear envelope folding. The presence of these inclusions could indicate intense ER activity since it forms from the outer nuclear membrane [33].

6. Encystment

The encystment (or encystation) is the given name for the parasite differentiation process of a trophozoite into a cyst (Figure 6). This process consists of several events and occurs in response to environmental or chemical stimuli. The chemical stimulus is a set of an alkaline pH, an increase of bile concentration and the presence of lactic acid released by bacteria that live in the gut [37]. The encystation process is a key for the parasite virulence mechanism and is responsible for the change to a resistant form that can survive in the outside environment for subsequent infection of a new host. This process also promotes the parasite immune evasion and is target to vaccine and drugs development [38, 39].

The encystation process is characterized by a gradual transformation of a flagellated trophozoite—which looks like a cut half pear—into a different structure called the cyst (Figure 6). The trophozoites lose their abilities to adhere, and there is a folding of the ventral disc, followed by its fragmentation [40]. The cell becomes rounded, internalizes the flagella as in an endocytic process and finally a filamentous layer involving the parasite creating the cyst wall (CW). Its superficial filaments connect cyst clusters [40]. Two layers form the CW: a filamentous layer and a membranous layer [41]. Biochemical analyses have focused on the filamentous layer, which is composed by 57% of proteins and 43% of carbohydrates [42].

The main protein components are the cyst wall proteins 1, 2 and 3 (CWP1, 2 and 3) and the HCNCp that belongs to a new class of Giardia's proteins, known as cysteine-rich protein, differs from the variant surface proteins (VSP) [29]. The β-1,3-N-acetyl-D-galactosamine polymer (GalNAc) makes up almost 86% of the carbohydrates that compose the filaments layer of CW [42]. The GalNAc polymer forms the CW fibrils that are covered by protein clusters, such as the CWP1s [43].
6.1. Encystation vesicles

6.1.1. Encystation-specific vesicles (ESVs)

Before the formation of CW, in the beginning of the encystation process, large 1-μm vesicles known as encystation specific vesicles (ESVs) appear (Figures 2c, 5d, 7–10) [44]. The protein content of the ESVs is basically CWPs 1–3 (Figures 7a and 10) that originate in the endoplasmic reticulum; afterwards, the encystation vesicles emerge from endoplasmic reticulum points (Figures 7c and 9a) [45]. This mechanism is not fully understood; however, the available data points to two hypotheses: (1) the CW material concentrates in a specialized endoplasmic reticulum sub-compartment, and afterwards, a lateral segregation occurs [46] and/or (2) the CWPs transport to the ESVs through vesicles containing COPII followed by a homotypic fusion [47].

Figure 6. Encystation process of G. intestinalis. (a) Scheme of changes from trophozoite to a rounded oval cyst. (b) Scanning electron microscopy of encystation process showing the cell differentiation: the trophozoite internalizes the flagella, becoming oval. During encystation, the caudal flagella form a tail. At the end, the mature cyst presents a cyst wall and flagella are not seen anymore (unpublished).
The ESVs maturation is less controversial: about 15–24 h post-encystment induction, before the CWP secretion, the ESVs recruit sequentially membrane peripheral proteins [48]. Thus, the ESVs and their content enter in a maturation way in which the CWPs are post-translationally modified. The presence of the protein disulfide isomerase 2 (PDI2) in ESVs indicates a post-translational mechanism [49] as well the CWP2 C terminal region cleavage by a specific encystation protease [50] and by the phosphorylation of newly synthesized CWPs [51].

Figure 7. Encystation-specific vesicles (ESVs) during differentiation of *G. intestinalis* by confocal microscopy (a and b) and transmission electron microscopy (TEM) (c). (a and b) Immunofluorescence of the parasite induced to encyst *in vitro* for 21 h and labeled with an anti-CWP1 antibody against the cyst wall. In (c) ESVs are electron-dense, membrane-bounded vesicles. Note that some ESVs are close to the nuclei and endoplasmic reticulum (arrows). N, nuclei; A, axonemes (unpublished).
6.1.2. Encystation carbohydrate-positive vesicles (ECVs)

For a long time, the understanding of how glycopolymers are transported to build the sugar portion of the CW remained an open question. This was mainly due to the lack of a marker that could track the carbohydrate portion of *Giardia*’s CW with strong specificity [52]. Some researchers used the *Dolichos biflorus* agglutinin (DBA) lectin, which has specificity to the GalNAc glycopolymer, to label the cyst wall of other parasites such as *Toxoplasma gondii* [53, 54]. Midlej and collaborators [55] used the DBA lectin as a tool to track the sugar moieties of *G. intestinalis* CW and were able to identify the encystation carbohydrate-positive vesicles

![Figure 8. Three-dimensional reconstruction of encysting G. intestinalis. (a–f) Dual-beam microscopy and 3D reconstruction of 21-h encysted parasites. Seven parasites were reconstructed; ESVs are yellow (arrows) (Figs. a-b) and are distributed nearby the nuclei colored by light blue (N) (Figs. e–f). Cell membranes are in different colors (big contours) (unpublished).](image-url)
The ECVs are 0.2–2 μm membrane-bounded organelles (Figure 9). By electron microscopy, they are electron-lucent, whereas ESVs are electron dense (Figure 9). Moreover, the ECVs do not react with antibodies against CWPs (Figure 10) [55]. These vesicles are only in those encysting cells and are involved in the *Giardia*’s CW biogenesis. The origin of ECVs seems to be related to the rough endoplasmic reticulum, because a budding vesicle was detected from this organelle in a similar way to what happens with the ESVs [56]. Thus, both
secretion products are synthesized in the endoplasmic reticulum, budded together and are later separated and transported to the protozoan periphery to be secreted via exocytosis [55].

