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Origin, evolution and function of the hemipteran perimicrovillar membrane with emphasis on Reduviidae that transmit Chagas disease

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Abstract

The peritrophic matrix is a chitin-protein structure that envelops the food bolus in the midgut of the majority of insects, but is absent in some groups which have, instead, an unusual extra-cellular lipoprotein membrane named the perimicrovillar membrane. The presence of the perimicrovillar membrane (PMM) allows these insects to exploit restricted ecological niches during all life stages. It is found only in some members of the superorder Paraneoptera and many of these species are of medical and economic importance. In this review we present an overview of the midgut and the digestive system of insects with an emphasis on the order Paraneoptera and differences found across phylogenetic groups. We discuss the importance of the PMM in Hemiptera and the apparent conservation of this structure among hemipteran groups, suggesting that the basic mechanism of PMM production is the same for different hemipteran species. We propose that the PMM is intimately involved in the interaction with parasites and as such should be a target for biological and chemical control of hemipteran insects of economic and medical importance.

Keywords: evolution, perimicrovillar membrane, insects, triatomines

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Introduction

The peritrophic membrane/matrix (PM) is a chitin-protein matrix that surrounds the food bolus in the midgut of the majority of insects (Bolognesi *et al.*, 2008). In some insects, however, the PM is absent and is replaced by an extra-cellular lipoprotein membrane called the perimicrovillar membrane (PMM) (Silva *et al.*, 2004). This PMM allows insects to exploit restricted ecological niches during all postembryonic stages (Terra & Ferreira, 2005; Damasceno-Sá *et al.*, 2007). The PMM is present only in some members of the superorder

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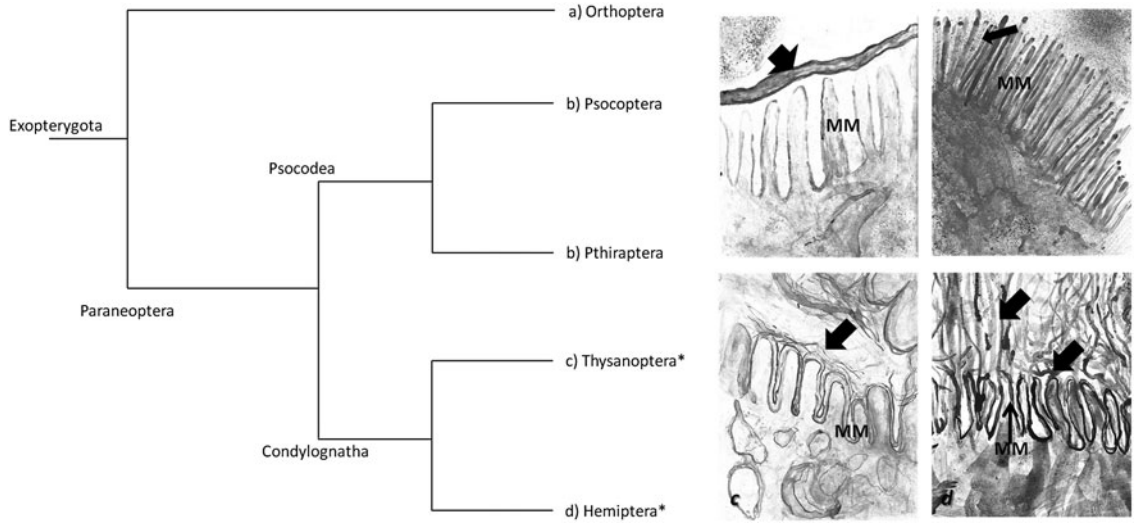

Fig. 1. Phylogeny of Paraneoptera and schematic representation of the different membranes in Exopterygoya insect orders. The Paraneoptera group includes two superorders Psocodea, which comprises the orders Psocopetra (booklice, bark lice and psocids) plus Phthiraptera (sucking and biting lice) and the superorder Condylognatha that includes the order Thysanoptera (thrips) and Hemiptera (suborders Homoptera and Heteroptera). The schematic representation of different membranes to separate the meal from the epithelium are: (a) peritrophic membrane in insects belonging to the Polyneoptera group; (b) peritrophic gel in Psocoptera (booklice) and Phthiraptera (lice); (c) kind of perimicrovillar membrane in Thysanoptera order; and d) perimicrovillar membrane in Hemiptera. Arrows = membranes of the midgut in the different orders of insects; DM = microvilli; asterisks show the orders which have perimicrovillar membrane.

Paraneoptera, including some species of medical and economic importance such as the Reduviidae, vectors of *Trypanosoma cruzi* (Lane & Harrison, 1979), the parasite that causes Chagas disease. Chagas disease (American trypanosomiasis) is a human disease endemic in large areas of Latin America.

This review provides an overview of the digestive tract in insects and changes that have occurred in different phylogenetic groups with an emphasis on the midgut of the Paraneoptera. Subsequently, we discuss the presence of the PMM and its interaction with pathogens and how the PMM may become a target to reduce populations of insects of economic and medical importance.

Insect digestive system

General morphology

The digestive system in insects comprises the salivary glands and the alimentary canal, which are involved in digestion, absorption and feces elimination (Terra & Ferreira, 2009). The salivary glands open into the cibarium and the saliva lubricates the mouthparts (Terra *et al.*, 1996). The alimentary canal, moreover, can broadly be divided into foregut, midgut and hindgut (Billingsley & Lehane, 1996).

The foregut begins at the mouth and includes the buccal cavity; the esophagus, crop and proventriculus. The crop is a storage organ in many insects although it also serves as a site for digestion in some species. The proventriculus is a triturating organ and in most insects serves as valve controlling the entry of food into the midgut (Chapman, 1998). The midgut is a tube with a ventriculus (anterior and posterior ventriculus) and sacs (gastric or midgut cecae) usually at the anterior end (Billingsley & Lehane, 1996). The midgut is the principal site for digestion and absorption of nutrients but there is, however, considerable variation in midgut arrangement and structure depending on the insect order and on the diet (Billingsley & Lehane, 1996; Terra & Ferreira, 2009). The last section of the digestive system is the hindgut which includes the ileum, colon and rectum. This is the section where water absorption and excretion occur (Billingsley & Lehane, 1996; Chapman, 1998). In the region of the sphincter (pylorus) separating the midgut from the hindgut, Malpighian tubules used for excretion and osmoregulation, end between midgut and hindgut (Terra, 1988).

