Parasitology

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An overview on *Leishmania* (*Mundinia*) *enriettii*: biology, immunopathology, LRV and extracellular vesicles during the host–parasite interaction

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Abstract

One of the *Leishmania* species known to be non-infective to humans is *Leishmania* (*Mundinia*) *enriettii* whose vertebrate host is the guinea pig *Cavia porcellus*. It is a good model for cutaneous leishmaniasis, chemotherapeutic and molecular studies. In the last years, an increased interest has emerged concerning the *L.* (*Mundinia*) subgenus after the finding of *Leishmania* (*M.*) *macropodum* in Australia and with the description of other new/putative species such as *L. (M.) martiniquensis* and '*L.* (*M.*) *siamensis*'. This review focused on histopathology, glycoconjugates and innate immunity. The presence of *Leishmania* RNA virus and shedding of extracellular vesicles by the parasite were also evaluated.

Leishmaniasis

Leishmaniasis is a disease caused by protozoans of the sub-family Leishmaniinae (Jirků *et al.* 2012; Espinosa *et al.* 2016). Those parasites are transmitted by the bite of infected female sand flies from the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World (Young and Duncan, 1994). The protozoan is able to infect rodents, marsupials, canids, hyraxes, edentates and primates (Grimaldi *et al.* 1989; Akhoundi *et al.* 2016). According to the World Health Organization, *leishmaniasis is one of the six most important neglected diseases* (de Guerra *et al.* 2007). In Brazil, most cases are due to *Leishmania braziliensis* (tegumentary leishmaniasis) and *Leishmania infantum* (visceral leishmaniasis).

Leishmania enriettii and *Leishmania* (*Mundinia*) subgenus

Among the 50 species of *Leishmania* reported, approximately 20 are infectious to humans (Akhoundi *et al.* 2016). One of the *Leishmania* species that is non-infective to humans is *Leishmania* (*Mundinia*) *enriettii* (Muniz and Medina, 1948; Machado *et al.* 1994; Lainson, 1997), whose vertebrate host is guinea pig *Cavia porcellus* (Rodentia: Cavida). The subgenus *L.* (*Mundinia*) has been recently established to accommodate those members formerly included within the *L. enriettii* complex (Espinosa *et al.* 2016; Paranaíba *et al.* 2017). The subgenus was inspired by Mun (Muniz) and din (Medina) to pay tribute to the researchers that reported this parasite.

No autochthonous cutaneous leishmaniasis (CL) cases were reported in Australia until 2003. However, strong evidence of *Leishmania* infecting red kangaroos (*Macropus rufus*) was provided later (Rose *et al.* 2004; Dougall *et al.* 2009, 2011). Recently, the name *Leishmania* (*M.*) *macropodum* was formally defined (Barratt *et al.* 2017) and the informal name *Leishmania* '*australiensis*' was discontinued to avoid usage of a *nomen nudum* (Australian Government, 2016). Besides the Australian isolate, other species and/or putative members of the *L.* (*Mundinia*) subgenus were reported in several parts of the world. Those included *Leishmania martiniquensis* in Martinica and Thailand (Boisseau-Garsaud *et al.* 2000; Desbois *et al.* 2014; Pothirat *et al.* 2014; Liautaud *et al.* 2015) and different isolates of '*Leishmania siamensis*' in Thailand (Bualert *et al.* 2012; Kanjanopas *et al.* 2013; Chusri *et al.* 2014), United States of America (Reuss *et al.* 2012), Ghana (Kwakye-Nuako *et al.* 2015) and Central Europe (Muller *et al.* 2009; Lobsiger *et al.* 2010) (Fig. 1). Since '*L. siamensis*' is not a taxonomically valid name, it should be used between quotation marks (Barratt *et al.* 2017; Cotton, 2017; Steverding, 2017). Based on the available literature, more studies are still needed to ascertain their current taxonomic status of those species/isolates using molecular

