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The innate immune response of triatomines against Trypanosoma cruzi and Trypanosoma rangeli with an unresolved question: Do triatomines have immune memory?

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ABSTRACT

The present work aimed to review the immune response from different triatomines against *Trypanosoma cruzi* and *Trypanosoma rangeli* and propose the study of immune memory in such insects. Trypanosoma use triatomines as vectors to reach and infect mammals. A key question to be answered about vector-parasite interaction is why the immune defense and resistance of the insect against the parasites vary. Up to date data shows that the defense of triatomines against parasites includes cellular (phagocytosis, nodulation and encapsulation) and humoral (antimicrobial peptides, phenoloxidase and reactive oxygen and nitrogen species) responses. The immune response varies depending on the triatomine species, the trypanosome strain and species, and the insect intestinal microbiota. Despite significant advances to understand parasite-insect interaction, it is still unknown if triatomines have immune memory against parasites and if this memory may derive from tolerance to parasites attack. Therefore, a closer study of such interaction could contribute and establish new proposals to control the parasite at the vector level to reduce parasite transmission to mammals, including men. For instance, if immune memory exists in the triatomines, it would be interesting to induce weak infections in insects to find out if subsequent infections are less intense and if the insects succeed in eliminating the parasites.

1. Introduction

Chagas disease, also called American Trypanosomiasis, is potentially lethal to humans and can be found in 21 Latin American countries. The disease has two completely different phases in humans. In the first instance, there is an acute infection, which extends for about two months, where the parasites circulate in the blood and infect some tissues such as the heart and skeletal and smooth muscle. At this point, in most cases, signs are mild and non-specific such as fever, headache, lymphadenopathy, paleness, muscle pain, breathing difficulty, and abdominal and/or thoracic pain. In the second phase of the disease, the chronic infection, the parasites are also infecting heart tissue, skeletal muscle and smooth muscle from the digestive tract. Despite no evident parasitemia, after several years, the infection may induce death due to cardiac arrhythmia and insufficiency caused by tissue destruction (World Health Organization, 2018). The etiological agent of such disease is the protozoa *Trypanosoma cruzi*, endemic from the South of the USA down to Argentina. It is mainly transmitted to humans through feces of the insect known as kissing bug (World Health Organization, 2018). Currently, many cases of Chagas disease reported are of oral transmission (Guarner, 2019). However, the capacity of a determined triatomine species to carry and support development up to the infecting stages of the parasite mainly depends on factors such as the immune response of the insect, the parasites' genetic identity, and feeding and defecating patterns (Azambuja and García, 2005).

All hematophagous species from the Triatominae and several from

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the *Rhodnius* genders have the capacity of transmitting *T. cruzi*, while *Rhodnius* can also transmit *T. rangeli* (Vallejo et al., 2009a). It is important to point out that even if *T. rangeli* infections are frequent in humans and are not considered pathogenic for them (Vallejo et al., 2009a), it can be considered pathogenic for *Rhodnius* (Guhl and Vallejo, 2003; Peterson and Graham, 2015). More studies are necessary to determine if *T. rangeli* is pathogenic for other species of triatomines (Peterson and Graham, 2015). The trypomastigotes of *T. rangeli* access the *Rhodnius'* intestine, where it evolves to short epimastigotes, replicate and then pass through the intestinal wall to reach the hemolymph. Then, the parasite invade salivary glands, where evolves into metacyclic trypomastigotes, the mammalian infective stage (Abad-Franch et al., 2013; da Rosa et al., 2014). *T. cruzi* enters the mammalians host through triatomine fecal contamination, but *T. rangeli* infects salivary glands and gains access to mammalians by biting (García et al., 2004a). These are the only two species of Trypanosoma that naturally infect humans in Latin America (Vallejo et al., 2015).

