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Sphingosine 1 Phosphate in Cell Signaling with Emphasis in Protozoan Infections

Carolina López-Guzmán[1], Jaime Carmona-Fonseca[1] and Amanda Maestre[1*]

[1]Grupo Salud y Comunidad, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia,

*Corresponding author: Amanda Maestre, Grupo Salud y Comunidad, Facultad de Medicina, Universidad de Antioquia, Medellín, Carrera 51 D Numero 62-29, office 303, Colombia. Tel: 574 219 6024; Fax: 574 219 6000; E-mail: aemaestre@gmail.com

Abstract

Problem: Protozoan infections represent a serious public health problem requiring novel approaches from the basic science perspective. Sphingosine 1 phosphate (S1P), is an important component of plasma membrane and, in protozoan infections, a role in infection persistence has been noted. The aim of this review is to summarize the current knowledge about sphingolipids (SL), specifically S1P, and their involvement in protozoan infections such as malaria.

Methodology: A non-systematic review in the databases Pubmed, Embase, Free Medical Journals, and Lilacs databases was performed using the following keywords: sphingosine 1 phosphate, malaria, protozoa infections, sphingolipids, S1P receptor (S1PR), immunity, receptors, signaling. The search was limited to articles published between January 1995 and December 2014. Selection of articles to be included was based on relevance to the field of interest, regardless of the language.

Results: The number of articles retrieved and those which fulfilled the inclusion criteria were, respectively, 4455 and 143.

Conclusions: The role of sphingolipids in protozoan infections is poorly understood, especially in plasmodial infection. S1P might act as immune modulator. SL might be promoters of cell invasion and pathology. They also exhibit potential as antimalarials and biomarkers of infection.

Key words:

Sphingosine 1 phosphate; Malaria; Protozoan infections; Sphingolipids; S1P receptor; Immunity; Signaling.

List of abbreviations

CD11b: Cluster of Differentiation 11b; CD45: Cluster of Differentiation 45; Cer: Ceramide; CNS: Central Nervous System; COX-2: Cyclooxygenase 2; DC: Dendritic Cell; EDG: Endotelian Differentiation Gene; ERK-1: Extracellular Regulated Kinases 1; ERK-2: Extracellular Regulated Kinases 2; GPCR: G-Protein Coupled Receptors; HDL: High Density Lipoprotein; HER2: Human Epidermal Growth Factor 2 Receptors; IL-6: Interleukin-6; NK: Natural Killer; PGE2: Prostaglandin E2; PV: Parasitophorous Vacuole; S1P: Sphingosine 1 Phosphate; S1PR: Sphingosine 1 Phosphate Receptor; SGPP 1: Sphingosine 1 Phosphate Phosphatases 1; SGPP 2: Sphingosine 1 Phosphate Phosphatases 2; SL: Sphingolipids; SphK 1: Sphingosine Kinase 1; SphK 2: Sphingosine Kinase 2; SphK: Sphingosine Kinase; TNF: Tumor Necrosis Factor; TVM: Tubovesicular Membranes.

Introduction

Malaria is the most lethal protozoan infection observed worldwide and highly endemic in 97 countries [1], where an estimated 3200 million people are exposed to mala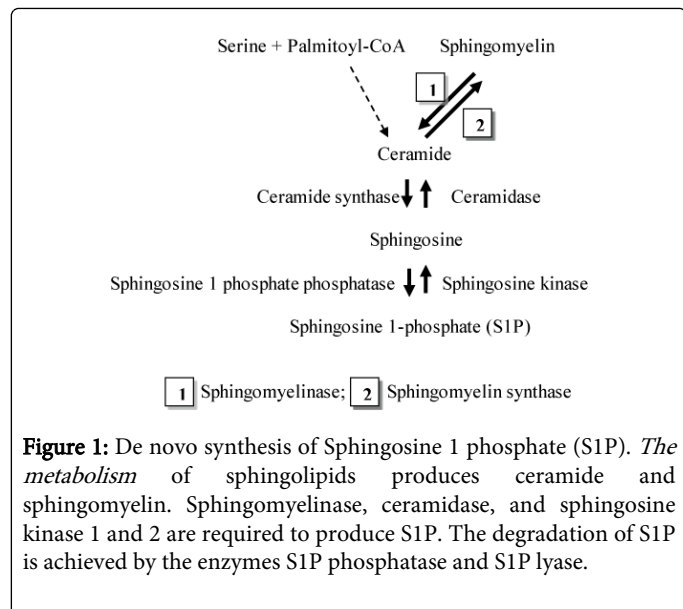ria [1]. Several basic mechanisms used by the parasite to induce disease or protection, remain to be elucidated, including the role of sphingolipids.