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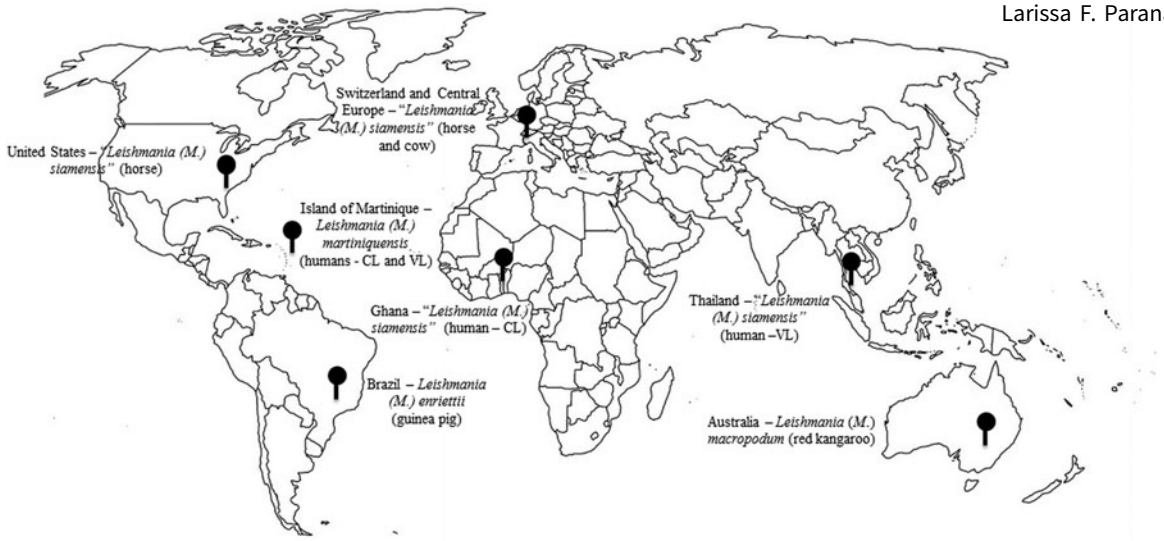

Fig. 1. Distributions and hosts of *Leishmania* species from the *L.* (*Mundinia*) subgenus. Legend: CL, cutaneous leishmaniasis; VL, visceral leishmaniasis.

approaches. This subject also opens the possibility of epidemiological studies in order to identify possible vectors and hosts.

Histopathology, glycoconjugates and innate immunity

The first histopathological description of *L. enriettii* lesion was reported soon after its discovery in guinea pigs. It is characterized by highly infected macrophages bearing a chronic inflammatory infiltrate, a profile very similar to other dermotropic *Leishmania* species (Medina, 2001). For this reason, *L. enriettii* has been successfully used as a CL model but it may vary depending on the host.

Similar to guinea pigs, hamsters may also develop and heal lesions. Nevertheless, those were not ulcerative and/or metastatic (Belehu and Turk, 1976). In red kangaroos, although a histopathological description was provided, it is still unknown if the lesions spontaneously healed in those hosts (Rose *et al.* 2004). Several studies of histopathological lesions caused by *L. enriettii* in guinea pigs were proposed (Paranaíba *et al.* 2015; Seblova *et al.* 2015). Depending on the strain, the lesions can appear between the third and sixth week and disappear between the 10th and the 14th week (Lobato Paraense, 1953; Bryceson *et al.* 1974; Medina, 2001). However, those papers did not use salivary gland extract (SGE) together with parasite inoculum to mimic natural transmission. Recently, two strains (L88 and Cobaia) of *L. enriettii* isolated in different years (1945 and 1985) exhibited different degrees of immunopathology in the guinea pigs. L88 strain was able to cause ulcerated lesions and those were exacerbated in the presence of SGE (Paranaíba *et al.* 2015). However, a missing step in the histopathology of *L. enriettii* is to compare different strains in the presence/absence of SGE.

Glycoconjugates of *Leishmania* are very important during the interaction of parasite and host. Lipophosphoglycan (LPG) and glycoinositolphospholipids (GIPLs) have been demonstrated to have an important role in the interaction with sand flies and the innate immune system (Assis *et al.* 2012; de Assis *et al.* 2012; Ibraim *et al.* 2013). The LPGs of L88 and Cobaia strains of *L. enriettii* were devoid of side-chains in their repeat units, similar to those found in *L. braziliensis* (Soares *et al.* 2005), *Leishmania donovani* (Sudan) (Sacks *et al.* 1995), *L. infantum* type I (Coelho-Finamore *et al.* 2011) and *Leishmania shawi* (Passero *et al.* 2015) (Fig. 2). Although the LPGs of both strains were similar, their GIPLs were polymorphic (Paranaíba *et al.* 2015). Further studies are still necessary to define the biochemical structure for *L. enriettii* GIPLs. Different from most *Leishmania* species, LPG and GIPLs from *L. enriettii* were very pro-inflammatory triggering the production of nitric oxide (NO) and pro-inflammatory cytokines [tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-12p40] in murine macrophages *via* TLR2/TLR4. Those properties varied intraspecifically where LPGs and GIPLs of L88 strain were more pro-inflammatory than those from Cobaia strain reflecting their immunopathology properties *in vivo*. L88 strain was able to cause ulcerative lesions, whereas Cobaia strain only developed a protuberance (Paranaíba *et al.* 2015).