The midgut epithelium of insects comprises three cell types: cells involved in enzyme secretion and absorption (digestive cells), those with endocrine functions (endocrine cells) and those that play a role in replacement of epithelium (regenerative cells) (Billingsley & Lehane, 1996; Pinheiro *et al.*, 2008; Teixeira *et al.*, 2015). Unlike many other animal groups, insects do not produce glycosylated proteins such as mucins to separate the meal from the epithelium (Tellam *et al.*, 1999), but have developed different membranes or matrices, often referred to as the PM, or PMM, that cover the surface of the intestinal tract and function as a protective lining for the epithelium.

PM

The PM was described by Balbiani (1890) as a membranous sac that directly surrounds the food in the lumen. The PM is not a cell component, but forms a cylindrical film or sheet that lines the lumen of the midgut between the midgut columnar cells and the ingested or digested food (fig. 1a). The PM is made up of a matrix of chitin, glycosaminoglycans and proteins (Eisemann & Binnington, 1994; Liu *et al.*, 2012; Moussian, 2013). Although it impedes direct contact of food with the striated border of columnar cells, this membrane permits the passage of digestive enzymes in the direction of the

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midgut lumen and the absorption of products resulting from digestion that are subsequently eliminated with the feces, preventing mechanical injury and hindering or impeding the entry of pathogens (Lehane & Billingsley 1996; Pinheiro *et al.*, 2008). Furthermore, the PM hinders the free movement of molecules, dividing the midgut lumen into two compartments: endoperitrophic space and ectoperitrophic space (Dow, 1987; Terra & Ferreira, 2009; Kuraishi *et al.*, 2011; Moussian, 2013; Teixeira *et al.*, 2015).

The structure of the PM is thought to result from chitin fibrils being interlocked with chitin-binding domains of peritrophins (Moussian, 2013). Mucin-like domains line the ectoperitrophic and endoperitrophic sides of the PM (Terra & Ferreira, 2012). As these domains are highly hydrated, they lubricate the surface of the PM, easing the movement of food inside the PM and in the ectoperitrophic fluid outside the PM (Terra, 2001; Terra & Ferreira, 2012). The PM is classified into two types (Peters, 1992; Marques-Silva *et al.*, 2005). Type I PM (primarily studied in lepidopteran larvae and dipteran adults) is produced along the midgut epithelium (Marques-Silva *et al.*, 2005; Teixeira, *et al.*, 2015) and is induced by the distension of the gut caused by food ingestion (Terra, 2001). This type of PM is found in Coleoptera, Dictyoptera, Ephemeroptera, Hymenoptera, Odonata, Orthoptera, Phasmida, larval Lepidoptera and adult hematophagous Diptera with subtle differences (Peters, 1992; Hegedus *et al.*, 2009). Type II PM is produced in a restricted region called the cardia that separates the foregut from the midgut (Marques-Silva *et al.*, 2005; Teixeira, *et al.*, 2015). This PM is found in some orders of Polyneoptera, such as Dermaptera, Isoptera and Embiodea and some species of Lepidoptera, and the larvae of Diptera (Hegedus *et al.*, 2009). PM production control is poorly understood; in some insects (i.e. mosquitoes), ingestion of a meal induces PM production, but whether this effect is direct (food in the midgut) or indirect (via endocrine pathways) is unknown (Peters, 1992). The protein components of PM I and PM II are similar. PM proteins have been classified into four types: class 1 proteins, thought to be digestive enzymes and food proteins loosely absorbed at the PM surface; class 2 proteins, proteins enclosed in membrane vesicles trapped between PM sheets; class 3 and 4 proteins, integral proteins of the PM named peritrophins, characterized by the presence of chitin-binding domains and mucin-like domains (Tellam *et al.*, 1999; Geer *et al.*, 2002). Furthermore, Tellam *et al.* (1999) proposed four classes of PM proteins based on the ease with which they can be removed from the PM. Class I proteins are removed with physiological buffers and represent loosely associated proteins, likely digestive enzymes and food remnants. Class II proteins are extractible with mild detergents, such as sodium dodecyl sulfate, that disrupt weak ionic interactions, whereas Class III proteins are released only with strong denaturants, such as urea. Class IV proteins cannot be removed by any means and are likely covalently linked to other proteins or chitin.

The PM has multiple functions which are associated with its ability to compartmentalize the gut. The compartmentalization increases the efficiency of the digestion of polymeric molecules (Silva *et al.*, 2004). The characteristics of the PM can be grouped according to their role in digestion: semipermeability, enzyme immobilization, counter-current flow, water and ion movement, all of which facilitate absorption (Ferreira *et al.*, 1994; Terra & Ferreira, 1994; Agrawal *et al.*, 2014); and protection of the midgut epithelium: food abrasion and invasion by microorganisms (Lehane, 1997; Bolognesi *et al.*, 2008; Hegedus *et al.*, 2009; Kuraishi *et al.*, 2011). The class III proteins known as peritrophins (nonmucin peritrophins and invertebrate intestinal mucins) are involved in the protection of the midgut epithelium (Hegedus *et al.*, 2009) Thus, insects lacking a PM may have the midgut cells damaged and may be subject to invasion by microorganisms (Tellam, 1996; Terra & Ferreira, 2012). Although protection is thought to be the ancestral function of PM, new functions have been added during the evolution of insect digestive tracts (Terra, 1988). These may include: (a) prevention of nonspecific binding of undigested material onto midgut membrane hydrolases and/or transport proteins; (b) prevention of enzyme excretion by permitting the endo-ectoperitrophic circulation of digestive enzymes; (c) mechanisms to ensure that monomers produced from food remain close to the surface of the midgut cells (Terra, 1988; Terra & Ferreira, 2012). These functions not only guarantee protection but also an effective digestive machinery. The presence of the PM is characteristic of almost all insects (Lehane, 1997; Hegedus *et al.*, 2009; Terra & Ferreira, 2009).