Sphingolipids (SL) are plasma membrane components in eukaryotic animal and plant cells involved in various signal transduction pathways [2,3]. Based on studies of their metabolism in animal models, some metabolites, particularly ceramide (Cer) and sphingosine 1 phosphate (S1P), are important signaling molecules in immunity and inflammation [4]. Knowledge of the particular characteristics of some of these metabolites may contribute to understanding the inflammatory processes that occur during several diseases and infections.

Among SL, S1P, a membrane phospholipid derived from the metabolism of sphingomyelin, plays an important role in inflammatory processes and is an important participant in cellular signalling of immune cells. [5-9].

Production of SL exerts different effects during protozoan infections. In some cases SL were reported to contribute to parasite´s survival, whereas in others they strengthen defense mechanisms by the host. [10,11]. In *Plasmodium spp.* SL are involved in the invasion process of the parasite into the host cell. [12]. However, little is known about the role of SL during plasmodial infection, including the mechanism of action and their effects on the host immune response. Furthermore, the function of some SL receptors in different cells of the immune system remains to be elucidated [13-15].

Inflammation is a crucial process in cell migration during protozoan infection and invasion. [2,16]. This process may involve de novo synthesis of various SL by the parasite [2] to promote survival and reproduction of the microorganism (Figure 1) [2].

Figure 1: De novo synthesis of Sphingosine 1 phosphate (S1P). *The metabolism* of sphingolipids produces ceramide and sphingomyelin. Sphingomyelinase, ceramidase, and sphingosine kinase 1 and 2 are required to produce S1P. The degradation of S1P is achieved by the enzymes S1P phosphatase and S1P lyase.

During plasmodial infection, inflammation is part of both the physiological and pathological responses, where hypoxia and tissue damage dominate [4,8,17,18]. Recent and ongoing studies are underway to expand and redirect research towards discovery of new molecules or metabolites which allow better characterization of the plasmodial infection [19].

Despite evidence of the participation of S1P in inflammatory responses, their specific role during invasion remains elusive. The aim of this review is to summarize the current knowledge about SL, specifically of S1P and their involvement in protozoan infections such as malaria.

Methods

A non-systematic review of the biomedical literature in the databases Pubmed, Embase, Free Medical Journals and Lilacs, was performed using the following keywords and combinations: sphingosine 1 phosphate (S1P), malaria, protozoa infections, sphingolipids (SL), S1P receptor (S1PR), immunity, receptors, signaling. The search was performed by one of the authors (CL-G) and limited to articles published between January 1995 and December 2014. Selection of articles was based on relevance to the field of interest, regardless of the language and included reports from studies in humans and animal models. The topics covered by this review are the following: Characteristics of sphingolipids, biosynthesis of S1P, characterization of S1P in the laboratory, expression of S1P in peripheral blood, activation and effects of the receptors for S1P (S1PR) in different cell populations, general actions of S1P, role of sphingolipids in protozoan infections, sphingolipids and plasmodial infections, role of S1P in plasmodial infection.

Results

The number of articles retrieved and those which fulfilled the inclusion criteria were, respectively: in Pubmed 4268 and 119, in Embase 37 and 2, in Free Medical Journals 100 and 18, in Lilacs 50 and 4. In total, 4455 articles were retrieved and 143 were selected.

Characteristics and biosynthesis of sphingosine 1 phosphate

SL is a complex lipid derived from sphingosine, an 18 carbon non-saturated amino-alcohol. Some SL possess a phosphate, known as phospho-sphingolipids (sphingomyelin), and some have a carbohydrate instead of a phosphate, and are known as glycosphingolipids (gangliosides, cerebrosides) [20,21]. All SL have three basic characteristics: a) a long-chain amino-alcohol called sphingosine (1, 3-dihydroxy-2-amino-4-octadecene); b) functional groups (- OH, NH2, - OH) are observed at carbons 1, 2 and 3; and, c) possess a ceramide residue. Ceramide is the fundamental structural unit of all SL and sphingosine is observed in all S1P [2,3].