In Table 1, it is possible to comparatively evaluate several innate immune components involved in LPG and GIPLs activation by

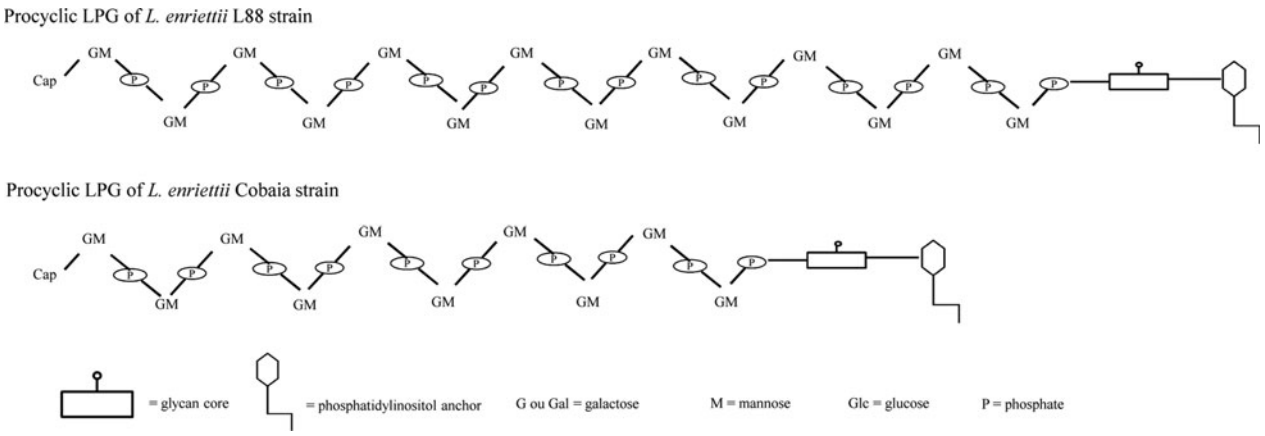

Fig. 2. Schematic diagram of lipophosphoglycan repeat units from *Leishmania enriettii* strains. The repeat units are 6-Gal(β1,4)Man(α1)-PO_4.

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Table 1. Innate immune components involved in LPG and GIPLs activation by different *Leishmania* species

Glycoconjugates/ species/strains	TH1										TH2			Receptors			Reference
	TNF-α	IL-1α	IL-1β	IL-2	IL-6	IL-12p70	IL-12p40	IFN-γ	IFN-β	NO	IL-10	IL-4	IL-5	TLR-2	TLR-4	NF-kB	
LPGs																	
Leishmania enriettii (L88/Cobaia)	+		–		+		+			+	–			+	+	+	Paranaíba *et al.* (2015)
Leishmania braziliensis (M2903)	+		+	–	+		–	–		+	–	–	–	+	+	+	Ibraim *et al.* (2013)
Leishmania infantum (BH46)	+		+	–	+		–	–		+	–	–	–	+	+	+	Ibraim *et al.* (2013)
Leishmania amazonensis (PH8/Josefa)	+		–		+		–			+	–			+	+	–	Nogueira *et al.* (2016)
Leishmania shawi (M15789)	+						+			+	+						Passero *et al.* (2015)
Leishmania major (Friedlin)	+						+							+		+	de Veer *et al.* (2003)
L. major (ASKH)	+							+						+		+	Becker *et al.* (2003)
Leishmania mexicana (M379)	+	+		+			+										Aebischer *et al.* (2005)
L. mexicana (N.D.)	+					+	+				+					+	Argueta-Donohué *et al.* (2008)
L. mexicana (N.D.)	+										+	–	–	+			Villaseñor-Cardoso *et al.* (2008)
Leishmania donovani (N.D.)	+									–						–	Privé and Descoteaux (2000)
L. donovani (AG83)							+			+							Balaraman *et al.* (2005)
L. amazonensis (Josefa)										+	+					+	Pereira *et al.* (2010)
L. amazonensis (Josefa)									+					+			Vivarini *et al.* (2011)
L. major (LV39)										+							Proudfoot *et al.* (1995)
GIPLs																	
L. enriettii (L88/Cobaia)	+		–		+		+			+	–			+	+	+	Paranaíba *et al.* (2015)
L. braziliensis (M2903)	+		–	–			–	–		+	–	–	–	+	+		Assis *et al.* (2012)