PMM

Among the few insects that lack a PM are adult ants (Hymenoptera), most adult moths and butterflies (Lepidoptera) and Bruchidae (Coleoptera) (Peters, 1992). One possible reason for this absence of PM in Hymenoptera and Lepidoptera is that these animals feed almost exclusively on low-molecular weight substances such as sugar, which does not require luminal digestion (Terra, 2001; Waniek, 2009). Rather than a PM, some insects have a peritrophic gel in their midgut which is the case of Bruchidae (Terra, 2001). Based on these data, it was concluded that the PM should be absent in insects lacking luminal digestion (Terra, 2001). However, in insects with a diluted diet and lacking a PM, they produce a second external membrane to the microvillar membrane (MM), which may have an analogous function and is called the PMM. This is the case of some members of Paraneoptera group (figs 1 and 2)

The PMM refers to a double membrane covering the MM of the intestine epithelial cells forming an outer microvillar (perimicrovillar) membrane which maintains a constant distance from the inner, or true, MM and projecting themselves towards the intestine lumen (fig. 1d) (Reger, 1971; Burgos & Gutiérrez, 1976; Billingsley & Downe, 1988). The PMM production depends on factors such as abdominal distention, diet content, activation of the neuroendocrine system leading to the release of prothoracicotropic hormone (PTTH) and ecdysone production (Billingsley & Downe 1988; Azambuja *et al.*, 1993; Nogueira *et al.*, 1997; Garcia *et al.*, 1998; Albuquerque-Cunha *et al.*, 2004).

The presence of the PMM is related to a modification of the alimentary canal that enables direct absorption of nutrients, such as essential amino acids, which occur in very low concentrations (Terra, 1990). Such modifications are believed to deal rapidly with large amounts of dilute fluid food to prevent hemolymph dilution. The functions of the PMM are similar to those of the PM, such as compartmentalization of the digestive process and a mechanical barrier to immobilize molecules and protection of intestinal epithelium. Unlike the PM, however, the PMM increases the absorption capacity of nutrients from diluted diets (Billingsley & Downe, 1988; Ferreira *et al.*, 1988; Billingsley, 1990; Terra & Ferreira, 2005).

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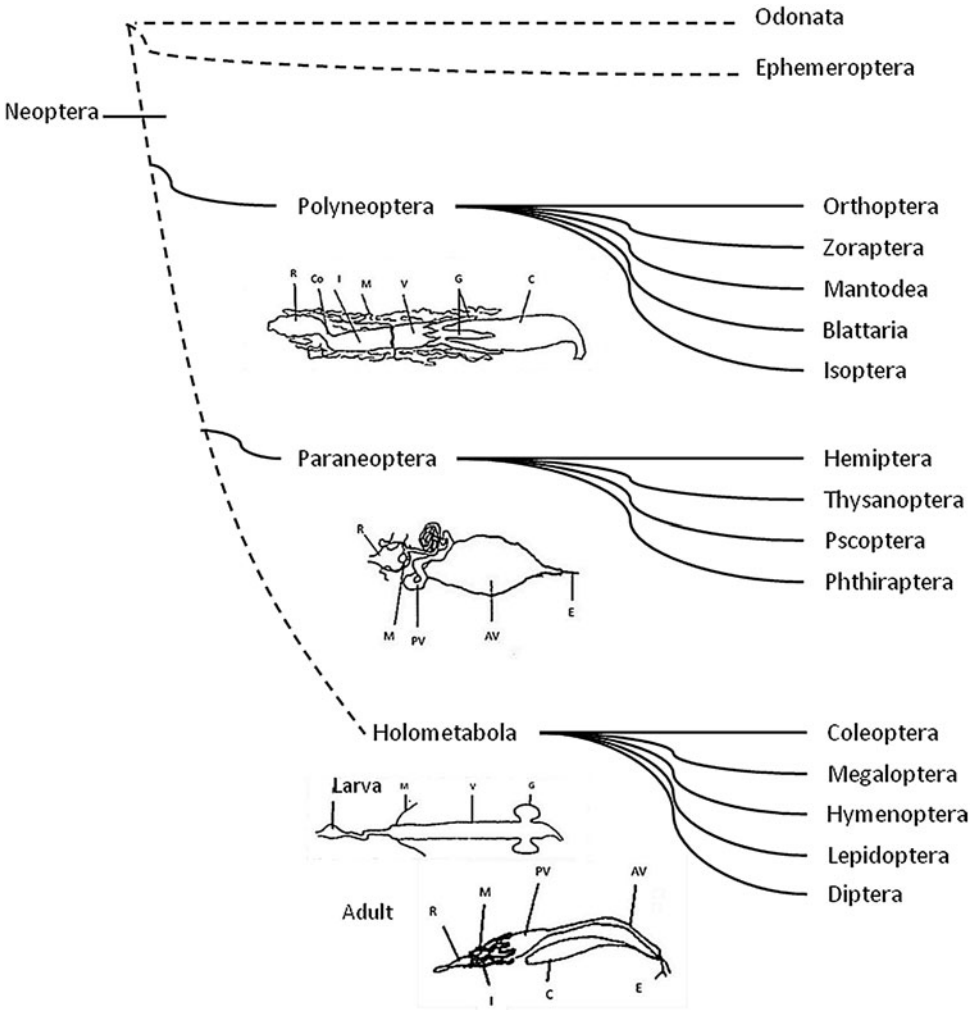

Fig. 2. Organization of gut compartments in the major insect orders. Neopteran insects are the common ancestor and include all the winged insects, except Ephemeroptera and Odonata. Polyneoptera, Paraneoptera and Holometabola have different features in the digestive physiology. C = crop; G = gastric cecae; V = ventriculus; M = Malpighian tubules; I = ileum; Co = colon; R = rectum; E = esophagus; AV = anterior ventriculus; PV = posterior ventriculus (midgut). (Intestinal representations were taken and modified from Terra, 1988).