Production of S1P is mediated by a sphingosine kinase (SphK), which has two isoforms, SphK 1 and SphK 2, with different physiological functions and cellular localizations. Each isoform is produced depending on the type of cell and the process that is required. For instance, SphK 1 is mainly localized to the cytosol, while SphK 2 can be detected in different intracellular compartments, including the nucleus and mitochondria [22,23]. Once S1P is phosphorylated by SphK 2, this acts as an endogenous histone deacetylase (HDAC) inhibitor and induces gene transcription [22].
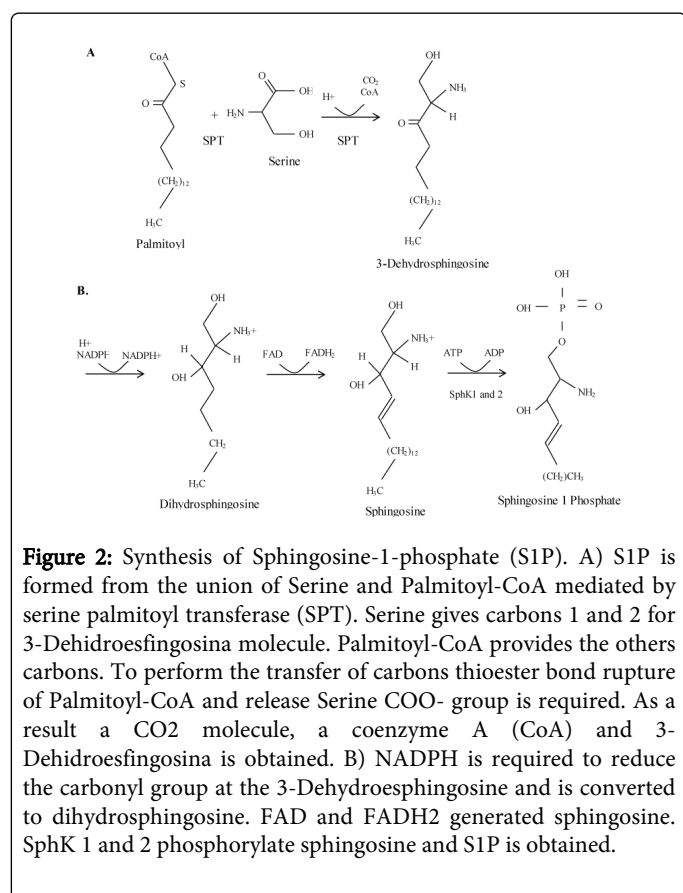
SphK 1 agonists include growth factors, hormones, and pro-inflammatory cytokines [4]. Phosphorylation of S1P via SphK 1 is associated with autoimmune diseases and cancer [4]. Therefore, inhibitors of SphK 1 are of great interest for development of novel therapeutic approaches based on modulation of cell proliferation and induction of apoptosis [4,22,24,25]. In contrast to SphK 1, SphK 2 suppresses cell growth and appears to increase apoptosis [24-28]. The basic aspects of the biosynthesis of S1P are presented in Figure 2 [20].