(*Continued*)

Table 1. (*Continued.*)

Glycoconjugates/ species/strains	TH1							TH2		Receptors			Reference
	TNF-α	IL-1α	IL-1β	IL-2	IL-6	IL-12p70	IL-12p40	IFN-γ	IFN-β	NO	IL-10	IL-4	IL-5	TLR-2	TLR-4	NF-kB	
L. infantum (PP75)	+		–	–			–	–		+	–	–	–	+	+		Assis *et al.* (2012)
L. shawi (M15789)	+						+			+	+						Passero *et al.* (2015)
L. major (Friedlin)	–						+							+		–	de Veer *et al.* (2003)
L. major (LV39)										–							Proudfoot *et al.* (1995)

N.D., strain not determined.

different *Leishmania* species. The higher pro-inflammatory activity of *L. enriettii* glycoconjugates may be important not only for the severity of the lesions in guinea pigs, but also for the activation of the immune system and subsequent healing. Most of those mechanisms are still unknown probably due to the lack of studies and the low veterinary importance of those animals.

Leishmania enriettii as a model for chemotherapeutic studies and molecular biology

Guinea pigs have the ability to spontaneously cure cutaneous lesions caused by *L. enriettii*. For this reason, chemotherapeutic tests with this parasite are very scarce and only few reports were available in the literature. This scenario is completely different from that of *Leishmania amazonensis*, another dermotropic species. This anergic species, commonly associated with treatment failure and natural drug resistance, is the most used model for *in vitro* chemotherapeutic studies (Rocha *et al.* 2013).

In 1961, *L. enriettii*-infected animals treated with Glucantime® exhibited a lesion regression. In spite of that, no effect was observed after *in vivo* treatment with Pentostam®, fuadin, tartar emetic and hydroxy-stilbamidine (Ercoli and Fink, 1962). Further, *in vivo* tests in *C. porcellus* and *in vitro* studies in macrophages infected with *L. enriettii* did not respond to treatment with furazolidone and nitrofurazone (Neal *et al.* 1988). On the other hand, levamisole-treated guinea pigs developed less severe lesions and metastases (Rezai *et al.* 1988). Aside from that, Glucantime® and Amphotericin B remain the first/second-line drugs for leishmaniasis treatment in different parts of the world. Occurrences of CL in kangaroos as an opportunistic agent (Dougall *et al.* 2011) highlights the importance of more studies in order to determine their role as hosts and perhaps to stimulate *in vivo* chemotherapeutic protocols for those and other animals.

Alike other *Leishmania* species, *L. enriettii* has been used as a model for molecular biology studies not only for developing transfection protocols but also for understanding multidrug resistance (MDR). Its LeMDR1 gene is an ABCB-type transporter having high similarity to mammalian phosphoglycan protein P and involved in vinblastine resistance (Chow *et al.* 1993). Resistance against this drug was demonstrated by many molecular approaches suggesting that accumulation inside intracellular compartments and further exocytosis was one of the mechanisms (Dodge *et al.* 2004). Later, vinblastine resistance mechanism was shown to be iron-dependent (Wong and Chow, 2006). More recently, synthetic flavonoid dimers were tested against pentamidin and sodium stibogluconate-resistant strains of *L. enriettii*. Some of those compounds, known to inhibit ATP-binding cassettes transporters, were able to reverse MDR in those parasites (Wong *et al.* 2007).