Based on the results from immunolocalization of the PMM-bound-α-glucosidase which was found in both MM and PMM (Albuquerque-Cunha *et al*., 2009, Allahyari *et al*., 2010), it has been suggested that PMM is formed by budding from the trans area of the Golgi complex, migrating as the internal membrane of double membrane vesicles, fusing their outer membranes with the MM and their inner membranes with the PMM (Silva *et al*., 1995; Damasceno-Sá *et al*., 2007). Despite these developmental differences, Silva *et al*. (1995) and Terra *et al*. (2006) proposed that the MM and PMM of posterior midgut cells have the same origin. Furthermore, MM and PMM share some biochemical properties as both are rich in sterols, Mg^2+-ATPase and Na+k+-ATPase reaction, glycoconjugates and carbohydrate-binding molecules (Ferreira *et al*., 1988; Albuquerque-Cunha *et al*., 2009). However, once both have fully developed, MM and PMM show some functional differences which may reflect the different intestinal microenvironments and the enzymatic dispersion to which they have been exposed (Albuquerque-Cunha *et al*., 2009). In relation to this, Bittencourt-Cunha *et al*. (2013) demonstrated that after a meal, *Rhodnius prolixus*, uses fatty acids from the lumen for the synthesis of different lipid and phospholipid classes that were organized into PMM.

Digestive pattern related to phylogeny of the insects

All insects can be grouped according to their digestive physiology and organization of the digestive system (fig. 2) (Terra, 1988; Lehane & Billingsley, 1996). Neopteran insects are the common ancestor and include all the winged insects, except Ephemeroptera (mayflies) and Odonata (dragonflies) and evolved along three main lines: Polyneoptera (including Orthoptera, Zoraptera, Mantodea, Blattaria, Isoptera); Paraneoptera (including Hemiptera, Thysanoptera, Psocoptera and Phthiraptera) and Holometabola (including Coleoptera,

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Megaloptera, Hymenoptera, Lepidoptera and Diptera) (fig. 2) (Wheeler, 2001; Misof *et al.*, 2014).

The Neoptera is the ancestor of Polyneoptera and evolved to Paraneoptera and Holometabola (fig. 2). Based on Terra *et al* (1996), the neopteran ancestors have different features in the digestive physiology: digestive enzymes may pass forward from midgut to crop; the hydrolases are free and small, able to pass through the PM; the endo-ecto peritrophic circulation of digestive enzymes is driven by the secretion of fluid by Malpighian tubules and fluid absorption in the midgut cecae; and finally, there is differentiation of an acid anterior midgut (with carbohydrase activity) and an alkaline posterior midgut (with protease activity). Generally this group has a large crop and relatively short midgut with diverticula (midgut caeca) at the anterior end.

Polyneoptera

This group has retained characteristics of their neopteran ancestor but has reduced the size of the crop; some insects have lost caeca and have a differentiation of hindgut structures associated with the utilization of refractory material (Terra *et al.*, 1996; Terra & Ferreira, 2009). The majority of digestion is carried out in the crop by digestive enzymes propelled by antiperistalsis from the midgut. Then, there is a transfer of digestive enzymes and partially digested food towards the ventriculus. The anterior ventriculus is acidic and has high carbohydrase activity, whereas the posterior ventriculus is alkaline and has high proteinase activity (Terra & Ferreira, 2012). In the midgut, the food bolus moves backwards by peristalsis. When the polymeric molecules have been digested they pass through the PM. Once the molecules pass through the PM (fig. 2a), they diffuse, along with digestive enzymes, into the ectoperitrophic space. Subsequently, with a countercurrent flux caused by secretion of fluid by the Malpighian tubules, the enzymes and nutrients are moved towards the midgut cecae where final digestion is completed and nutrient absorption occurs (Terra & Ferreira, 2009, 2012). The Polyneoptera group includes different orders such Dictyoptera (Blattaria and Mantodea), Orthoptera, Phasmatodea, which gave rise to Paraneoptera and Holometabola (fig. 2).

Paraneoptera

In this group of insects the PM is absent and is replaced by a variety of membranes on the MM that performs the same role of absorption of essential nutrients from a diluted diet (i.e. amino acids that are present in very low concentrations) (Silva *et al.*, 2004). The ancestral origin of Paranoptera group (see 'Adaptation of the midgut Paraneoptera Insects' below) may have had adaptations to deal rapidly with large amounts of dilute fluid food. This group have an alimentary tract in the form of a simple tube (Kollien *et al.*, 2004) distinguished by modifications of the crop, anterior caeca and endo-ectoperitrophic circulation of digestive enzymes and polymer and oligomer hydrolases, all associated with the lack of midgut luminal digestion (Terra *et al.*, 1996). Therefore, the fluid food is stored essentially undigested in the anterior part of the midgut before concentration and partial enzymatic hydrolysis, passing rapidly through the narrow posterior part of the midgut into the hindgut (Kollien *et al.*, 2004; Waniek, 2009).

Holometabola

This group has similar water fluxes and circulation of enzymes as does the Polyneoptera, except that the fluid secretion occurs in the posterior ventriculus instead of the Malpighian tubules. The posterior midgut fluid does not contain waste, as does the Malpighian tubular fluid (Terra & Ferreira, 2012). It should be noted, however, that there may be considerable variation in the digestive systems of insects: Holometabolous (lower Holometabola- Coleoptera, Hymenoptera; and higher Holometabola- Diptera, Lepidoptera, Trichoptera), or between larvae and adults of the same groups. The compartmentalization, however, seems to be conserved, facilitating the digestion of polymeric food in more restricted environments (Terra *et al.*, 1987, 1996).