Characterization of S1P in the laboratory

In general, S1P is measured in human plasma [29,30] using different ELISA or EIA test [18]. In addition to the detection of free S1P [31], specific S1P receptors (S1PR1 - S1PR5) present in tissue, can be evaluated [32]. Analysis of SL in human samples requires assay standardization and validation in each laboratory in order to guarantee precision and reproducibility. The stability and concentration of these molecules can be easily affected if several variables are not controlled, including adequate selection of the technique, the experience of the personnel and precise control of the laboratory temperature [33]. Particularly in the case of S1P, levels increase after repeated cycles of freezing and thawing of the sample [33]. S1P values remain stable if plasma is obtained immediately after blood withdrawal [2, 29]. If plasma separation is delayed, S1P values might be above to 200 nM [2, 28, 29, 33]. Furthermore, red blood cells are rich in S1P (>2000 nM in 1×10^{10} cells, resembling a hematocrit of 100%), levels significantly rise if hemolysis occurs [3,30]. S1P and other SL can also be measured using hydrophilic interaction liquid chromatography (HILIC, SeQuant ™ ZIC ®-HILIC column) [34] and mass spectrometry [35-38].
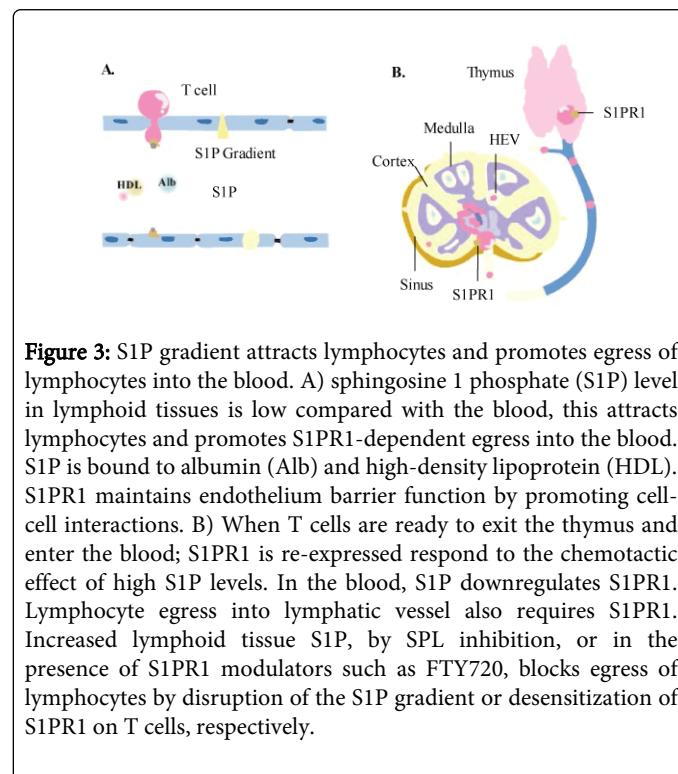
Expression of S1P in peripheral blood

Control of S1P levels is carried out by enzymes such as S1P lyase and sphingosine 1 phosphate phosphatases 1 and 2 (SGPP 1 and 2) [3,39]. The former degrades S1P in an irreversible manner, while the latter pair result in a reversible reaction [40,41]. Under normal physiological conditions, the highest levels of S1P are detected in the circulation [42,43] and they range from 200 nM in humans to 700 nM in mice [3,42,44]. This high content of S1P probably results from the absence of S1P lyase and the expression of SphK in these cells [3,4,44]. Accordingly, one can expect a rise of plasma S1P in conditions such as malaria, where hemolysis is significant. Other cell populations such as platelets and mast cells also produce and secrete large quantities of S1P but only when activated, therefore, they might not strongly affect basal levels of this SL [5].

Figure 2: Synthesis of Sphingosine-1-phosphate (S1P). A) S1P is formed from the union of Serine and Palmitoyl-CoA mediated by serine palmitoyl transferase (SPT). Serine gives carbons 1 and 2 for 3-Dehidroesfingosina molecule. Palmitoyl-CoA provides the others carbons. To perform the transfer of carbons thioester bond rupture of Palmitoyl-CoA and release Serine COO- group is required. As a result a CO_2 molecule, a coenzyme A (CoA) and 3-Dehidroesfingosina is obtained. B) NADPH is required to reduce the carbonyl group at the 3-Dehydroesphingosine and is converted to dihydrosphingosine. FAD and FADH2 generated sphingosine. SphK 1 and 2 phosphorylate sphingosine and S1P is obtained.

In the circulation, S1P attaches to high density lipoproteins (HDL) and albumin and it recognizes five types of cell membranes receptors, initially named Endotelial differentiation gene (EDG), but currently known as Sphingosine-1-phosphate Receptors (S1PR) [45-47]. S1PR exhibit differential affinity for diverse subunits of G-protein coupled receptors (GPCR) [48] and this is required for the multiple actions of S1P [46,49,50]. Endothelial cells mainly express S1PR1 and S1PR3, while lymphocytes and smooth muscle cells of vessels express higher proportions of S1PR1, S1PR2 and S1PR3 [51]. S1PR3, but not S1PR4 and S1PR5, is also expressed in cardiovascular tissue [52]. S1PR4 is expressed in hematopoietic and lymphoid tissues, while S1PR5 is mainly expressed in white matter of the central nervous system (CNS) and the spleen [5]. In addition, researchers reported in 2005 the presence of S1PR3 and S1PR5 in placental tissue [53], and, in 2008, the presence of S1PR1, S1PR2 and S1PR3, was confirmed in this tissue [54].

S1P effects vary according to the receptor activated at the cellular level. Accordingly, S1PR1 appears to play an important role in lymphocyte egress from the thymus and secondary lymphoid tissues [55] (Figure 3). Meanwhile, S1PR2 induces expression of COX-2, which in turn increases production of prostaglandin E2 (PGE2). Therefore, the inhibition of S1P/S1PR2 axis-dependent signalling pathways might represent a novel approach in the treatment of chronic inflammatory diseases [9,56].