Some reports have looked at differentially expressed genes in *L. enriettii* in the two stages as a means to understand parasite developmental biology. During *Leishmania* life cycle, parasite alternates from a promastigote form in the sand fly to an amastigote form in the vertebrate host. Among several morphological changes, differentially expressed proteins are also observed such as tubulin. This protein is very important for flagellum assembly, a structure absent/unapparent in the amastigotes and their genes are tandemly arranged in the genome (Landfear *et al.* 1983). Although α- and β-tubulin genes are equally arranged in both forms, their mRNA expression levels are higher in the promastigote stage (Landfear and Wirth, 1985). Besides those studies on tubulins, two publications also reported on membrane glucose transporters. Glucose is a very important carbohydrate for trypanosomatids and its uptake occurs not only extracellularly, but also from the cytosol to the glycosome. They are also a family of tandem repeated genes, whose mRNAs were almost exclusively

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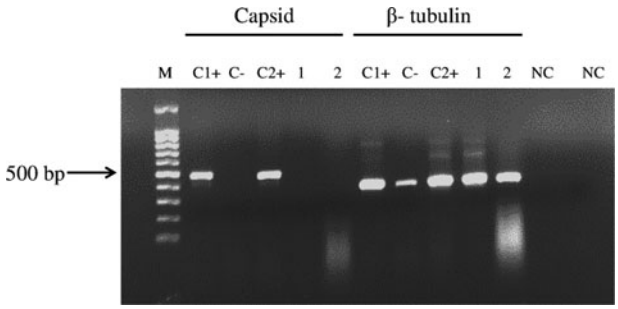

Fig. 3. LRV1/LRV2 absence in two *Leishmania enriettii* strains (L88 and Cobaia). Legend: M, molecular marker; C1+, LVR1-positive control (*Leishmania guyanensis* reference strain M4147); C−, LRV1-negative control (*Leishmania braziliensis* reference strain M2903); C2+, LVR2-positive control (*Leishmania major* reference strain ASKH); lane 1, strain L88; lane 2, strain Cobaia; NC, negative controls (capsid and *β*-tubulin).

expressed in the insect's promastigotes encoding for two isoforms (iso-1 and iso-2) (Stack *et al.* 1990; Langford *et al.* 1994). Later on, with the development of more advanced molecular protocols, alike other *Leishmania* species, *L. enriettii* was also used for transient and stable transfections with different genes (Laban and Wirth, 1989; Laban *et al.* 1990; Tobin *et al.* 1991). Those results were published in outstanding journals and were landmarks for standardizing those protocols in other *Leishmania*/trypanosomatid species. Although *L. enriettii* was used with the model for molecular biology studies, a lot is still to be accomplished, especially regarding virulence and target genes for parasite typing.

Leishmania enriettii: the *Leishmania* RNA virus and extracellular vesicles

The first report of viruses or virus-like particles (VLPs) uncovered in protozoans of the sub-family Leishmaniinae (Jirků *et al.* 2012; Espinosa *et al.* 2016) have been found in the promastigotes of *Leishmania hertigi* species in culture. The VLPs were immediately observed in the cytoplasm of these parasites when examined by the electronic microscope, particles were spherical with 55–60 diameter (Molyneux, 1974).

The *Leishmania* RNA virus (LRV) (Totiviridae) was reported to infect *Leishmania* species from subgenera *Viannia* (LRV1) and *Leishmania* (LRV2). LRV1 is a double-stranded RNA (dsRNA) virus first described in *Leishmania guyanensis* strains from the Amazon region (Guilbride *et al.* 1992). The molecular structure of the LRV2 virus is different from LRV1 (Scheffter *et al.* 1995). Many studies have found a correlation between LRV1 and severity of pathology, a mechanism dependent on TLR3 activation by the viral dsRNA (Ives *et al.* 2011). More recently, the finding of LRV was expanded in other Latin American countries including Bolivia, Peru and French Guiana (Adaui *et al.* 2016; Ginouvès *et al.* 2016; Macedo *et al.* 2016), confirming that biogeographically this virus seems confined to the northern regions of South America. The presence of LRV1-infected strains was already detected in a biopsy from patients with CL from Caratinga, Minas Gerais state, Brazil (Ogg *et al.* 2003). However, a presence of LVR1 in parasites isolated from patients was not detected in Minas Gerais state and other regions of Brazil, suggesting that the frequency of LRV1 in *L. braziliensis*