T. cruzi and *T. rangeli* regularly infect triatomines' digestive tract. Still, *T. rangeli* cannot be transmitted to mammalian hosts through fecal contamination. In the case of the triatomines *Rhodnius, T. rangeli* can also infect salivary glands, and therefore, these triatomine species are the only ones that serve as *T. rangeli* vectors for mammalian hosts (Vallejo et al., 2015). The phylogenetic closeness between *T. cruzi* and *T. rangeli* usually hinders Chagas disease's diagnostic in patients living in geographic areas where both species of parasites are endemic (Grisard et al., 2010). The study of the genetic diversity between and within species is helping to unravel this problem. In the case of *T. cruzi,* genetic polymorphism has allowed classifying different strains within six Discrete Typing Units (DTUs), DTU I-IV (Zingales et al., 2009). Additionally, one more *T. cruzi* strain isolated from bats in Brazil showed unique ribosomal PCR patterns that could not be grouped with any of the other six DTUs previously reported and was included in an independent genotype group (Tcbat) (Lima et al., 2015). Further, within the DTU-I, four haplotypes have been described (Herrera et al., 2007; Falla et al., 2009). Similarly, after studying the sequences of *T. rangeli* kDNA and the miniexon gene, two phylogenetic groups (KP1+ and KP1-) were described (Vallejo et al., 2003). On the one hand, some association has been observed between KP1 (+) *T. rangeli* and triatomines that belong to the prolixus group: *R. prolixus, R. robustus (type I, II, III, IV)* and *R. neglectus, R. nasutus, R. domesticus* (Vallejo et al., 2003; Urrea et al., 2005, Urrea et al., 2011), or robustus lineage, including *R. robustus* type V (Abad-Franch and Monteiro, 2007; Abad-Franch et al., 2009). On the other hand, there is an association between KP1 (-) *T. rangeli* and triatomines belonging to the pallescens group: *R. pallescens, R. colombiensis* and *R. ecuatoriensis* (Vallejo et al., 2003; Urrea et al., 2005, Urrea et al., 2011) or pictipes lineage, including *R. pictipes* (Abad-Franch and Monteiro, 2007; Abad-Franch et al., 2009*)*. Barreto-Santana et al. (2015) analyzed the susceptibility of four species of *Rhodnius* to a Brazilian strain of *T. rangeli* and showed that infectivity was more significant and more efficient in triatomines from the same region as the strain. Also, Dworak et al. (2017) verified the influence of sympatry in the interaction of *T. cruzi* with triatomines and propose that some *T. cruzi* strains are biologically adapted to triatomine populations of the same geographic area. Genetic diversity allows adaptation of the parasite to the vector, the host, and even displays virulence differences in both vector and host. Sometimes parasites were lethal to the vector, as reported by (Aparicio-Burgos et al., 2011; Aparicio-Burgos et al., 2015). Therefore, a more closely study of the interactions between *T. cruzi* and *T. rangeli* and the triatomines could contribute to better understand the interactions occurring among parasite-vector-host (Vallejo et al., 2015). The improvement in knowledge of the insects' immune system could be a key element in understanding such interaction. Hence, this review analyzes the immune response of triatomines against different strains of *T. cruzi* and *T. rangeli*, in an attempt to summarize the variations observed in these interactions. Finally, evidence and examples of immunological memory from different arthropods are presented as a basis for proposing the same response in triatomines against trypanosomes and why these studies are recommended.

1.1. The immune response of triatomines against T. cruzi

In the last few years, several researchers have focused on the study of the immune response from different species of the vector against *T. cruzi* and *T. rangeli* (Azambuja et al., 2016; Salcedo-Porras and Lowenberger, 2019; Guarneri, 2020). In tables 1 and 2, the main findings of the immune response and parasite elimination from triatomines are described and in general, is shown that not all triatomines are equally susceptible to infection by *T. cruzi*.

Data suggests that the immune system greatly influenced the insect's susceptibility to the parasite. Besides *T. cruzi* development is restricted to the digestive tract, some authors explored its survival in the hemocele through parasite inoculation in the insect or incubation *in vitro* with hemolymph. Mello et al. (1995) observed that the PO combats parasites in an interaction between *R. prolixus* and *T. cruzi* "Dm28c". Later, Mello et al. (1996) evaluated the development of *T. cruzi* "Y", "2-CI-B" and "Dm28c" strains in nymphal stages of *R. prolixus* and found that the infection level in the midgut and survival in hemolymph for an extended period, is influenced by the parasite strain. There is a relationship between the *T. cruzi* strains' infectivity and the in-vitro agglutination capacity of intestinal lectins. Waniek et al. (2011) compared the transcript abundance of *T. brasiliensis* def1 in the anterior and posterior midgut infected with *T. cruzi* strain TBRA/BR/1999/JCA3 (TcII). The authors found a highly increased def1 transcript abundance at 20 days after the infective blood, suggesting a potential function of intestinal defensin in the parasite population control (Table 1).