Figure 3: S1P gradient attracts lymphocytes and promotes egress of lymphocytes into the blood. A) sphingosine 1 phosphate (S1P) level in lymphoid tissues is low compared with the blood, this attracts lymphocytes and promotes S1PR1-dependent egress into the blood. S1P is bound to albumin (Alb) and high-density lipoprotein (HDL). S1PR1 maintains endothelium barrier function by promoting cell-cell interactions. B) When T cells are ready to exit the thymus and enter the blood; S1PR1 is re-expressed respond to the chemotactic effect of high S1P levels. In the blood, S1P downregulates S1PR1. Lymphocyte egress into lymphatic vessel also requires S1PR1. Increased lymphoid tissue S1P, by SPL inhibition, or in the presence of S1PR1 modulators such as FTY720, blocks egress of lymphocytes by disruption of the S1P gradient or desensitization of S1PR1 on T cells, respectively.

In the placenta, *in vitro* tests using BEWO cells (trophoblast lineage), confirmed the importance of the interaction between S1P and S1PR2 to regulate secretion of pro-inflammatory cytokines such as IL-6 [57]. In other tissues, S1PR3 reduces production and secretion of pro-inflammatory cytokines by CD45 (+), CD11b (+), Gr1 (-) and Ly6C (-) cells [58]. This receptor is involved in regeneration of damaged tissues and arteriogenesis without impairment of macrophage phagocytic activity [58]. In some monocytes exhibiting an anti-inflammatory subtype profile, the expression of S1PR3 is predominant [59].

High levels of S1PR4 are associated with malignancy. For instance, in breast cancer, the receptor can be used as a biomarker to establish prognosis [60]. In addition, S1P binding to S1PR4 stimulates activation of extracellular regulated kinases 1 and 2 (ERK-1/2). ERK-1/2 act on human epidermal growth factor 2 receptors (HER2) [61]. The functional interaction of S1PR4 with an oncogene (HER2) provides evidence that S1PR4 might have an important role in breast cancer progression [60-63].

Finally, S1PR5 was implicated in NK cells and monocytes migration [64], but controversial results were reported in mice in which S1P was not involved in chemotaxis of monocytes [65]. Table 1 describes the

association between S1PR and the actions on cells of the immune system. Collectively, these reports confirm the importance of S1P on cell migration and inflammation in the immune system and the ubiquity of their receptors present in diverse cell types and in several tissues.

Cell Type	Receptor	Functions			
		Chemotaxis	Differentiation	Effector Responses	References
Innate immune cells					
Dendritic cells	S1PR1	↑/↔	↑	↑	[13,99,100]
	S1PR2	ND	ND	ND	[13]
	S1PR3	↑	↑	↑	[14,101]
	S1PR4	ND	ND	ND	[13]
	S1PR5	ND	ND	ND	[13]
Eosinophils	S1PR1	↑	ND	ND	[102]
	S1PR2	ND	ND	ND	[102]
	S1PR3	ND	ND	ND	[102]
Macrophages	S1PR1	ND	ND	↑	[103,104]
	S1PR2	↑	ND	↑	[104]
Mast cells	S1PR1	↑	ND	ND	[15]
	S1PR2	↓	ND	↑	[15,105]
NK cells	S1PR5	↑	ND	ND	[64,106,107]
Neutrophils	S1PR1	↑	ND	ND	[108,109]
Adaptive immune cells					
T cells	S1PR1	↑	↑	↑/↓	[76,110]
	S1PR4	↑/↔	↓	↓	[111,112]
B cells	S1PR1	↑	ND	ND	[113]
	S1PR3	ND	ND	ND	[113]
NKT cells	S1PR1	↑	ND	ND	[107]
	S1PR2	ND	ND	ND	[107]
	S1PR4	ND	ND	ND	[107]

Table 1: S1P receptors and effects on immune cells. (↑) denotes a stimulatory effect on the indicated immune function; (↓) inhibition; (↔) no effect on function; ND indicates that this was not determined. Table adapted from [5].