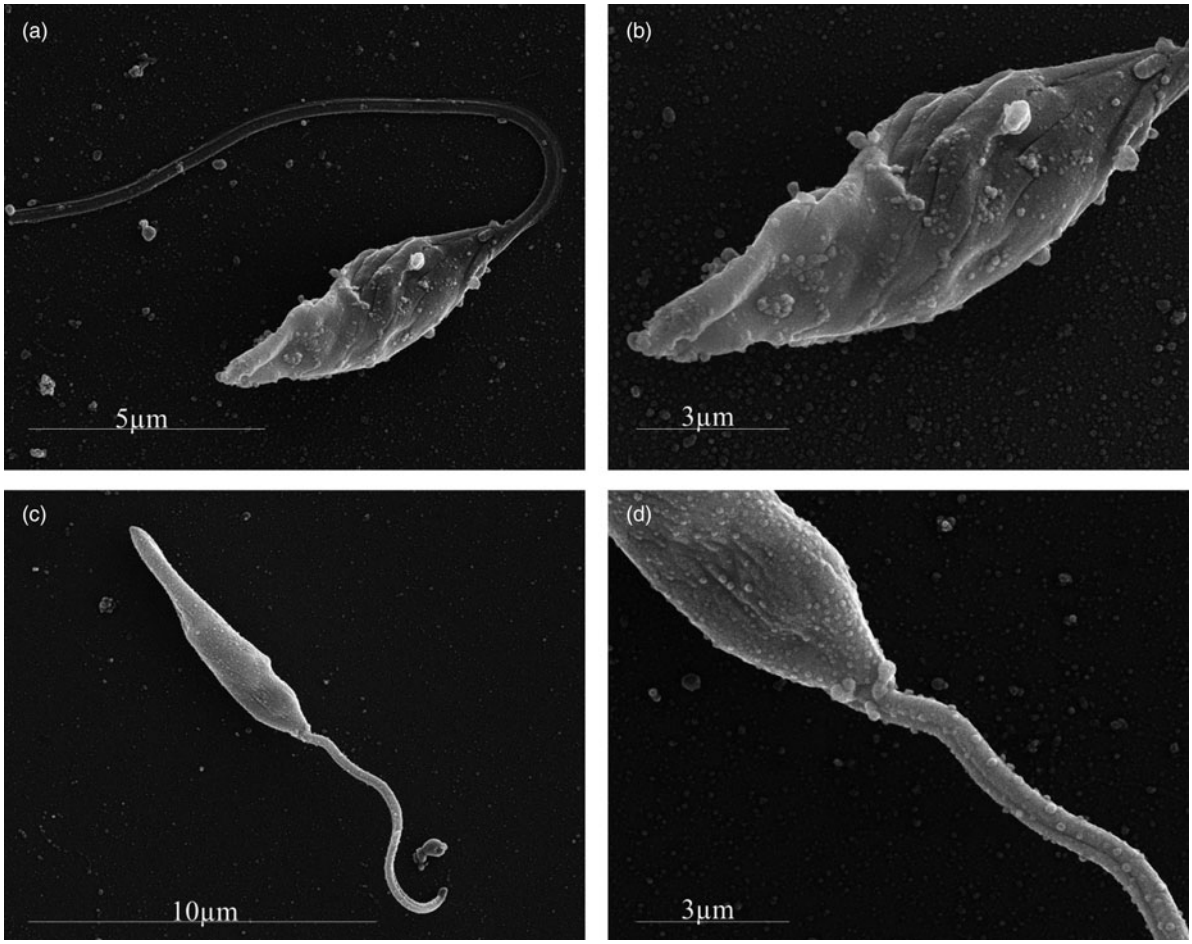

Fig. 4. Extracellular vesicles release by *Leishmania enriettii* strains (L88 and Cobaia strain). Scanning electron microscopy (SEM) of parasite membrane shedding after incubation in culture medium (a–d, bars: 3–10 *µ*m). (a, b) *L. enriettii* L88 strain, (c, d) *L. enriettii* Cobaia strain. Magnification: (a) 26 468; (b) 50 000; (c) 15 276 and (d) 50 000.