The trypanolytic factor present in *R. prolixus, R. robustus* and *R. stali* hemolymph could be the reason for the low vector competence of these species to *T. cruzi* DTU II (Table 1; Mejia et al., 2009). It is unknown whether this factor is produced, against specific *T. cruzi* genotypes, by the hemolymph or a residual factor produced by other corporal tissues, such as the fat body (Vallejo et al., 2015). Moreover, salivary glands of triatomines can limit parasite development by the presence of trypanolytic factors. In *T. infestans* saliva, a trypanolytic membrane pore forming protein, trialisine, fights the parasite, playing an essential role in controlling the microorganism in salivary glands (Amino et al., 2002).

Moreover, the vector's gut microbiota plays an important role as an immune response regulator to *T. cruzi* infection (Castro et al., 2012; Vallejo et al., 2009a). For instance, it has been reported that *R. prolixus* is able to control DTU II *T. cruzi* strains but not those of DTU I (Vallejo et al., 2009b). *T. cruzi* DTU I, strain Dm28c, besides developing better than DTU II, Y strain it reduces the number of the intestinal microbiota of *R. prolixus* (Castro et al., 2012; Vieira et al., 2016). Buarque et al. (2016) characterized a new antimicrobial product from the anterior midgut of *T. infestans* (TiAP) and the results indicated that the infection by *T. cruzi* increases the expression of TiAP to inhibit microbiota growth. This inhibition is essential for parasite establishment in the triatomine anterior midgut. *T. rangeli* (Macias strain) also has been shown to modify the microbiota of *R. prolixus* gut and successfully colonize it (Vieira et al., 2015).

1.2. Triatomine immune response against Trypanosoma rangeli

Some differences have been observed in the triatomine capacity to react against *T. rangeli* at the species level. Gregorio and Ratcliffe (1991) collected and analyzed different triatomine tissues (hemolymph, midgut, hindgut and salivary glands) from *R. prolixus* and *T. infestans*, and exposed them to *T. rangeli* in-vitro. It was observed that midgut and hindgut from *T. infestans* are able to agglutinate parasites. This characteristic was also observed in hemolymph from *R. prolixus.* On the other hand, lytic activity against the parasite was observed in salivary glands from *T. infestans*, while no lytic activity was observed in this tissue when coming from *R. prolixus*. This finding partially explains why *R. prolixus* is

Table 1
Triatomine response (immune system or parasite clearance) against *Trypanosoma cruzi.*

Triatomine species	Stage	Strain	Immune response or parasite clearance*	Reference
Rhodnius prolixus	Adults	Dm28c	Hemolymph (*in vitro*): Lysozyme activity, PO activity, Parasites agglutination	Mello et al., 1995
	5th	Y, 2-Cl-B, Dm28c	Parasite clearance (*in vivo*): Only Y was eliminated (not found in feces) Parasites agglutination in the gut (*in vitro*): Only Dm28c and 2-Cl-B were agglutinated Parasite clearance in hemolymph (*in vitro*): Only Y was eliminated Parasites agglutination in Hemolymph (*in vitro*): Only 2-Cl-B was agglutinated	Mello et al., 1996
	5th and adults	nd	Midgut and hemolymph (*in vitro*): Parasites were agglutinated Stomach (*in vitro*): Parasites were not agglutinated	Pereira et al., 1981
	5th	Dm28c	Gut (*in vitro*): PO activity, Reactive Nitrogen Species	Castro et al., 2012
	5th	Dm28c, Y	Fat body (*in vivo*): Only the antimicrobial peptides *prol, defA, defC* were activated against both strains Anterior midgut (*in vivo*): The antimicrobial peptides *defB defC* and *prol* were only activated against Dm28c Posterior midgut (*in vivo*): The antimicrobial peptide *prol* was activated against both strains, *defC* was only activated against Dm28c and *defB* was not activated	Vieira et al., 2016
	4th	TcI, TcII	Feces: Only TcII were cleared	Mejía et al., 2009
Rhodnius pallescens	4th	TcI, TcII	Only TcII were cleared	Mejía et al., 2009
Rhodnius robustus	4th	TcI, TcII	Only TcII were cleared	Mejía et al., 2009
Panstrongylus geniculatus	4th	TcI, TcII	Parasites were not cleared	Mejía et al., 2009
Triatoma infestans	adults	Y	Salivary glands (*in vitro*): Trialysin activity	Amino et al., 2002
	4th	TcI, TcII	Parasites were not cleared	Mejía et al., 2009
Triatoma brasiliensis	5th	TBRA/BR/1999/JCA3 (TcII)	Anterior midgut and posterior midgut *(in vivo*): The antimicrobial peptide *Def1* was activated	Waniek et al., 2011
	4th	TcII		
Triatoma dimidiata			Parasites were not cleared	Mejía et al., 2009