General actions of S1P

S1P exerts intracellular (as a second messenger) and extracellular (binding to GPCR) functions [7,66,67]. S1P is highly bioactive and is involved in diverse physiological processes with several patho-physiological effects at the cellular level including growth regulation, death, senescence, apoptosis, differentiation, proliferation, migration, adhesion, inflammation, cytoskeleton re-organization, angiogenesis, [60,68,69], and interleukin secretion [57,70], among others. In addition, roles in multiple sclerosis [7], cancer [62,71,72], atherosclerosis [73] and osteoporosis [74,75], are reported. Characteristically, S1P can act in an autocrine or paracrine fashion [4].

Taking into account the above, the SphK/S1P/S1PR axis is of interest for researchers exploring diverse aspects of inflammation. Activation of this axis results in emergence of T cells from the thymus [76] (Figure 3), exit of lymphocyte from lymphoid organs [77] and in turn, promotes the release of mature NK cells from bone marrow sinusoids [64,65]. Furthermore, expression of diverse pro-inflammation interleukins [57] can be induced by activation of this axis. In organs such as the placenta, S1P exhibits dual actions during diverse conditions. On one hand, S1P regulates endothelial permeability and vascular tone [78] and participates in proliferation, growth, and formation of the syncytiotrophoblast [79]. On the other hand, S1P inhibits placental trophoblast differentiation during pre-eclampsia [53].

Several S1P agonists and antagonists have been used to simulate and study its biological effects; some of these are listed in Table 2. Among the agonists widely studied is FTY720, a pro-drug that is endogenously phosphorylated (FTY720-P) [80] which inhibits egress of lymphocytes from lymphoid organs by promoting internalization and degradation of S1PR1 in these cells [76]. This effect results in immune-suppression, preventing transplant rejection and inducing clinical improvement in cases of multiple sclerosis [80].

Name	Mechanism	Disease	References
FTY720 (Fingolimod,Gilenya)	-Prodrug; phosphorylated by SphK2. -S1PR1, S1PR3-5 agonist - Downregulates S1P1	-FDA approved for multiple sclerosis* -Dermatitis, Arthritis, Allergy	[13,80]
SK1-1 (BML-258)	-SphK1 inhibitor	-Glioblastoma -Leukemia	[114,115]
Safingol L-threo-dihydrosphingosine	-pan SphK inhibitor	-Solid tumors (Phase 1)*	[116]
SK1-2	SphK1 inhibitor Induces proteasomal and lysosomal degradation of SphK1	-Pancreatic cancer -Leukemia	[117,118]
ABC294640	SphK2 inhibitor Estrogen receptor agonist	-Cancer -Inflammatory bowel disease	[119,120]
ABC294735	pan SphK inhibitor	-Cancer	[121]
SKI-II (SKI-2, SPHK I2)	SphK1 inhibitor	-Asthma	[122]
THI 2-acetyl-4(5)-[1(R)	S1P Lyase inhibitor	-Ischemia/reperfusion injury	[123]
LX2931	S1P Lyase inhibitor	-Rheumatoid arthritis (Phase II) *	[124]
SKI 5C	SphK1 inhibitor	-Sepsis	[125]
SEW2871	S1PR1 agonist	-Diabetic nephropathy -Renal protection	[126,127]
JTE013	S1PR2 antagonist	-Anaphylaxis -Cancer	[128] [71]
AAL®	Prodrug; phosphorylated by SphK2 S1PR1/S1PR3 agonist	-Influenza	[129]
AUY954	S1PR1 agonist	-Experimental autoimmune neuritis	[130]

Table 2: Small molecules targeting S1P and applications in health. *Effects in humans. All other compounds have only been tested in animal models.

Role of sphingolipids in protozoan infections

SL are involved in the interactions between the parasite and their host cells, and potentially contribute to survival of the parasite and the host´s defense [10]. The following section summarizes the current knowledge on SL, their synthesis and their role in several of the major groups of parasitic protozoan.

Trypanosomatids are a group of protozoa of which *Trypanosoma cruzi*, *Trypanosoma brucei* and *Leishmania spp.* are notorious in causing disease in human populations. These parasites infect 20-30 million people worldwide and tropism for different tissues is reflected in the wide range of conditions: from self-limited skin lesions to life threating brain, intestine and heart damage [81,82]. Other protozoa such as *Toxoplasma gondii*, *Giardia spp.* and *Entameoba histolytica*, are also pathogens with a wide geographic distribution and can result in severe disease in humans [10,83].