Adaptations of the midgut in Paraneoptera insects

The Paraneoptera group is subdivided in Psocodea and Condylognatha that have marked differences in their digestive tracts (Terra, 1988).

Psocodea

This group includes the orders Psocoptera (booklice) and Phthiraptera (lice). As a particular feature of the midgut, they have a peritrophic gel (fig. 2b) that covers the midgut columnar cells instead of a PM (Terra, 2001; Silva *et al.*, 2004). The absence of the PM in this group is thought to be related to their type of food and the countercurrent flows and their small size that allows for easy and efficient diffusion of digested products to the midgut surface (Terra & Ferreira, 2012). The digestion in Psocodea insects occurs in a few hours, implying serine proteases for digestion and an alkaline pH value for the midgut lumen (Waniek *et al.*, 2005). The absence of PM was confirmed by Silva *et al.* (2004) who observed, via transmission electron microscopy, dark material among midgut MM of booklice, which corresponds to the remains of a peritrophic gel that separates cells and midgut contents and an absence of α-glucosidase bound to the peritrophic gel demonstrated by immunocytolocalisation tests Essentially it can be said that Psocodea does not have a PMM but a primitive membrane form, the peritrophic gel (fig. 1).

Condylognatha

This group gave rise to the Thysanoptera and Hemiptera, but there are few general characteristic of the midgut in these two orders.

Thysanopterans have particular modifications at the midgut cells. Current studies suggest that the MM of midgut cells have two different types of glycocalyx, not seen in other insects. In the anterior region of the midgut the MM are surrounded by a myelin-like membrane that encloses several MM in a bundle. This structure is similar to a PMM and provides a form of protection for the MM in a region where cells are involved in secretory activity (Kitajima, 1975). In the posterior region of the midgut the MM have numerous rod-like projections arranged to form continuous layers characterized by dense material in the intercellular space that are more similar to a PMM (fig. 1c, table 1) (Del Bene *et al.*, 1991).

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Table 1. Characteristics of the PMM in Thysanoptera and Hemiptera.

Order	Suborder	Infraorders	Common name	Characteristics	References
Thysanoptera			Thunderflies Thunderbugs	• Estructure similar to a PMM, involved in absorption and secretory activity	Del Bene *et al.* (1991) Kitajima (1975)
			Storm flies	• Presence of α-glucosidases	Parrella *et al.* (2003)
			Storm bugs	• Economically important insect	Riley *et al.* (2011)
			Corn lice	• Vector of 20 tospoviruses	Ullman *et al.* (2002)
Hemiptera	Homoptera	Sternorrhyncha	Aphids	• Phloem feeders	Ashford *et al.* (2000)
			Whiteflies Scake	• PMM with modification that help in hydrolysus of sucrose and phloem amino acid.	Cristofoletti *et al.* (2003) Douglas (2003)
				• α-glucosidases involved in the hydrolysis of dietary sucrose and in the osmoregulation	Fonseca *et al.* (2010) Silva *et al.* (2004)
				• Problem in agriculture	Zhong *et al.* (2013)
		Auchenorrhyncha	Cicadas	• Xylem-suckers	Fonseca *et al.* (2010)
			Leafhoppers Treehoppers	• Filter chamber linked to the PMM, suitable structure to deal with an extremely diluted diet	Terra (1988) Wu *et al.* (2006)
			Planthoppers	• α-glucosidase acts to control the osmolarity	Zhong *et al.* (2013)
			Spittlebugs	• Presence of PMM	
				• PMM in the management of the pests	
	Heteroptera	Pentatomomorpha	Stink bugs	• Seed-sucker, phytophagous	Silva &Terra (1994)
			Flat bugs	• Presence of PMM	Silve *et al.* (1995)
			Seed bugs	• α-glucosidase	
		Cimicomorpha	bed bugs Bat bugs	• All members are adapted to feeding on animals as their prey or host (predators or hematophagous)	Alves *et al.* (2007) Castro *et al.* (2012)
			Assassin bugs	• Presence of PMM	Cortez *et al.* (2012)
			Kissing bug	• α-glucosidase linked with the synthesis of hemozoin	Lane & Harrison (1979)
				• Bed bugs and kissing bugs are a highly specialized hematophagous	Mury *et al.* (2009) Reinhard & Siva-Jothy (2006)
				• Reduviidae are generally predators of other insects and some contribute to biological control	Silva *et al.* (2007) Silverman *et al.* (2001)
				• Triatominae subfamily are blood suckers and are vectors of protozoan T. *cruzi*	Terra (1988)
				• PMM in the management of vectors insects	

Features of the PMM in Hemiptera

The order Hemiptera comprises two suborders: Homoptera and Heteroptera (table 1). The Homoptera includes: Sternorrhyncha (Coccidae, scale insects; Aphididae, aphids; Aleyrodidae, whitefly) and Auchenorrhyncha (Fulgoroidae, planthopper; Cercopidae, spittle bugs; Cicadidae, cicadas; Cicadellidae, leafhoppers; Membracidae, treehoppers), all terrestrial plant feeders (Cranston & Gullan, 2009). The Heteroptera comprises Pentatomomorpha (Lygaeoidae, seed bugs; Pyrrhocoroidea, cotton strainers; Coreoidae, squash bugs; Pentatomidae, shield bugs, chust bugs and stink bugs) and Cimicomorpha (Cimicidae, bed bugs; Reduviidae, assassin bugs) that have different feeding strategies that include predation, sap sucking and hematophagy (Terra *et al.*, 1996; Misof *et al.*, 2014).

Sternorrhyncha (Homoptera) species are phloem feeders and most studies have evaluated the digestive systems in aphids, whiteflies and scale insects (Ashford *et al.*, 2000; Douglas, 2003; Fonseca *et. al.*, 2010; Zhong *et al.*, 2013). The data suggest modifications associated with the PMM, that originate from multimembrane vesicles from Golgi (Cristofoletti *et al.*, 2003) and which help in the hydrolysis of sucrose and absorbing dilute phloem amino acids (Terra, 1990).