* *In vitro* refers to tests in laboratory exposing the parasite to triatomine fluids, hemolymph, feces, or macerated tissues (body fat, anterior midgut, posterior midgut, rectum and/or salivary glands).
In vivo refers to feeding insects with infected blood and response sampled in hemolymph, tissues or feces.
nd, not specified by the author.

able to transmit *T. rangeli* through saliva.

The capacity of hemolymph from 10 different species of triatomines (*T. infestans, T. dimidiata T. maculata, R. pallescens, R. colombiensis, R. ecuadoriensis, R. stali, R. robustus* and domestic and wild *R. prolixus)* to control the parasite, allowed to detect trypanolytic activity against two *T. rangeli* strains; P53 (KP1 -) and "Duran" (KP1 +). Barreto-Santana et al. (2015) analyzed the susceptibility of four Rhodnius species (*Rhodnius robustus, Rhodnius neglectus, Rhodnius nasutus* and *Rhodnius pictipes*) to a Brazilian strain of *T. rangeli* (SC-58/KP1-), and showed that infectivity in intestinal, hemolymphatic and glandular tissue and the transmission of *T. rangeli* (SC58/KP1-) by bite, were greater and more efficient in *R. pictipes*. Another study used two *T. rangeli* strains, KP1 (-) I/COL/CO/98/P53 and KP1 (+) I/PRX/CO/84/P19), isolated from salivary glands from *R. colombiensis* and *R. prolixus,* respectively, and tested against *R. prolixus* hemolymph. Four lytic fractions separated through gel filtration chromatography (GFC) were identified. The G1 fraction had higher trypanolytic activity than the remaining fractions (G2, G3 and G4). The protein extracted from G1 fraction acts as a biologic barrier against KP1 (-) *T. rangeli* strains infections, since it is responsible for the inhibition of parasite development and therefore renders this triatomine *(R. prolixus*) resistant to this subpopulation of parasites. When *R. prolixus* is infected with *T. rangeli* KP1 (+) type, the protein does not recognize the parasite and then it could be transmitted through saliva to the vertebrate hosts (Pulido et al., 2008). More recently, Vallejo et al. (2015) showed that opposite to short epimastigotes from *T. rangeli* KPI (-) strains that were sensitive to *R. prolixus* hemolymph, long epimastigotes were resistant. Hemolymph from other triatomine species (*R. pallescens, R. colombiensis, R. ecuadoriensis, Triatoma dimidiata* and *Triatoma maculata)* did not demonstrate trypanolytic activity in hemolymph (Table 2).