7. Mitosomes

Mitosomes are organelles described by Tovar and collaborators [57]. This name means “crypton” and was used to indicate it as reduced mitochondria. It is part of the mitochondria-related organelles as the hydrogenosomes found in Trichomonas [58]. Although the mitosomes are related to mitochondria, it lacks several mitochondrial characteristics and functions, such as ATP synthesis, the citric acid cycle, oxidative phosphorylation, heme biosynthesis, presence of DNA, lipid metabolism and the amino acid and urea cycles [59]. On the other hand, mitosomes present mitochondrial characteristics, such as biosynthesis of Fe-S clusters,
The presence of a TOM and TIM protein family transport machinery and a double membrane (Figure 11a–c) [60].

The mitosomes are small organelles, 200 nm in size, distributed over the cytoplasm, although some of them are placed between the flagellar axonemes. Because of that, they are divided into two distinct groups: the peripheral and central mitosomes (Figure 11d and e), which are dispersed in the cell and between nuclei, respectively [57]. The presence of an iron-sulfur complex (IscS and IscU proteins) makes its identification and characterization easier [61]. Mitosomes are also present, besides the IscS and IscU proteins, chaperones, such as Cnp60 and HSP70 [62]. During the encystation process, the mitosomes change their behavior, modulating Cpn60 and HSP70, and also alter their shape (Figure 11d and e) [62].

Figure 11. Mitosomes of *G. intestinalis*. Electron tomography (figures a–c) and super-resolution-structured illumination microscopy (SR-SIM) (figures d and e) of peripheral and central mitosomes. (a–c) Mitosomes in a non-encysted parasite are identified by their double-bound membrane (black arrows). Some mitosomes are elongated or ovoid organelles. (b) Three-dimensional reconstruction of mitosomes in green. (c) After reconstruction, the 3D model was placed on electron tomography micrograph. VD, ventral disc; M, mitosome; Mt., microtubules. (d and e) SR-SIM, vegetative cell (d) and cyst (e). Mitosomes are labeled using an antibody anti-IscU (green fluorescence). The super-resolution microscopy revealed that the central mitosome (white arrow) is seen as a unique tiny organelle between the nuclei (d). The spots of the central mitosome are better visualized in the inset, presenting a different axis angle (d). (e) Cyst mitosomes observed by SR-SIM. Nuclei are labeled with DAPI (blue) (from Midlej et al. [62]).
Thus, the current knowledge concerning mitosomes is still limited. There are a number of unanswered questions related to the biology of this organelle and its proteins as well as related to the importance of mitosomes in the parasite life cycle.

8. Golgi complex

There is still controversy regarding the presence of a Golgi complex in *G. intestinalis*. This organelle is usually characterized by the presence of several stacked cisternae, which are often located around the nucleus and close to the endoplasmic reticulum. Until now, an organelle that fits with these criteria has not been identified in *G. intestinalis*.

Some groups proposed a similarity between the ESVs and the Golgi complex [47, 52, 63–65] supported by: (1) COPI and COPII association with the ESVs [47]; (2) the ESVs are sensitive for Brefeldin A, a drug known to inhibit the anterograde Golgi cisternae movement [63]; (3) the ESVs dependence of GTPases Sar1 and Arf1 for biogenesis and maturation, respectively [64]. However, the ESVs present some characteristics that do not fit with those presented by a classical Golgi: (1) the ESVs appear only during the encystation process; (2) no classical Golgi markers such as GM130, galactosyl transferases or the trans-Golgi network marker Rab6 are present in the parasite; (3) the ESVs do not present morphological characteristics that define this organelle as a Golgi, in accordance with parameters that have been well defined for many years. This is considered a strong argument for the absence of a typical Golgi in *G. intestinalis* [65]. Thus, it is hard to directly test if the ESVs are in fact similar to the Golgi complex or if this organelle evolved independently.

9. Final remarks

The endomembrane system of *Giardia* is well adapted to changes that are encountered in the gut environment and outside the warm and nutritious body. The cysts ensure the efficacy of the parasite in host colonization. Despite the low complexity of organelles and machinery involved, *G. intestinalis* constitutes a model for the investigation of synthesis, transport and assembly of simple but highly effective biopolymers [43, 52].

There are several questions to be answered regarding the biology of Giardia—for example, the right pathway of endocytic and exocytic materials, the formation of the cyst wall, each protein segregation and polymerization in the formation of the cyst wall, the glycosylation phenomena of secreted proteins, the role of each nucleus in the whole process of the Giardia life cycle, among others.

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