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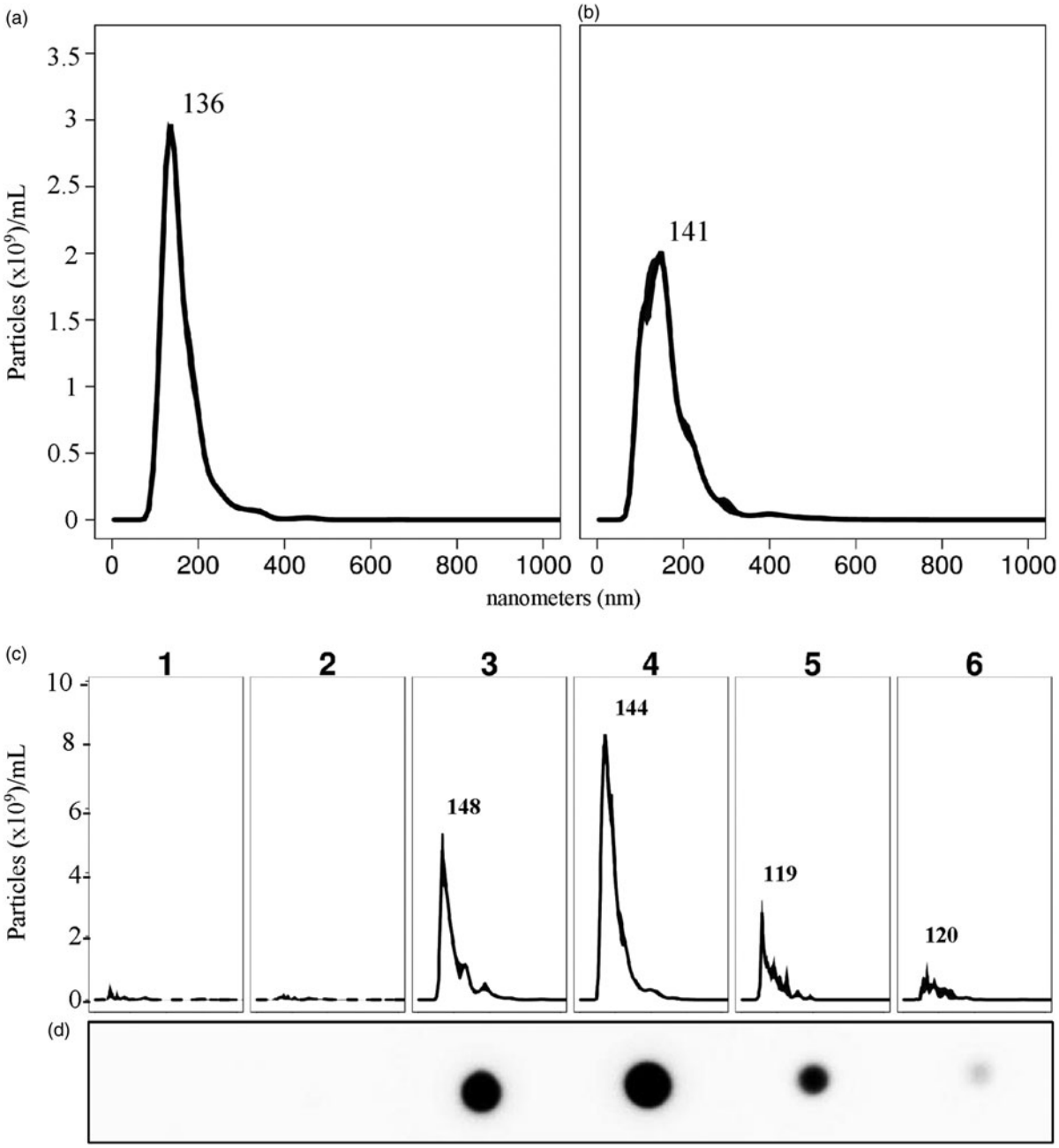

Fig. 5. Nanoparticle tracking analysis (NTA) and dot-blot from *Leishmania enriettii* strains (L88 and Cobaia). (a) NTA analysis from EVs released by L88 and (b) Cobaia strains (c); size exclusion chromatoghraphy (SEC) of EVs from Cobaia strain, and (d) gp63 detection of EV-containing fractions probed with mAb anti-gp63 (1:500).

strains seems to be very low in these localities (Pereira *et al.* 2013; Macedo *et al.* 2016). Regarding the *L.* (*Mundinia*) subgenus, the occurrence of LRV1/2 is a promising field for future investigations.