Several cellular and humoral mechanisms involved in the interaction of *R. prolixus* with *T. rangeli* have been discovered. Some of them limit parasite development (Vallejo et al., 2009a; Table 2). Among the immune system elements that have been identified in triatomines we can highlight lysozymes, lectins and lytic factors (Mello et al., 1995, Mello et al., 1999; Gomes et al., 1999; Gregorio and Ratcliffe, 1991; Pereira et al., 1981), the prophenoloxidase (PPO) system that results in PO activation (Mello et al., 1995; Gomes et al., 1999, 2003; Garcia et al., 2004b; Gregorio and Ratcliffe, 1991), phagocytosis and hemocyte micro-aggregation (Mello et al., 1995; Gregorio and Ratcliffe, 1991; García et al., 2004b, Figueiredo et al., 2008), RNS such as nitric oxide, ROS such as anion superoxide (Whitten et al., 2001, Whitten et al., 2007) and the signaling molecules eicosanoids and PAF (Garcia et al., 2004a). There is also evidence of melanization in hemocyte micro-aggregations, called nodule formation, as a defense mechanism against the parasite. Alvarenga et al. (1990) described these melanized nodules in response to biological challenges. Although *T. rangeli* long epimastigotes forms suppress the PPO system that produces melanin (Gomes et al., 1999, 2003). In that report, the authors concluded that *T. rangeli* epimastigotes could interrupt the average physiologic capacity of the fat body to activate the PPO.

It has been shown that the insect has some capacity to control infection but that it is dependent on the infecting strain. H14 and Choachi *T. rangeli* strains do not have the same ability to colonize *R. prolixus* digestive tract (Whitten et al., 2007; Machado et al., 2001;

Table 2
Triatomine response (immune system or parasite clearance) against Trypanosoma rangeli.

Triatomine species	Stage	Strain	Immune response or Parasite clearance	Reference
Rhodnius prolixus	Adults	R 1306	In hemolymph (*in vitro*): Parasites were agglutinated, Parasites were not cleared In salivary glands (*in vitro*): Parasites were not cleared	Gregorio and Ratcliffe, 1991
	Adults	Clone 1 San Agustin	In hemolymph (*in vivo*): Parasites were not cleared, Parasite were not agglutinated, Lysozyme activity, PPO activity	Mello et al., 1995
	Adults	H14	In hemolymph (*in vivo*): PPO activity In fat body (*in vivo*): No protease activity	Gomes et al., 1999, 2003
	5th and adults	I/COL/CO/98/P53 (KP1-) I/PRX/CO/84/P19 (KP1+)	In hemolymph (*in vitro*): Only KP1- were cleared	Pulido et al., 2008
	5th	H14	In hemolymph (*in vivo*): Hemocyte agglutination, PPO activity	Garcia et al., 2004a, 2004b
	4th and 5th	Choachi H14	In hemolymph (*in vivo*): PPO activity only against H14 and Choachi short forms, Superoxide production only against H14	Whitten et al., 2001
	4th	Macias	Anterior and posterior midgut (*in vivo*): Only antimicrobial peptide, *Def C* was activated	Vieira et al., 2015
	3th and 5th	Choachi	Crop, fat body, mid gut, rectum, salivary glands (*in vivo*): Nitric oxide expression	Whitten et al., 2007
	nd	KP1 (-) KP1 (+)	Hemolymph (not specified if *in vivo* or *in vitro* by the author): Only KP1 – were cleared	Vallejo et al., 2015
Rhodnius pallescens	nd	KP1 (-) KP1 (+)	Parasites were not cleared	Vallejo et al., 2015
Rhodnius colombiensis	nd	KP1 (-) KP1 (+)	Parasites were not cleared	Vallejo et al., 2015
Rhodnius ecuadoriensis	nd	KP1 (-) KP1 (+)	Parasites were not cleared	Vallejo et al., 2015
Triatoma infestans	Adults	R 1306	In digestive tract (*in vitro*): Parasites were agglutinated In salivary glands (*in vitro*): Parasites were cleared In gut extract: Parasites were not cleared	Gregorio and Ratcliffe, 1991
Triatoma dimidiata	nd	KP1 (-) KP1 (+)	Parasites were not cleared	Vallejo et al., 2015
Triatoma maculata	nd	KP1 (-) KP1 (+)	Parasites were not cleared	Vallejo et al., 2015

* *In vitro* refers to tests in laboratory exposing the parasite to triatomine fluids, hemolymph, feces, or macerated tissues (body fat, anterior midgut, posterior midgut, rectum and/or salivary glands).
In vivo refers to feeding insects with infected blood and response sampled in hemolymph, tissues or feces.
nd, not specified by the author.