SL can present as intracellular lipids or transport proteins [84,85], and controversy remains as to the ability of parasites to uptake and process ceramide and gangliosides already present in the host cells [86]. More clear is the fact that SL are important for protozoa as they are involved in invasion, and parasite survival and multiplication under adverse conditions [2]. It was reported by Pratt, *et al.* that *de novo* synthesis of inositolphosphoryl ceramide is involved in *T. gondii* multiplication, particularly when the parasite undergoes stress [2]. Table 3 details the different types of SL observed in the life cycle of some protozoa.

Sphingolipids and plasmodial infections

Many facts about *Plamodium spp.* metabolism and other biological processes such as invasion remain unknown. Therefore, studies aimed at understanding crucial survival paths of the parasite might result in development of novel therapeutic approaches.

As discussed earlier, the location of SL in the cell membrane is highly strategic in several vital processes of parasites. Particularly in *Plasmodium spp,* cell invasion can be strongly affected by the presence and characteristics of SL. This was known experimentally with measures of viscosity and thermal fluctuations of the RBC membrane [12]. *Plasmodium spp* have the potential to invade and colonize erythrocytes of any age, depending on the species. Once inside the erythrocyte, the parasite cytoplasm and cell membrane undergo major changes [87] in order to modify the erythrocyte cytoskeleton and the environment and to evade specific immune responses [87]. One of the features of *Plasmodium spp* infected erythrocytes is an increase in sphingolipid synthesis [88]. While uninfected, erythrocytes membranes are impermeable to sphingomyelin, but the membrane of infected cells allows two-way passage of SL and nutrients [88,89].

Species	Sphingolipids identified	References
Leishmania major	SM, IPC	[131,132]
Trypanosoma brucei	IPC	[133]
	EPC (in peripheral blood)	[134]
	SM	[135]
	Glycosyl-cer	[136]
Trypanosoma cruzi	SM, IPC	[137,138]
Toxoplasma gondii	Glycosyl-cer, SM, IPC	[2,139]
Trichomonas vaginalis	SM, IPC	[140]
Giardia lamblia	SM	[83]
Plasmodium falciparum	Glycosyl-cer, SM	[88,141,142]

Table 3: Sphingolipids in parasitic protozoa. SM: Sphingomyelin; IPC: Inositolphosphoryl Ceramide; EPC: Ethanolamine Phosphorylceramide.

Intracellular development of *P. falciparum* depends on the formation of a cytosol system consisting of a novel network of tubovesicular membranes (TVM) within the host cell [90-92]. The parasitized cell membrane (PM) and an inner parasitophorous vacuole (PV) originate in the parasite. The TVM network is in charge of repairing the gap caused by the parasite after invasion and is induced during the intra-vacuolar development of the parasite [90-92]. The sphingomyelin formation by the parasite is an essential requirement for construction of the TVM [90,91,93] (Figure 4). SL are important constituents during the process of cell invasion by the parasite, and are major determinants of the immune response elicited by the invasive micro-organism.

Role of S1P in plasmodial infection

During infection, a group of SL facilitates cellular infection and damage, but another group contributes to damage attenuation [18]. Sphingosine 1 phosphate is part of the later and has a protective effect, particularly during cerebral malaria [18]. However, the role of S1P has not been explored in other forms of malaria. Further involvement of S1P in other severe manifestations of the disease might be expected as additional studies are performed.

One of the mechanisms which might be involved in the protection observed during severe malaria might include reduced activity of S1P