Auchenorryncha (Homoptera) species, principally cicadas, leafhoppers, treehoppers, planthoppers and spittlebugs, are xylem-feeders. This group of insects acquired a filter chamber linked to the PMM, in the conical segment and anterior and posterior extensions of the midgut (Zhong *et al.*, 2013). These filter chambers with the PMM provide a suitable mechanism to deal with an extremely diluted diet (Terra, 1988; Fonseca *et al.*, 2010). Xylem fluid is a diet poor in organic nutrients and hypotonic to the hemolymph; these insects require obligate bacterial symbionts to synthesize essential amino acids (Wu *et al.*, 2006).

The compartmentalization of digestion in Heteroptera is known mainly from the Pentatomorpha: *Dysdercus peruvianus* a seed-sucker bug; and Cimicomorpha: *R. prolixus* a hematophagous bug (Lane & Harrison, 1979; Silva & Terra, 1994). Despite having different diets, these insects share digestive system similarities including the presence of the PMM (Lane & Harrison, 1979). The anterior midgut of these insects is used to store food and absorb water and also absorbs glucose in Pentatomomorpha (Bifano *et al.*, 2010). The digestion and protein absorption of amino acids occurs in the posterior midgut. Most protein digestion in Heteroptera occurs in the lumen with the aid of cysteine and/or aspartic proteinases, mainly cathepsins and ends in the perimicrovillar space under the action of aminopeptidases and dipeptidases (Terra & Ferreira, 1994; Balczun *et al.*, 2012).

In phloem feeding Sternorrhyncha, α-glucosidases are involved in the hydrolysis of dietary sucrose and in the osmoregulation in the midgut lumen through their transglycosidase activity (Ashford *et al.*, 2000). Members of Auchenorrhyncha, feed on xylem contents, that have low concentrations of organic compounds and it is possible that the membrane-bound α-glucosidase acts to control the osmolarity, following the passage of the meal into the midgut (Terra & Ferreira, 2005; Fonseca *et al.*, 2010). Silva *et al.* (2004) confirmed the existence of an integral protein α-glucosidase in the PMM that works as a biochemical marker for the PMM. This protein was first described in the seed-sucker bug *D. peruvianus* (Silva & Terra, 1995; Silva *et al.*, 1995) and kissing bugs *R. prolixus* and *Triatoma infestans* (Burgos & Gutiérrez, 1976; Terra, 1988). Subsequently, α-glucosidases have been described in different groups of hemipteran insects and they are involved in different functions other than digestion (Allahyari *et al.*, 2010; Fialho *et al.*, 2013). In the hematophagus bug, *R. prolixus*, the perimicrovillar-associated α-glucosidase has been linked with the synthesis of hemozoin that protects the bug from the oxidative stress caused by the release of hemin, a product of the hemoglobin digestion (Oliveira *et al.*, 2000; Silva *et al.*, 2007; Mury *et al.*, 2009).

The presence of integral proteins in the Paraneoptera group confirmed the presence of a PMM in Hemipterans and Thysanopterans (fig. 1), but not in Psocopterans and Phthirapterans, suggesting that α-glucosidases and PMM of Thysanoptera and Hemiptera are homologous (Silva *et al.*, 2004). Despite a common origin and composition of the PMM (Terra, 1990; Albuquerque-Cunha *et al.*, 2004, 2009), the synthesis of the PMM can vary among species, which can be explained by different feeding behaviors (Damasceno-Sá *et al.*, 2007; Azevedo *et al.*, 2009; Fialho *et al.*, 2009, 2012). In the hematophagous *Cimex hemipterus* (Hemiptera: Cimicidae), *Triatoma pallidipennis* and others triatomine species (Hemiptera: Reduviidae), of Cimicomorpha infraorder, the PMM is evident 20 and 15 days post feeding, respectively (Billingsley & Downe, 1986; Azevedo *et al.*, 2009; Gutiérrez-Cabrera *et al.*, 2014). In the phytophagous cotton stainer, *D. peruvianus* (Hemiptera: Pyrrhocoridae) and sunn pest, *Eurygaster integriceps* (Hemiptera: Scutelleridae), both of the Pentatomomorpha infraorder, the PMM covers all the cells 30 and 20 h post-feeding, respectively (Damasceno-Sá *et al.*, 2007; Mehrabadi & Bandani, 2011). While in the zoophytophagous *Brontocoris tabidus* (Hemiptera: Pentatomidae), also of Pentatomomorpha infraorder, the PMM is evident in both the starved and fed condition (Fialho *et al.*, 2009, 2013).

Therefore, the development of PMM in hemipterans varies according to how frequently the animal has access to food: in phytophagous and zoophytophagous species access to food seems frequent (Damasceno-Sá *et al.*, 2007; Fialho *et al.*, 2009), while in blood-suckers such access is less frequent as hosts are harder to find (Nogueira *et al.*, 1997; Azevedo *et al.*, 2009).

Economic and public health importance of species with PMM

The Thysanoptera is a worldwide order of nearly 6000 species, many of which are economically important insects: they cause direct damage to plants as a result of their feeding and indirect damage as vectors of plant pathogens (Ullman *et al.*, 1989; Shipp *et al.*, 1998). For example, at least 14 species of thrips transmit 20 tospoviruses (genus *Tospovirus*, family Bunyaviridae), a major group of plant viruses affecting >1000 host-plant species many of them important for human use (table 1) (Ullman *et al.*, 2002; Parrella *et al.*, 2003; Riley *et al.*, 2011).

The Hemiptera contains many species of medical and economic importance. This order has a high biodiversity, is adapted to a large number of habitats, exploits different diets such as phloem and xylem sap, seed sucking, predation and hematophagy. Most are vectors of viruses, bacteria and protozoa and as such are a serious problem in agriculture and public health (Dedryver *et al.*, 2010; Fonseca *et al.*, 2010). Some hemipterans of economic importance to humans include: aphids and whiteflies as phloem-suckers; planthoppers, cicadas, cercopids and leafhoppers as xylem-suckers; seed bugs, cotton strainers and squash bugs that are phytophagous terrestrial bugs and include many plant pests; and finally, bed bugs and assassin bugs that include ectoparasites and vectors of human parasites and pathogens.

