Journal of Theoretical Biology 340 (2014) 23–29

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Can we heal Chagas infection?

S.P. Vega Royero, G.J. Sibona *

IFEG - CONICET and FAMAF, Universidad Nacional de Córdoba, Medina Allende s/n, 5000 Córdoba, Argentina

HIGHLIGHTS

- A model for the parasite-antibody competition between *T. rangeli* and antibodies.
- The model reproduces experimental data from murine models.
- A preinfection with *T. rangeli* induces a temporary protection against Chagas.
- A preinfection could reduce the in-house vectorial parasitemia.

ARTICLE INFO

Article history:
Received 13 May 2013
Received in revised form
1 September 2013
Accepted 3 September 2013
Available online 9 September 2013

Keywords:
Trypanosoma rangeli
Trypanosoma cruzi
Chagas disease
Mathematical modeling

ABSTRACT

We present a model for the parasite-antibody dynamical competition between *Trypanosoma rangeli* and its antibodies during the acute phase of an infection in a mammal host. The model reproduces experimental data from murine models found in the literature and allows us to demonstrate that a preinfection with *T. rangeli* induces a temporary protective effect against Chagas disease. As the mammal immune system is able to eliminate a single *T. rangeli* infection, the host high antibody levels, needed to resist the Chagas infection, are reduced with time, returning the system to the initial healthy state. Our results suggest that a preinfection with *T. rangeli* could be used to reduce the in-house vectorial parasitemia through repeated vaccination of domestic animals.

1. Introduction

Chagas disease is a condition caused by the intracellular protozoan parasite *Trypanosoma cruzi*. It is endemic in Latin America, affecting nearly 10–12 million people and killing more than 15,000 people each year (World Expert Committee, 2002). Nowadays, due to human migration, it is possible to find Chagas cases in some countries of Europe and North America. Usual transmission to humans is through the bite of haematophagus triatomine bugs, but it could also occur by blood transfusion, congenital transplacental, organ transplant and laboratory accidental infection. The parasite *T. cruzi* moves among mammals (reservoirs), humans and triatomine insects (vectors), having three different morphological stages during its life cycle. Under natural conditions, Chagas disease transmission cycle begins when a triatomine acquires the parasitic infection by feeding on the blood of an infected animal or human. Once inside, in the epimastigote stage, the parasite divides rapidly in the insect gut. When the triatomine takes another blood meal, it defecates on the skin of the mammal, depositing parasites (but in the metacyclic trypomastigote stage). *T. cruzi* is introduced into the mammal body by the bite wound, through other cuts and abrasions or through the soft skin of eyes and mouth. Once the parasites are inside, they can penetrate in the host cells, transforming into amastigotes which reproduce by binary fission. After a period of time the cell is full of new parasites and bursts, releasing them into the bloodstream, again in the trypomastigote circulatory stage. In turn, these trypomastigotes can penetrate a new cell or be ingested during other bug bite.

There are others trypanosomes, like *Trypanosoma rangeli*, widespread in Latin American countries. *T. rangeli* is also transmitted by the bite of triatomines, but the contagion is through insect saliva (not faeces), and it is non-pathogenic to a vertebrate host (Guhl and Vallejo, 2003). Due to its innocuity, there are few studies of this parasite, and its life cycle in mammals remains unclear. There are some studies showing the presence of amastigote forms in experimentally infected mice. In particular, Urdaneta-Morales and Tejero (1986) reported intracellular nest, or pseudocysts, containing amastigotes and trypomastigotes of this parasite in heart, liver and spleen of a lactating male white mice (NMRI strain) from a 12-day-old culture of the Dog-82 strain of *T. rangeli*. Osorio et al. (1995) also observed *amastigote-like* forms in an *in vitro* experimental infection of the U937 histiocytic cell line. Remarkably, both studies cited above agreed that observed intracellular forms were

* Corresponding author. Tel.: +54 351 4334051.
E-mail address: sibona@famaf.unc.edu.ar (G.J. Sibona).

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http://dx.doi.org/10.1016/j.jtbi.2013.09.002

rare and lacked replication. In contrast, other experiments did not found any intracellular forms. For instance Eger-Mangrich et al. (2001) observed low infectivity but no-intracellular *T. rangeli* replication (Choachi, Macias, and SC-58 clone B1 strains) in Vero cells and murine promonocytes. Añez et al. (1985) observed only circulating blood forms in Albino mice and *Didelphis Marsupialis* bitten four times by *R. prolixus* triatomines infected with the *T. rangeli* parasite. Koerich et al. (2002) developed a method to induce high *T. rangeli* differentiation *in vitro*, testing the infectivity of those culture-derived trypomastigotes in Balb-C mice, and finding just blood-circulating parasites. Considering all these studies, we will assume that *T. rangeli* trypomastigotes reproduce by binary fission in the bloodstream, neglecting the existence of any intracellular form.

Both parasites, *T. cruzi* and *T. rangeli*, share endemic areas and vectors, and the two have a strong antigenic relationship (Basso et al., 1991). As a consequence, mixed *T. cruzi–T. rangeli* infections can occur, making a Chagas disease diagnosis difficult, and a cross reaction between them is possible. Based on this, several researchers, like Basso et al. (1991, 2004, 2007, 2008), Cervetta et al. (2002), Marini et al. (2011), Zuñiga et al. (1997) and Paláu et al. (2003) have proposed a vaccination procedure for Chagas disease. They performed experiments in mice and dogs, using *T. rangeli* epimastigotes to generate protection against a posterior *T. cruzi* infection by inducing an overproduction of antibodies. They found that the *T. cruzi* parasitemia level was lower and lasted a shorter period of time in preinfected animals. The immunization schedule elicited B and T specific responses against *T. cruzi*, associated with high levels of specific antibodies and a particular pattern of cytokines, ending in a strong reduction in the mortality rate among infected mice. More than 95% of vaccinated mice survived an otherwise lethal *T. cruzi* infection, displaying a significantly reduced parasitemia during the acute phase of Chagas disease (Cervetta et al., 2002). The results suggest that it might be possible to reduce the vectorial parasitemia through vaccination of domestic animals. As dogs and poultry are known to play a major role in the domestic cycle of *T. cruzi*, this might represent an appropriate strategy to reduce parasite transmission to humans.

