Review Article

Parasite–Vector Interaction of Chagas Disease: A Mini-Review

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Abstract. *Trypanosoma cruzi* is a protozoan of great importance to public health: it has infected millions of people in the world and is the etiologic agent of Chagas disease, which can cause cardiac and gastrointestinal disorders in patients and may even lead to death. The main vector of transmission of this parasite is triatomine bugs, which have a habit of defecating while feeding on blood and passing the parasite to their own hosts through their feces. Although it has been argued that *T. cruzi* is not pathogenic for this vector, other studies indicate that the success of the infection depends on several molecules and factors, including the insect’s intestinal microbiota, which may experience changes as a result of infection that include decreased fitness. Moreover, the effects of infection depend on the insect species, the parasite strain, and environmental conditions involved. However, the parasite–vector interaction is still underexplored. A deeper understanding of this relationship is an important tool for discovering new approaches to *T. cruzi* transmission and Chagas disease.

The *Trypanosoma cruzi* (Chagas, 1909) protozoan is a parasite belonging to the order Kinetoplastida and the family Trypanosomatidae that acts as an etiologic agent of Chagas disease.¹ Also known as American trypanosomiasis, this disease is neglected² and potentially life-threatening³; although most infected individuals are asymptomatic and do not exhibit clinical symptoms of the disease, 30–40% of patients develop cardiac diseases, gastrointestinal disorders, or both.⁴ The treatment available consists of benznidazole and nifurtimox, but the effectiveness of both drugs decreases as the time after infection increases; ideally, treatment is administered in the early acute phase. In addition, these drugs cannot be used by pregnant women or patients with neurological or psychiatric disorders.³ Although there is still a considerable lack of interest among pharmaceutical companies to perform research and create programs to combat Chagas disease, this illness represents a major public health problem. It is the most prevalent parasitic disease in the Americas and makes an important contribution to morbidity and mortality rates in countries where it is endemic.⁵

It is estimated that approximately 6,000,000–7,000,000 people worldwide are infected with *T. cruzi*, and most cases are located in Latin America.³ However, Chagas disease has spread to nonendemic areas and has been reported in countries such as Canada, the United States, Japan, Australia, New Zealand, Switzerland, Italy, and Spain.⁶ This spread arises from the congenital transmission of the parasite or through contaminated blood transfusions. Although *T. cruzi* transmission can also occur during infected donor organ transplantation, laboratory accidents, or the ingestion of contaminated food, the main transmission pathway of this parasite is through a vector: triatomine insects.^{7,8} Triatomines have a habit of defecating while feeding on blood and, if they are infected with *T. cruzi*,

the parasite is released through the feces in infectious form (trypomastigotes).⁹

Triatomines have hemimetabolous development, which includes an egg phase, five nymphal stages and, finally, the adult phase. Hematophagy occurs in all stages after hatching, and the insects usually bite at night.¹⁰ These bugs belong to the order Hemiptera, the suborder Heteroptera, the family Reduviidae, and the subfamily Triatominae. The 152 known species of triatomine bugs are divided into 18 genera and 5 tribes,^{11–15} all of which have the potential to act as *T. cruzi* vectors. Enhancing the knowledge on the relationship between the parasite and these vector species may aid in the creation of simple techniques for diagnosing triatomine infections, such as xenodiagnosis. The rate of infectivity seems to vary between species of triatomine bugs, and it has been shown that, although the domestic species are of immense importance in the transmission of the parasite, it is the wild vectors which have higher levels of infectivity.¹⁶

There are seven discrete typing units of *T. cruzi* classified based on different molecular markers,¹⁷ namely TcI, TcII, TcIII, TcIV, TcV, TcVI, and TcVII.^{18,19} This protozoan is known to be harmful to humans and other mammals. Although it has been argued that this species is not pathogenic for its triatomine hosts, small changes in insect fecundity can harm host fitness, as observed in a study on *Panstrongylus megistus* (Burmeister, 1835). The study found that development, mortality rates, and the time between molting periods in the infected group were similar to those of the control group; however, the number of eggs laid by infected females was 3.5 times lower, and the infected group exhibited a decrease in both the number of fertile eggs and the hatching rate.²⁰ However, knowledge on the parasite–vector relationship is still very scarce and some of the available information is poorly understood or conflicting.²¹ Although the relationship between these organisms is generally considered harmonious and although *T. cruzi* does not seem to be pathogenic to its invertebrate hosts, some studies have reported adverse effects of this infection,²¹ and this finding will be discussed in this mini-review.