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Cimicidae (bed bugs) are a highly specialized hematophagous taxon that parasitizes primarily humans, birds and bats (Reinhardt & Siva-Jothy, 2007). Bed bugs are capable of carrying different infectious agents such as bacteria, protozoa and viruses that may cause diseases such as typhus, anthrax, plague, relapsing fever, tularemia, Q fever, leishmania, hepatitis B virus and HIV (Burton, 1963; Ryckman *et al.*, 1981); however, the cimicids rarely transmit them to their hosts (Goddard & deShazo, 2009; Silverman *et al.*, 2001). These insects also can harbor trypanosomes (Bower & Woo, 1981; Gardner & Molyneux, 1988), including *T. cruzi* the causative agent of Chagas disease (Chang & Chao, 1999). Although the trypanosomes such as *Trypanosoma* (*Megatrypanum*) *incertum* (Gardner & Molyneux, 1988) and *Trypanosoma* (*Schizotrypanum*) *hedricki* (Bower & Woo, 1981) have been found in bed bugs, this taxon had not been considered a major vector of any human parasite. However, recently Salazar *et al* (2015) showed that bed bug (*Cimex lecturarius*) seems to be a competent vector of *T. cruzi*. Bed bugs efficiently acquired *T. cruzi* on feeding on infected mice and then transmitted the parasite back to susceptible hosts both during cohabitation and through contaminated feces placed on broken host skin by researchers (Salazar *et al.*, 2015).

In contrast, the Reduviidae (assassin bugs) is one of the largest families of the Hemiptera and many are predators of other insects and some contribute to biological control. However, some species of the Triatominae sub-family are blood feeders and are important vectors of the protozoan *T. cruzi*, the causative agent of Chagas' disease that affects an estimated 6–7 million people, mainly in Latin America (WHO, 2015). The interactions between *T. cruzi* and the PMM of the triatomine vectors are keys to the success of the parasite in the midgut (Alves *et al.*, 2007). Bed bugs and triatomine bugs, share many similarities. Besides belonging to the same infraorder, both are exclusively hematophagous and develop the PMM, although the blood sucking lifestyle of each insect has evolved independently.

Despite their importance in agriculture and public health, there are few studies of these insects on the morphology and ultrastructure of their midguts with particular attention to the interaction with the pathogens that could lead to novel control measures.

Importance of the PMM in the control of insects of economic importance: the case of vectors of Chagas disease

Understanding the function and structure of the PMM may provide us with a target to control insects of economic and/or health importance. As an example, we will use the case of vectors of Chagas disease. This disease is caused by the protozoan *T. cruzi* which proliferates and multiplies in the insect vector especially in the rectum. During the blood meal some bugs defecate and deposit the infected feces on the skin or mucosa. The bite causes a skin wound that allows the parasite to enter underneath the skin (Brenière *et al.*, 2010). Although this transmission is complex to facilitate transmission of the protozoan (Takano-Lee & Edman, 2002), Chagas disease is highly dependent on the interaction of triatomines and the parasite (Kollien & Schaub, 2000; Azambuja *et al.*, 2005).

The life cycle of *T. cruzi* in the vector has three stages of development (Kollien & Schaub, 2000; Azambuja *et al.*, 2005). The first stage occurs when the triatomine ingests blood containing trypomastigotes from the vertebrate host. In the second stage, a few hours after ingestion, the trypomastigotes transform into epimastogotes in the anterior midgut (Azambuja *et al.*, 2005); thus establishing the infection in the insect (Garcia *et al.*, 2010). Subsequently, the epimastigotes pass to the midgut where they attach to the PMM and multiply by binary division (Garcia & Azambuja, 1991: Kollien *et al.*, 1998; Alves *et al.*, 2007). The posterior midgut is the region of greatest digestive activity and where the greatest concentration of metabolites should occur (Schaub, 1989). In the final stage, the epimastigotes pass to the rectum, adhere to the rectal cuticle by hydrophobic interactions and multiply to very large numbers and transform into the metacyclic trypomastigotes which are eliminated with the feces and urine and are able to infect the vertebrate hosts (Kollien *et al.*, 1998; Kollien & Schaub, 2000; Azambuja *et al.*, 2005).

Experimental studies highlight the importance of the interactions between the parasite and the PMM, because PMM disruption is correlated with a blockage not only of epimastigote multiplication but also of *T. cruzi* development in the triatomine vector (Garcia *et al.*, 1989; Gonzalez & Garcia, 1992; Cortez *et al.*, 2002, 2012). In regions where PMM is absent or poorly developed, the parasite rarely comes in contact with the MM of the intestine and thus fail to multiply (Gonzalez *et al.*, 1999; Kollien & Schaub, 2000; Azambuja *et al.*, 2005). These inhibitory effects could be counteracted by either head transplantation or ecdysone therapy. Furthermore, a simple oral ingestion of PMM is able to rescue *T. cruzi* development in either decapitated or azadirachtin-treated insects (Gonzalez *et al.*, 1999; Cortez *et al.*, 2002, 2012), indicating that the PTTH–ecdysone pathway interferes with *T. cruzi* survival and development in its vectors (Nogueira *et al.*, 1997; Gonzalez *et al.*, 1999). These results demonstrate the importance of the insect's endocrine system and the PMM in establishing *T. c*ruzi infections in the vector.