In the last years mathematical modeling had become a useful tool to study the defense mechanisms against parasite/bacteria (Okamoto and Amarasekare, 2012; Arciero et al., 2010; Day et al., 2006). In particular, our group has developed a model to describe the interaction between *T. cruzi* and the immune system (Condat et al., 2003; Sibona and Condat, 2002) during the acute phase of Chagas disease. This model was improved and extended (Sibona et al., 2005; Vega et al., 2011) leading to a good description of the experimental data found in the literature. The model accurately predicts all possible outcomes of the disease: healing, death, and chronic infection, with stationary or quasi-cyclical populations, and allows us to estimate the damage generated by direct parasitic action. For *T. rangeli* instead, this work is the first attempt to reproduce its interaction with the mammal immune system; its aim is to elucidate the parasite dynamics inside the host and build the basis to reproduce Basso's experiments (Cervetta et al., 2002). Here we give a possible explanation to the cross-reaction activity observed between the two parasite populations (*T. rangeli* and *T. cruzi*) through the competition between them and with several antibodies species. Our final goal is to answer the question if *T. rangeli* could be used as a vaccine against Chagas disease.

The rest of the paper is organized as follows. In Section 2, we model the time evolution of the acute stage of a *T. rangeli* infection, based on a previous mathematical model for *T. cruzi* that neglects intracellular replication (Condat et al., 2003). We analyze the properties of this model, showing the time evolution of the populations and the long time steady state values associated with them. Next, in Section 3, we study the heterologous *T. rangeli–T. cruzi* infection, assuming for the evolution of the *T. cruzi* population a model that includes the different stages of the parasite life cycle inside the host (Sibona et al., 2005). We study also, how the phase diagram (in terms of an effective parasite reproduction rate and the antibody generation rate) of a single *T. cruzi* infection is modified by the presence of *T. rangeli*. In Section 4, we examine in detail the acute phase of the Chagas infection for a host pre-infected with *T. rangeli*, showing that the combined model can reproduce the features observed in mixed infections experiments, and confirming Basso's postulates. In particular, we found that a preinfection with *T. rangeli* causes an activation of the immune system (increasing the antibody levels) during a certain period of time. This protective effect disappears when the immune system returns to the initial values, causing the loss of host immunity.

2. *Trypanosoma rangeli*

2.1. The model

This is the first attempt to model a *T. rangeli* parasite infection. The model offers a great opportunity to identify and analyze the different aspects of parasite life cycle inside the host. Considering the absence of evidence of active intracellular replication (Eger-Mangrich et al., 2001; Añez et al., 1985; Koerich et al., 2002), we will work on a previous version of the Chagas infection model (Condat et al., 2003; Sibona and Condat, 2002), which only takes into account the extracellular replication of the parasite. In the present model, the number $m(t)$ of *T. rangeli* parasites increases at a rate κ_m due to reproduction by binary fission, and decreases due to the interaction with antibodies. Assuming that there are N antibody species capable of mediate parasite removal, we quantify the likelihood of antibody-mediated parasite removal upon an encounter through the set of coefficients $\alpha_{i,m}(t)$. The time dependence of the parasite number is then described by the equation

$$\frac{dm(t)}{dt} = \kappa_m m(t) - \sum_{i=1}^{N} \alpha_{i,m}(t) a_i(t) m(t) \tag{1}$$

where $a_i(t)$ is the number of antibodies of species i at time t. This number increases at rate $\gamma_{i,m}$ due to the parasite-induced activation of the immune system associated to the *T. rangeli* presence. However, the production process is not instantaneous and the model considers that there is a delay $\theta_{i,m}$ between the parasite population growth dynamics and antibody creation. The model also assumes that antibody species i has an intrinsic lifetime τ_i and an equilibrium population a_{i0} in the absence of parasites. A relatively large initial population of specific antibodies (larger than a_{i0}) could mean that a previous infection took place in the host and the immune system is already activated. With these considerations the evolution equation for the antibody population is

$$\frac{da_i(t)}{dt} = \gamma_{i,m} m(t-\theta_{i,m}) - \alpha_{i,m}(t) a_i(t) m(t) + \frac{1}{\tau_i}[a_{i0} - a_i(t)] \tag{2}$$

To model the optimization process of the antibodies specificity, we assume that the removal efficiency $\alpha_{i,m}(t)$ is governed by an exponential learning process

$$\alpha_{i,m}(t) = \alpha_{Ai,m} + \alpha_{Bi,m}(1 - \exp[-t/T_i]) \tag{3}$$

This function describes a smooth increase of the antibody efficiency from an initial value $\alpha_{Ai,m}$ to a saturation value $\alpha_{Ai,m} + \alpha_{Bi,m}$ with a "learning time" T_i for each antibody species i.

2.2. Steady states

The model analysis is simplified by considering first the outcomes for a single antibody species at the asymptotic ($t \to \infty$)