In this context, previous studies showed that L88 strain of *L. enriettii* caused more severe lesion than Cobaia strain (Paranaíba *et al.* 2015). However, no information on LRV1/LRV2 on *L. enriettii* was available at that time. A capsid PCR using primers for LRV1/LRV2 (Macedo *et al.* 2016) did not detect the virus in both *L. enriettii* strains (Fig. 3). Those data reinforced the role of the glycoconjugates in the severity of the pathology and perhaps are strain-specific. Those data are in accordance with previous published papers showing that LRV1 prevalence is higher in the Amazon and Northern parts of South America (Cantanhêde *et al.* 2015; Ito *et al.* 2015; Adaui *et al.* 2016; Ginouvès *et al.* 2016), whereas in the Southeast its finding is rare (Pereira *et al.* 2013; Macedo *et al.* 2016).

Another unknown aspect of the host–parasite interaction in *L. enriettii* is the release of extracellular vesicles (EVs) by the parasite. The first report on EVs in *Leishmania* was in *L. donovani* (Silverman *et al.* 2010). In this species, those vesicles abrogated immune response favouring parasite development by several mechanisms. A recent study has determined the role of EVs during the interaction between *L. infantum* and the sand fly *Lutzomyia longipalpis* (Atayde *et al.* 2015). EVs have been the focus of great interest not only in *Leishmania* but also in other pathogens [reviewed by (Marcilla *et al.* 2014; Campos *et al.* 2015; Szempruch *et al.* 2016)]. EVs have importance not only in intercellular communication but also during the host–parasite interaction not only in *Leishmania* but also in other parasites (Szempruch *et al.* 2016). For example, *Trichomonas vaginalis* EVs are determinant for tissue tropism and attachment, whereas in *Trypanosoma brucei* they confer resistance to trypanosome

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lytic factors (Stephens and Hajduk, 2011; Twu *et al.* 2013). In *Trypanosoma cruzi*, EVs were determinant during the invasion, adhesion and modulation of the immune system (Trocoli Torrecilhas *et al.* 2009; Torrecilhas *et al.* 2012; Nogueira *et al.* 2015). However, it is still unknown if these subcellular structures were present in *L. enriettii* strains. The basic vesiculation protocol was performed and both strains (L88 and Cobaia) shed vesicles, as demonstrated by scanning electron microscope (SEM) analysis (Fig. 4). Nanoparticle tracking analysis (NTA) quantitatively confirmed SEM studies (Fig. 5a and b). The EVs released by L88 and Cobaia strains had similar size distributions with modal sizes of 136 (±1·5) nm and 141 (±5·4) nm, respectively. After normalization by cultured parasite concentrations, a slightly higher amount of EVs was observed for the Cobaia strain. EVs from the Cobaia strain were isolated by size exclusion chromatography and fractions were analysed by NTA and dot-blot for the detection of gp63 (Fig. 5c and d). The gp63 glycoprotein is a virulence factor found in *Leishmania*-derived EVs resulting in some of their immunomodulatory properties (Hassani *et al.* 2014). Therefore, the detection of gp63 in the same fractions in which particles were detected by NTA, not only corroborates their vesicular nature but also suggests that *L. enriettii* EVs are likely to be involved in the immunomodulation of host cells. However, more studies are necessary to qualitatively compare the EVs contents, not only their surface antigens, but also their miRNA cargo. Those features could help to understand the differences in the immunopathology of both strains.

Concluding remarks

Many aspects of *L. enriettii* and the other newly members of the *L.* (*Mundinia*) subgenus are still unknown. This comprehensive review aimed to explore and update most of the knowledge of those protozoans. Regarding *L. martiniquensis* and '*L. siamensis*', many studies are still needed to address their current taxonomical status and to determine many epidemiological aspects, such as vertebrate and invertebrate hosts. In the case of *L. enriettii* from Brazil, there is still a lack of information on the wild reservoir and confirmation of the sand fly vector. Finally, we preliminary demonstrated the release of EVs by *L. enriettii* and demonstrate the absence of LRV1 and LRV2 in those strains. Those data reinforce the need for more studies in order to understand the complexity of factors involved in the immunopathology of this species in the host–parasite interface.

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