According to Albuquerque-Cunha *et al.* (2004, 2009), the PMM in triatomines is composed of glycoconjugates. The carbohydrates attached to the proteins of the insect cells are usually involved in insect–pathogen interactions (Pereira, 1981; Nogueira *et al.*, 2007). In triatomines a variety of glycoconjugates including mannose, glucose, galactosamine, N-acetyl-galactosamine, N-acetyl-glucosamine and sialic acid (Gutiérrez-Cabrera *et al.*, 2014) have been identified. These sugar residues attached to the PMM proteins play an important role in the binding of epimastigotes to the surface of intestinal epithelial cells that allows the parasite to complete its life cycle in the vector (Garcia *et al.*, 2007, 2010). In *R. prolixus* mannose and sialic acid are essential in the interaction with *T. cruzi* (Alves *et al.*, 2007; Albuquerque-Cunha *et al.*, 2009).

Conclusion and future considerations

Digestion of insects takes place in initial, intermediate, and final phases. These phases are separated spatially and temporally by morphological features of the gut. The morphological features may have evolved by adapting to different diets. However, the dietary approach alone cannot explain the presence or absence of some structures and cannot provide a clear explanation for the absence of peritrophic matrix in all Hemiptera, despite their contrasting dietary habits. However, based on the digestive events of different taxa and their diets, the insects may be grouped according to their digestive physiology and phylogenetic position, with regards to a common ancestor.

With regard to the origin and evolution of PMM, the Condylognathan ancestor of the Thysanoptera and

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Hemiptera likely fed on phloem sap obtained from plant tissues pierced by oral stylets, the so-called 'punch and suck' mechanism (Silva *et al.*, 2004). This diet would be low in proteins, low carbohydrate polymers, relatively poor in free amino acids but rich in sucrose. These condylognathan ancestors may have lost the PM and the enzymes involved in initial and intermediate protein digestion due to the lack of luminal digestion. When very low concentrations of essential amino acids are present, absorption may be maximized by the PMM (Terra, 1988; Terra & Ferreira, 1994). The PMM would transport actively potassium ions from the perimicrovillar space into the midgut cells, generating a concentration gradient between the sap in the lumen and that in the perimicrovillar space. This concentration gradient would be used as a driving force for the absorption of organic substances, such as amino acids, through carriers in the PMM. The organic substances, once in the perimicrovillar space, would be absorbed through carriers at the surface of the MM. The α-glucosidase bound to PMM efficiently cleaves sap sucrose without being excreted.

The hemipteran ancestor acquires piercing-sucking mouthparts adapted to suck xylem and phloem sap (Gillott, 1995), thus becoming able to obtain liquids directly from the plant's vascular system. Organic compounds obtained from the xylem and phloem must be concentrated to be absorbed by the perimicrovillar system. Therefore, the evolution of Heteroptera was associated with the ability to digest proteins after losing the appropriate digestive enzymes and maintaining a compartmentalization of digestion by PMM as a substitute of PM (Terra & Ferreira, 2012).

Many thysanopterans and hemipterans are species of medical and economic importance and the PMM may be targeted to control insects or to regulate and modulate interactions with pathogens. The development of the PMM varies according to species and depends on how frequently the insect has access to food (Nogueira *et al.*, 1997; Damasceno-Sá *et al.*, 2007; Azevedo *et al.*, 2009; Fialho *et al.*, 2009). Therefore, it is necessary to carry out morphological and biochemical studies to obtain detailed information on the insect digestive tract, to identify fundamental parameters we might target to develop novel strategies to control agriculturally and medically-important insects.

In the specific case of triatomine vectors of Chagas disease, there are several mechanisms that regulate the interactions between host and *T. cruzi* in the alimentary tract of the insect vector. The PMM could be an excellent target to reduce the susceptibility of the insect vector to parasites because *T. cruzi* epimastigotes interact intimately with these membranes and this is essential for parasite development in the gut (Burgos *et al.*, 1989; Gonzalez *et al.*, 1999; Gutiérrez-Cabrera *et al.*, 2014).

Several authors have studied the effects of antisera produced against antigens from the vector gut on parasite infections in various insect orders, highlighting, for example, antibodies that recognize the PM that can also block its development (East *et al.*, 1993; Eisemann *et al.*, 1993; Tellam & Eisemann, 1998; Wijffels *et al.*, 1999; Otranto & Stevens, 2002; Foy *et al.*, 2003). Based on these observations, Gonzalez *et al.* (2006) used an antiserum against PMM and observed changes in the PMM organization in the posterior midgut of *R. prolixus* that had ingested the antisera. Those changes were not important for triatomine survival but the antiserum acted as a transmission-reducing compound that significantly reduced *T. cruzi* infection in the vector. It is possible that the PMM proteins become unavailable for the parasite after recognition by the antiserum consequently disrupting *T. cruzi* development. A better understanding of the PMM composition and function can clarify fundamental steps of the process of triatomine digestion, hemozoin formation and the *T. cruzi* life cycle.

Different studies have shown that glycoconjugates and carbohydrate-binding molecules are associated with the plasma membrane of insect cells and are usually involved in the interactions with pathogens (Rudin & Hecker, 1989; Jacobson & Doyle, 1996; Dinglasan & Jacobs-Lorena, 2005). The PMM contains a variety of glycoconjugates, such as mannose, as the major sugar residues (Albuquerque-Cunha *et al.*, 2009; Gutiérrez-Cabrera *et al.*, 2014). It has been proposed that these sugar-binding molecules are involved in the binding of *T. cruzi* epimastigotes to the midgut epithelial cell surface (Pereira *et al.*, 1981; Bonay *et al.*, 2001; Nogueira *et al.*, 2007). However, much remains to be learned about the biochemical composition of the PMM and the mechanisms of interaction with parasites.

There is an increasing need to develop either new vector control methods or alternative strategies to block transmission of parasites such as *T. cruzi*. Studies evaluating immunization using components from midguts must be extended by refining the native antigens and expanding our knowledge of the proteins from the digestive tract and the PMM of epidemiologically important triatomines to identify target molecules essential to parasite development in the insect vector. This requires a further understanding about the origin, biogenesis, function, composition and development of PMM in the Thysanoptera and Hemiptera and in more detail, to recognize which molecules are present in the digestive tract and the PMM and how they may modulate insect physiology and parasite development and multiplication.

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