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Immunopathology during African Trypanosomosis

Jennifer Cnops[1,2], Magdalena Radwanska[3] and Stefan Magez[1,2*]

[1]Laboratory of Cellular and Molecular Immunology, Vrije Universiteit Brussel, Brussels, Belgium
[2]Department of Structural Biology, Vlaams Instituut voor Biotechnologie (VIB), Brussels, Belgium
[3]Ghent University Global Campus, Incheon, South Korea

Abstract

African trypanosomes are the causative agents of Human African Trypanosomosis (HAT), otherwise termed 'Sleeping Sickness', and Animal African Trypanosomosis (AAT) or 'Nagana'. These parasites infect humans and animals throughout the African continent, where they cause death and impair economic development. In this review we describe the events leading to the onset of inflammation in the mouse model for trypanosomosis, and we describe two important pathological features associated to the acute pro-inflammatory reaction: anemia and B cell destruction.

Keywords: Sleeping sickness; African trypanosomosis; *Trypanosoma brucei brucei*; *Trypanosoma congolense*; *Trypanosoma vivax*

Introduction

Human African Trypanosomosis (HAT) can be caused by *Trypanosome brucei gambiense* or *Trypanosoma brucei rhodesiense*. *T. b. gambiense* is responsible for 98% of all HAT cases and is endemic in West and Central Africa. *T. b. rhodesiense* infection accounts for the remaining 2% of HAT cases and is prevalent in East Africa. HAT can be divided into two stages: an early haemolymphatic stage and a late meningoencephalitic stage. During the early stage the parasite proliferates in the blood and lymphatic system. When the parasite crosses the blood brain barrier, the late stage begins. Both stages accommodate their own symptoms [1-3], but in general HAT is a wasting disease in which a progressive loss of fitness occurs [4]. The characteristic sleep disturbances, responsible for the name Sleeping Sickness, cause a deregulation of the circadian rhythm [1,3].

AAT can be caused by *Trypanosoma brucei brucei, Trypanosoma congolense, Trypanosoma equiperdum, Trypanosoma simiae, Trypanosoma suis* and *Trypanosoma vivax*. AAT is a similar wasting disease as HAT and affects both wild and domestic animals. AAT has an immense impact on agriculture and economic development of the affected rural areas. According to the Food and Agricultural organization (FAO) the total losses, in terms of agricultural Gross Domestic Product, is estimated at US$ 4.75 billion per year [4].

Antigenic variation is an organized mechanism of surface coat switching that trypanosomes employ to evade the host immune system [5,6]. The surface coat of African trypanosomes consists of 107 densely packed copies of a variant surface glycoprotein (VSG). This surface coat is highly immunogenic and permits the host to rapidly mount an anti-VSG immune response; however African trypanosomes can simply switch to a different coat of VSGs, previously unseen by the host's immune system. The *T. brucei* genome contains approximately 1000 non-expressed VSG genes and pseudo-genes, giving the parasite a virtual unlimited number of VSG's to employ throughout the infection [7-10]. New mosaic VSGs can be composed of silent VSG genes and pseudo-genes via partial gene conversion. VSG expression follows a loose hierarchy and mosaic VSGs appear increasingly as the infection proceeds, contributing immensely to antigenic variation and infection chronicity [11].

Attempts to eradicate HAT from the African continent are hampered by the large animal reservoir in which the parasite resides [12]. This reservoir allows tsetse flies to keep transmitting the disease to humans. Hence, prophylactic vaccination is the only way to protect the human population from HAT. However, over the last decades different vaccination strategies have been designed, but not a single one obtained effective sterile immunity [13]. This is due to the fact that African trypanosomes possess multiple mechanisms to evade and manipulate the host immune system to ensure their survival and hence transmission potential. Due to the VSG antigenic variation system, parasites can continue to escape the host immune system. The increasing suppression of the immune system as the infection progresses further ensures parasite survival.

An alternative to sterile immunity is anti-disease vaccination targeting infection-associated pathology.

Immunopathology

Upon infection, the extracellular parasites replicate and proliferate in the host's bloodstream and lymphatics where they are constantly exposed to the host's immune system. This evokes a strong type 1 immune response [14-16], and together with antibodies and cytotoxic effector molecules this allows the host to control the first parasitemia peak [17]. However, African trypanosomes have acquired various mechanisms to manipulate and evade the host immune response, evading effective elimination and establishing a chronic infection [18]. Hence the bloodstream no longer poses a hostile threat, but has become a niche where trypanosomes thrive and obligatory await transmission through the bites of tsetse flies, ideally without causing severe infection-associated pathology to their host. However, as the infection progresses, the immune system becomes increasingly exhausted and suppressed [19,20], leading to loss of parasitemia control, severe inflammation-associated pathology and ultimately death of the infected host. *T. b. brucei* infection in C57Bl/6 mice is a commonly used mouse model to study the immune response and the host parasite immune interface. This infection model is characterized by low levels of parasitemia accompanied by high levels of pathology (weight loss & anemia) [16].