Vallejo et al., 2009b). Macias strain from *T. rangeli* can modify the natural intestinal microbiota composition from some triatomines during infection (Vieira et al., 2015). Short epimastigotes of KP1(+) *T. rangeli* strain, were able to colonize the gut, reach the hemocele and replicate within hemocytes of *T. infestans, T. brazillensis, T. sordida, T. vitticeps* and *Panstrongylus megistus*. All triatomine species included in that study were susceptible to infection by the parasite (De Stefani-Márquez et al., 2006). The infection success of *T. rangeli* to Rhodnius genus is dependent on the parasite immune modulation in the digestive tract before it reaches the hemocele (Garcia et al., 2004a). Therefore, once the parasite enters the hemocele of the insect, the humoral and cellular responses are depressed, which allows the parasite to develop to infective forms (Azambuja and García, 2005; Azambuja et al., 2005; García et al., 2009; García et al., 2012). Additionally, the successful infection of *T. rangeli*, represented as the ability to generate metacyclic trypomastigotes within the invertebrate host, is associated to the production of ecto-phosphatases (Gomes et al., 2008; Dos-Santos et al., 2012, 2013; Freitas-Mesquita and Meyer-Fernándes, 2014). If *T. rangeli* KPI (+) infects triatomines of the *R. prolixus, R. robustus or R. neglectus* species, the short epimastigotes cross the digestive tract wall, reach the hemocele, invade hemocytes and reproduce in there. Then short epimastigotes develop into long epimastigotes, which adhere to salivary glands and invade them, where metacyclic trypomastigotes are produced. In contrast, when *T. rangeli* KPI (-) infects *R. prolixus* or *R. robustus,* the short epimastigotes cross the intestinal wall and reach the hemocele, they are immediately killed by trypanolytic factors present in the hemolymph (Vallejo et al., 2015).

In summary, according to the information above presented, four components in the interaction parasite-vector are determinant in the infection: triatomine species (and possibly, its virulence), parasite genotype, the cellular and humoral immune response of the insect and the intestinal microbiota of the triatomine (Schaub, 2009; Garcia et al., 2010; Garcia et al., 2012).

1.3. Invertebrate immune memory: a potential new avenue for research in triatomines?

Recent studies performed in ctenophores, insects, crustaceans, and mollusks, shows a complex invertebrate immune system (Cooper, 2018), including immune memory capability (Milutinovic and Kurtz, 2016; Contreras-Garduño et al., 2016; Lanz-Mendoza and Contreras-Garduño, 2018). In invertebrates, immune memory is termed immune priming and is an enhanced specific protection resulting from past experience with a pathogen or parasite (Little and Kraaijeveld, 2004; Kurtz, 2005). It is important to note that immune priming is a specific protection that may occur at the level of species or even strain of the same species and that it is not an enhanced and non-specific response (Milutinovic and Kurtz, 2016; Contreras-Garduño et al., 2016; Lanz-Mendoza and

Contreras-Garduño, 2018).

The flour beetle (*Tribolium confusum*) larvae infected with gregarines, an intestinal parasite of Coleoptera, show reduced infection when they were re-infected in adult stages, when compared to adult beetles not infected in larval stages (Thomas and Rudolf, 2010). In a similar study, *Anopheles albimanus* challenged earlier with *Plasmodium berghei*, were less infected and had a higher survival rate than mosquitoes that had no early contact with the parasite. This resistance to the protozoan lasted most of the mosquitoes' adult life (Contreras–Garduño et al., 2014; Contreras–Garduño et al., 2015). The infection of *A. albimanus* with *P. berguei* revealed a biphasic immune response, just as seen in vertebrates during the memory process (Contreras–Garduño et al., 2015). It is known now that the invertebrate's immune memory is so specific that it can recognize even pathogen strains (Kurtz and Franz, 2003; Roth et al., 2009). Besides, it is well known that the specific immune protection is transmitted from parents to offspring, a phenomenon termed immune priming or memory, across generations (Tetreau et al., 2019). In *Apis mellifera*, queens protect their offspring specifically against *Paenibacillus larvae* and in *Galleria mellonella*, such specific protection may last for 25 generations with constant exposure of parasites to the host (Dubovskiy et al., 2013).