Studies indicate that bacteria play a protective role against *T. cruzi* in triatomines. Intestinal microbiota composition can

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interfere with infection effectiveness, and a test showed that use of antibiotics made it easier for the parasite to increase its competence in the intestine of *Rhodnius prolixus* Stål, 1859.²² The success of the infection appears to depend on a balance between the microorganism and protozoan populations because both compete for resources in the intestine; furthermore, microbiota can indirectly increase the expression of antiparasitic molecules and induce immune response in the insect.²³ However, sequencing and analysis of the *R. prolixus* genome suggest that either the insect immune system is not affected by *T. cruzi*, or the parasite is not affected by antimicrobial peptides produced as a consequence of the infection. These findings indicate that *T. cruzi* developed avoidance or tolerance mechanisms against invertebrate host defenses.²⁴

In addition, the dynamic control of epimastigote and trypomastigote populations is crucial for the parasite to be able to colonize the insect gut, because *T. cruzi* is exposed to different environments during its life cycle, including different digestive tracts and different invertebrate hosts.²⁵ For the parasite to adapt to different parts of the insect and for infection to be achieved, several factors and molecules are necessary. Evidence indicates that physiological molecules with antagonistic redox status assist in the proliferation and differentiation of *T. cruzi*.²⁶ Oxidant molecules such as heme stimulate the proliferation of noninfective epimastigotes,^{27,28} and antioxidant molecules such as urate promote metacyclogenesis, an event in which epimastigotes create infective and nonproliferative trypomastigote forms.²⁹ Thus, a clearer understanding of the role of these molecules in the interaction between these organisms is an important target for the development of strategies for treating Chagas disease.²⁶

In a study comparing *Triatoma infestans* (Klug, 1834) specimens infected with *T. cruzi* in the first feeding after hatching to uninfected triatomines used as control, there was no significant increase in mortality rates or any developmental delays in the insects.³⁰ Another study found that in the same triatomine species, colonization by the parasite does not cause harmful changes to the intestinal tissue.³¹ On the other hand, numerous physiological, morphological, and behavioral factors of an organism can be modified when it hosts a parasite. For example, infection by *T. cruzi* increases the ability of *Mepraia spinolai* (Porter, 1934) hosts to detect vertebrate and decreases their time between feeding and defecation. These changes are likely to enhance parasite transmission and, consequently, reflect the epidemiological importance of this vector in Chagas disease.³²

Furthermore, Fellet et al.²¹ observed losses in reproductive performance in a study on *R. prolixus*. The parasite may reduce insect fitness and affect host survival.^{21,33,34} In addition, studies have found that infection by *T. cruzi* increased the mortality rate of *M. spinolai*, reduced the oviposition and hatching rate of *P. megistus* eggs, decreased reproductive fitness of *R. prolixus* under temperature conditions similar to those of the natural environment in which this species is found, and in the case of some strains, may have extended the molting period and reduced insect longevity.³³ In another study, infected *Triatoma dimidiata* (Latreille, 1811) specimens were found to have larger wings than uninfected insects; these findings suggest a possible relationship between this difference in morphology and host dispersion potential, which could contribute to the protozoan transmission.³⁴

Thus, the effects of *T. cruzi* on triatomines vary depending on different factors, including the parasite strain, the triatomine species, and the environmental conditions involved (including temperature and nutritional status). Therefore, the adverse effects described previously and on the limited amount of research specifically focused on the interactions between triatomines and *T. cruzi* show this is an area that can be studied in greater detail.³³ Moreover, the best way to intervene in the transmission of this parasite is through its vector. Other studies, for example, have confirmed that treatment with azadirachtin decreases the total number of flagella and blocks metacyclogenesis,³⁵ and there is evidence that this tetranortriterpenoid has different effects on different triatomine species and *T. cruzi* strains.³⁶ Thus, research into the interactions between these organisms are likely to increase in the future, and a better understanding of different species' interactions with this parasite can provide important information for the development of new approaches for the control of Chagas disease.³⁷

Because metabolic interaction between an intracellular parasite and host cell is essential for colonization to be successful³⁸ and because the relationship between parasites and vectors results in two-way interactions that impact other members of the vectors' community, it is important to improve our knowledge and understanding of the influence of *T. cruzi* infection on triatomines.³⁹ This parasite-vector relationship is relevant and should be explored further to increase the knowledge on the consequences of infection by this parasite, which is of great importance to public health in many countries.

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