***Corresponding author**: Stefan Magez, Laboratory of Cellular and Molecular Immunology, Vrije Universiteit Brussel, Brussels, Belgium, Tel: 32-(0)2-629 19; E-mail: stemagez@vub.ac.be

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The onset of inflammation: IFNγ as a crucial driver

After the onset of infection, parasite antigens are continuously released into the host bloodstream and lymphatics. Shedded VSG molecules and parasite DNA are considered to be the two major pathogen associated molecular patterns (PAMPS) implicated in the initiation of the immune response [21]. Consequently, NK and NKT cells are quickly activated [22]. NK and NKT cells can be directly activated through their pattern recognition receptors and T cell receptors respectively, or indirectly through the production of IL-15 and IL-12 by myeloid cells [23-27]. Upon activation, NK and NKT cells produce IFNγ. Subsequently CD8 T cells and CD4 T cells are activated and contribute to the IFNγ production during early infection [22]. Antigen-specific T cell activation during *T. b. brucei* infection has been extensively described [28-30], and a T cell-dependent antibody response is critical for control of the first parasitemia peak [17,31]. However, non-specific activation of CD8 T cells has also been reported via a molecule called Trypanosome Lymphocyte Triggering Factor (TLTF), which acts directly on CD8 T cells to induce IFNγ production [32]. Concomitantly to early lymphocyte activation, trypanosome PAMPS activate monocytes, neutrophils, macrophages and DCs via their PRR [21,33]. IFNγ further activates these cells and the production of trypanocidal factors including TNF, reactive nitrogen intermediates and reactive oxygen intermediates is induced [21,34-36]. Antigen presenting cells are then recruited to secondary lymphoid organs where they initiate trypanosome-specific adaptive immunity.

IFNγ is a crucial driver of the type 1 immune response during murine trypanosome infection. Without IFNγ, the characteristic early pro-inflammatory cytokines are absent and there is no recruitment or activation of myeloid cells [22]. Interestingly, this coincides with a higher and prolonged parasitemia peak and a reduced survival time [37,38]. In this respect IFNγ has been denoted a protective function, despite its implication in infection-associated inflammation and its associated pathologies.

A strong type 1 inflammatory reaction is not a unique characteristic of murine trypanosome infections. Pathology of human trypanosomosis involves a similar detrimental inflammatory reaction as pro-inflammatory mediators, among which IFNγ, are found in elevated levels in serum and cerebral spine fluid of infected patients, and correlate to signs of inflammation and neurological disorders [39-42]. Likewise, during bovine African trypanosomosis in cattle, production of pro-inflammatory cytokines correlates to disease severity [43,44]. The strong type 1 pro-inflammatory response therefore seems to be a hallmark of the general host-pathogen interaction during trypanosomosis.

For the host it seems that although the inflammatory response induces inflammation-associated pathologies, it aids in parasite control and consequently survival via (i) activation of myeloid cells and consequent induction of trypanocidal mediators and (ii) the induction of parasite-specific antibodies [45]. On the other hand, while the induction of this amount of inflammation is detrimental for the survival of the parasite as an individual, a better control of the entire parasite population is beneficial as this leads to a prolonged host survival and consequently infection chronicity and enhanced transmission potential. Indeed, the parasite has no 'intention' of killing the host as a dead host, equals a dead parasite.

Inflammation associated pathology: anemia and B cell destruction

A first pathology directly linked to IFNγ-driven inflammatory reaction is acute anemia. In mice, IFNγ, produced early in the infection by NK, NKT and CD8 T cells activates and recruits monocytes and neutrophils to liver and spleen [22,46]. Here monocytes differentiate to monocyte-derived macrophages [22]. Due to the pro-inflammatory environment and direct IFNγ signaling, these cells display enhanced phagocytosis of circulating RBC. This results in a 50% reduction in RBC numbers within 48 hours after control of the first parasitemia peak [47].

In trypanosome-infected cattle, anemia is induced early in the infection and hyper-activated macrophages are correlated to massive erythrophagocytosis in spleen and liver [44,48-50]. Similarly, during human trypanosomosis, enhanced erythrophagocytosis of damaged RBC is also described [51], although it is not clear at what point during the infection anemia is induced. While anemia contributes to pathology, there is no evidence of anemia-induced mortality in trypanosome-infected mice or natural hosts [1-3,16,48,52,53].