In the specific case of triatomines, immune memory within or across generations has not been studied. It would be interesting to find out if triatomines have immune memory against *T. cruzi* and/or *T. rangeli* and their virulence factors. As described above, the interaction triatomine-Trypanosome is complex, and it would be interesting to find out if immune memory is present or not in this interaction. For example, regarding this topic, given that immune memory in invertebrates is conditioned by the pathogen (species, strain, and virulence), the immunological memory of invertebrates should not be discarded when a specific interaction of a host species and its pathogen is under investigation (Medina-Gómez et al., 2018a; Medina-Gómez et al., 2018b). The wide range of trypanosomes virulence factors and the wide range of triatomine immune responses against parasites make the investigation of the immune memory essential to discover the reason for the success or failure of infection and immune memory. A study that includes different triatomine species, challenged with a diversity of *T. cruzi* or *T. rangeli* strains, would provide an adequate model to understand such interaction better. Additionally, it would be interesting to find out whether inherited epigenetic factors are involved in the wide range of immune responses of triatomines *versus* trypanosomes, based on the suspicion that such epigenetic factors somehow control protection of the progeny (Little et al., 2003; Tetreau et al., 2019; Castro-Vargas et al., 2017; Gegner et al., 2019; Mukherjee and Vilcinskas, 2019).

Finnaly, here we assumed that immune response is the only mechanism against *Trypanosoma*, but it has been also demonstrated that microbiota from the insects gut may interact with their parasites (Campos et al., 2007; Vallejo et al., 2009a; Castro et al., 2012; Ribeiro et al., 2014; Vieira et al., 2015; Vieira et al., 2018; Gumiel et al., 2015; Rodríguez-Ruano et al., 2018; Waltmann et al., 2019; Hu et al., 2020; Fredensborg et al., 2020; Jiménez-Cortés et al., 2020; Salcedo-Porras et al., 2020; Vogel and Coon, 2020) and there is species, regional and ontogenetic variation in the insect-microbiota interaction (Kieran et al., 2019; Arias-Giraldo et al., 2020; Brown et al., 2020). Regarding the topic of immune priming, it has also proposed that insects microbiome may play an important role on its outcome and performance (Futo et al., 2016, 2017). However, there is conflicting results in insect vectors because for example, in *Anopheles albimanus* against *Plasmodium berghei*, the mosquitoe resistance is mediated by gut bacteria (Rodrígues et al., 2010) or not mediated by gut bacteria, but, by the immune response (a truly immune memory; Contreras-Garduño et al., 2015). Future work in triatomines should test whether, its microbiome affect or not the immune priming outcome and performance, and if such impact exist, whether there is variation according to species, population and ontogeny.

2. Conclusion

Innate immune system activity of triatomines against *T. cruzi* and *T. rangeli* depends not only on the triatomine species but also on *T. cruzi* /*T. rangeli* strain involved in the infection. During a trypanosome infection in triatomines, the parasite can invade the digestive system, the hemolymph and/or the salivary glands. The innate immune system of triatomines activates defense mechanisms that involve hemocytes, the prophenoloxidase pathway, lytic activity, oxidative and nitrosative stress, antimicrobial peptides expression among other defense mechanisms. All of these mechanisms are part of the insects immediate defense to control infections. It is not known if all these mechanisms respond the triatomines system to induce a stronger defense reaction against secondary infections, but it seams likely that it can happen and should be studied in detail. Epigentic mechanisms (Castro-Vargas et al., 2017; Mukherjee and Vilcinskas, 2019) and endoreplication (Contreras-Garduño et al., 2015) should also be taken into account as well as how the immune system recognize specifically the immune invaders and were and how the parasites specific traits are stored and recall after specific subsecuent infections. It is important to consider that interaction between different parasite's and/or insect's species (or strains) may influence the efficiency of the immune response of triatomines to parasites, since the parasite can be locally adapted to damage or not the insect host, and the host may or may not be able to eliminate the infection. Further research needs to be done, analyzing the co-evolution between different phylogenetic groups of triatomines and parasites to comprehend if there is a specific immune memory response at the level of gene by gene and/or gene by environment. The increasing triatomine-trypanosome interaction from the immune priming point of view, will enrich the knowledge about insects' immune system complexity, and will probably provide information that would contribute to designing new strategies to prevent vector-mediated *T. cruzi* human infection.

Declaration of Competing Interest

We have any conflict of interest.

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