Further thoughts on where we stand on the autoimmunity hypothesis of Chagas disease

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The notion that Chagas disease could be autoimmune in nature has stirred controversy since it was proposed in the mid-1970s. In his recent Trends in Parasitology article [1], Kierszenbaum eloquently describes and critiques key experimental results supporting and refuting an autoimmune mechanism of pathogenesis, as he has done in several other reviews of a similar nature [2–4]. Several points merit further discussion.

Although some experimental models of autoimmunity rely solely on self-protein–peptide immunization for ‘purely autoimmune’ disease induction, it is usually accepted that, in infection-based diseases such as Chagas disease, the infectious agent is essential for the initiation of pathogenesis and that potential for further aggravation results from autoimmune responses. In fact, many mechanisms of inflammation other than autoimmunity – including direct cytolysis, antiparasitic immunity and microvascular spasm – have been demonstrated in humans or animals. The tremendous variability in the outcome of Trypanosoma cruzi infection and the wide range of disease severity, even among those with cardiomyopathy, make it unreasonable to consider Chagas disease a single illness with a single pathogenic mechanism. A troubling assertion in Kierszenbaum’s article is that the autoimmunity hypothesis has somehow discouraged the development of vaccines and new trypanocidal drugs [1]. As stated elsewhere [5–7], although infection induces autoimmunity, the parasite is central to the initiation of disease and, thus, eradication of the parasite would be beneficial. This is especially true in Chagas disease because, as mentioned, autoimmunity is unlikely to be the sole effecter of tissue inflammation. The concern that a vaccine might induce autoimmunity assumes that the latter must result from molecular mimicry and that a successful vaccine must contain the mimic antigen. Neither assumption is true. In the immunogenetically susceptible host, autoimmunity can result from bystander activation after tissue damage. Disease that results primarily from tissue damage is a more reasonable hypothesis because it provides a common mechanism for the cardiac autoimmunity that is seen in other viral (e.g. coxsackievirus and encephalomyocarditis virus) and bacterial (e.g. Streptococcus pyogenes) infections and in non-infectious insults (e.g. myocardial infarction) to the heart.

Should autoimmunity be a major concern in Chagas disease? The existing discrepancies require further investigation. Although no role has been established for functional pathogenic autoimmunity, the evidence that both humoral and cellular autoreactivity can develop in some instances is overwhelming (for review, see Refs [5,8]). Although it has been shown that cardiac myosin-specific autoimmunity is not essential for cardiac inflammation in early, acute experimental Chagas disease, these results do not preclude a role for autoimmunity in the inflammation observed in later, chronic stages of the disease when T. cruzi is virtually absent [9]. Furthermore, cell-mediated autoreactivity to non-myosin cardiac antigens has not yet been investigated thoroughly. There have been numerous attempts to prove that autoimmunity is pathogenic in Chagas disease and Kierszenbaum is correct in asserting that this is a daunting task. It is possible to make a case for a pathogenic role of autoimmunity in Chagas disease using carefully executed experiments showing that antibody or T-cell transfer from animals infected with T. cruzi to naive recipients results in myocarditis. Prior reports of the successful transfer of disease have produced conflicting results or suffer from flaws in experimental design [10,11].

Without experimental proof that it is pathogenic, autoimmunity will continue to be considered an effect of infection-induced dysregulation of the immune response rather than a contributing cause of inflammation. Perhaps autoimmunity in Chagas disease is irrelevant. Without additional experimentation that clearly dissociates the autoimmune, antiparasitic and other non-immune components of tissue inflammation, the issue will remain unresolved.

Kierszenbaum emphasizes that Chagas disease research is particularly challenging [1]. It is likely that several pathogenic mechanisms operate to different extents depending on the immunogenetics of the host, the
virulence of the parasites, and other physiological factors. The difficulty arises when investigators attempt to study only one mechanism in the setting of active infection, when other coincident mechanisms can confound the results. An important point raised by Kierszenbaum is the cautionary note regarding optimism related to progress in vector control because this could quickly become insufficient if resistant insects began to emerge. A collective effort is essential for reducing or eradicating Chagas disease and, although further investigation of the mechanisms of pathogenesis is a key component of this endeavor, the pursuit of answers about the autoimmunity hypothesis cannot be allowed to hinder such progress. Instead, all research must be unified and have a common aim of developing vaccines and discovering drugs to treat the millions of people currently infected with T. cruzi or suffering from chronic Chagas disease.

References
10. dos Santos, R.R. et al. (1992) Anti-CD4 abrogates rejection and reestablishes long-term tolerance to syngeneic newborn hearts grafted in mice chronically infected with Trypanosoma cruzi. J. Exp. Med. 175, 29–38