lyase. Studies on an experimental model of *Plasmodium berghei* ANKA (PbA) confirmed that S1P lyase deficiency led to high S1P bioavailability and reduction in severity, with higher survival rates [18]. Compounds with a proven effect on the regulation of S1P in mice have been tested in humans in the context of modulation of the immune system [18].
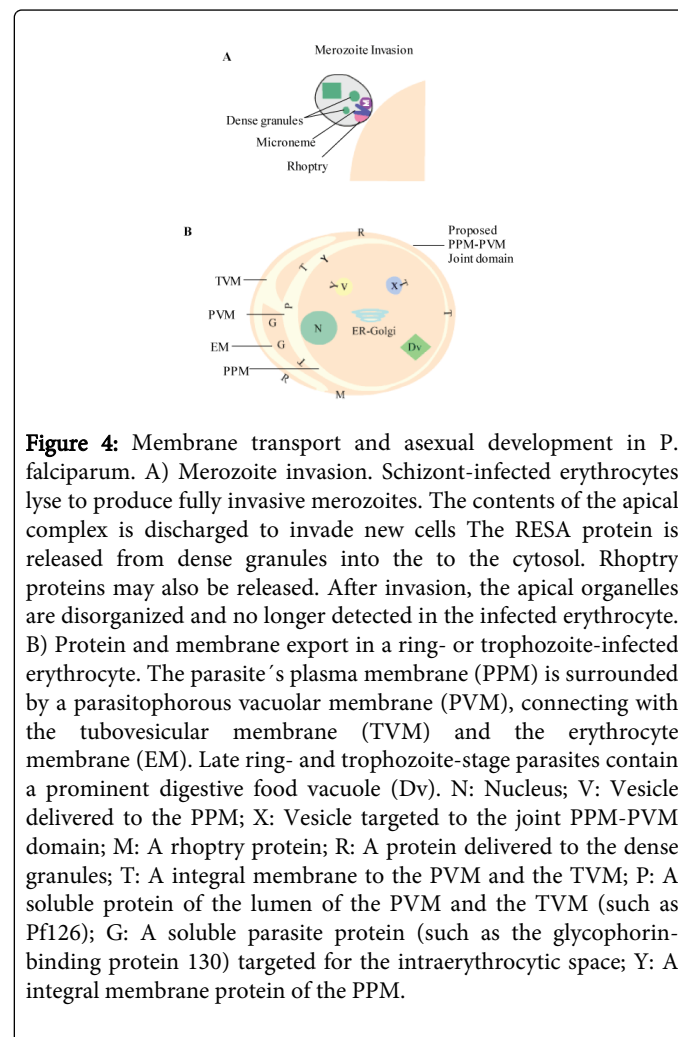

Figure 4: Membrane transport and asexual development in P. falciparum. A) Merozoite invasion. Schizont-infected erythrocytes lyse to produce fully invasive merozoites. The contents of the apical complex is discharged to invade new cells The RESA protein is released from dense granules into the to the cytosol. Rhoptry proteins may also be released. After invasion, the apical organelles are disorganized and no longer detected in the infected erythrocyte. B) Protein and membrane export in a ring- or trophozoite-infected erythrocyte. The parasite´s plasma membrane (PPM) is surrounded by a parasitophorous vacuolar membrane (PVM), connecting with the tubovesicular membrane (TVM) and the erythrocyte membrane (EM). Late ring- and trophozoite-stage parasites contain a prominent digestive food vacuole (Dv). N: Nucleus; V: Vesicle delivered to the PPM; X: Vesicle targeted to the joint PPM-PVM domain; M: A rhoptry protein; R: A protein delivered to the dense granules; T: A integral membrane to the PVM and the TVM; P: A soluble protein of the lumen of the PVM and the TVM (such as Pf126); G: A soluble parasite protein (such as the glycophorin-binding protein 130) targeted for the intraerythrocytic space; Y: A integral membrane protein of the PPM.

Plasmodium spp obtain SL from endogenous and exogenous sources [86,90,94]. Therefore, therapeutic agents able to limit the exogenous supply of SL are anti-malarial candidates. For this, chemicals and structure-related compounds found in humans have been tested for their ability to limit intracellular growth and replication of the parasite since they limit membrane formation and TVM network establishment once within the red cell and reduce formation of transport networks [94]. Further studies aimed at understanding the origin and route of lipid compounds required to maintain integrity of the red cell membrane during the intracellular phase of the parasite, can contribute to understanding the immune mechanisms of evasion used by *Plasmodium spp* [95].

Conclusions and future trends

SL play an important role both as intracellular or extracellular constituent lipids [84,85]. They perform important activities as signalling molecules during cell differentiation, proliferation,

apoptosis, and inflammation [24,76,96]. Information on their importance during plasmodial infection is scarce, but S1P may be involved in immunomodulation during cerebral malaria, with significant protection from disease and death observed in animal models [18]. In addition, sphingomyelin allows formation of a TVM network in the infected cell [89,90,97], which is crucial for parasites survival [92,93].

An important aspect worth highlighting is the ability of protozoan parasites to regulate production of some SL, such as ceramide [86,98], resulting in potential auto-regulation of cell signaling by the parasite.

In order to understand the mechanisms of action and potential use of SL as antimalarials or as biomarkers of infection, further studies in animal models and human populations are required. Finally, insight into the metabolism of SL as mediators and promoters of cell invasion and their requirement by the parasite to induce development of the TVM network should be pursued.

Acknowledgments

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