Induction of anemia could be a way for the host to control the infection. Pro-inflammatory signals, in addition to increased RBC phagocytosis, can result in higher iron retention in erythrophagocytozing cells. As iron is an essential nutrient for the parasite, deprivation of iron could limit parasite growth. Indeed, iron starvation is a frequently employed host tactic to battle invading pathogens [54]. It is possible that this protective effect significantly outweighs the detrimental effect of anemia, and has therefore been selected throughout the evolution as a consequence of host-pathogen interactions. Indeed, in the chronic phase of murine *T. b. brucei* infection, enhanced RBC phagocytosis leads to higher iron retention in erythrophagocytic cells [14,55]. However, during the acute infection stage both genes for iron export and iron retention are upregulated in phagocytozing cells, and serum iron concentrations increase [14,55]. In this way, enhanced iron availability in the blood can aid individual parasites in their survival during the first proliferation stage and perhaps protect them from immediate eradication. Iron retention in the chronic infection stage could ensure chronic parasitemia control, prolonged survival and hence augmented transmission potential.

A second murine *T. b. brucei*-infection associated pathology, which is at least partly associated to inflammation, is the destruction of the B cell compartment. In mice, immediately after the acute infection phase, various splenic B cell subsets disappear [56,45,57-59]. Multiple factors can contribute to this phenomenon. First of all, polyclonal B cell activation can immediately contribute to exhaustion of the splenic Marginal zone B (MZB) and Follicular B (FoB) cells. Although this has not been described for trypanosome infections, IFNγ plays a major role in the induction of polyclonal B cell activation during *Plasmodium chabaudi* infections [60]. Hence it could be hypothesized that IFNγ can play a similar role during *T. b. brucei* infections. Secondly, the continuous induction of new humoral responses with each new VSG coat and parasitemia wave, could lead to an excess of B cell activation, resulting in exhaustion. In addition, IFNγ induces apoptosis in FoB cells and is crucial for the disappearance of the FoB compartment [61]. Finally, B cell lymphopoiesis in the bone marrow is reduced under influence of the ongoing inflammatory reaction, preventing replenishment of mature splenic B cell subsets [62]. Coinciding with B cell disappearance, the induction of a protective memory response is inhibited [52,45] and vaccination experiments against unrelated pathogens show that trypanosomes destroy previously induced vaccine-induced memory against unrelated pathogens [45,63]. Curative treatment with diminazene aceturate or suramin effectively restores B cell lymphopoiesis and leads to the repopulation of B cells in the spleen,

however it does not re-establish the lost memory B cell compartment [64].

Although polyclonal B cell activation is also a characteristic of trypanosome infections in humans and cattle [19,65-68], it is not known whether destruction of B cell compartment occurs in these natural hosts. In light of these results, Lejon et al. (2014), conducted a field trial on *T. b. gambiense* infected individuals. In this study, immunological memory was assessed by measuring anti-measles antibodies of vaccinated subjects before and after anti-trypanosomosis treatment. Anti-measles antibodies were significantly lower in HAT patients compared to controls, and although they remained lower after treatment, the levels were above the cut off value assumed by the manufacturer to provide protection. These results are promising; however, it must be kept in mind that antibody quantification is a sub-optimal tool for the investigation of immunological memory as polyclonal B cell activation can replace the measles-specific antibodies by low-affinity cross-reactive antibodies. Hence a functional characterization is necessary to determine if the antibodies maintain their protective capacity. Further investigation into a functional antibody assay should confirm these results. In addition, B cell memory destruction needs to be investigated in *T. b. rhodesiense* infections, as these are more virulent and elicit more inflammation and pathology.

It seems quite unlikely that B cell destruction by itself is beneficial to the host as control of parasitemia (and consequent survival) relies partly on induction of parasite-specific antibodies [17,28]. Could it be that destruction of the B cell compartment is an unwanted side effect of the strong pro-inflammatory response generated during the acute infection phase? And what would be different about African trypanosome infections compared to other infections causing acute inflammation that do not elicit B cell destruction?

In addition to antigenic variation, destruction of the B cell compartment could be an evasion strategy by which trypanosomes ensure infection chronicity and transmission potential. This could give the parasite an opportunity to re-use previously expressed VSGs during the chronic infection phase. A recent study by Hall et al. (2014) revealed that during the chronic infection phase, the parasite recycles previously expressed VSG genes to synthesize new mosaic VSGs [11]. If these mosaic genes would contain previously expressed epitopes, the parasite would benefit from B cell memory loss. However, the authors suggest that these mosaic genes are antigenically distinct, implying that there is no need for B cell memory destruction. Again the question arises whether B cell destruction could merely be an unintended side effect of the strong, IFNγ-driven pro-inflammatory environment coinciding with peak parasitemia, rather than an additional evasion strategy developed by the parasite. In this respect it is interesting to mention that in contrast to *T. b. brucei* infection, murine *Plasmodium chabaudi* infection leads to a temporary disappearance of splenic B cells. Splenic B cells disappear during the initial strong Th1 response, characterized by high levels of IFNγ, and reestablish themselves after the infection switches to a Th2 inflammatory environment [60]. It is possible that B cell destruction is an artifact of more virulent murine *T. b. brucei* infection models, and that this does not accurately reflect host-pathogen interactions. B cell destruction during low virulent *T. brucei* infections should be investigated.

Conclusion

African trypanosomes elicit a strong pro-inflammatory reaction early in the infection. While this inflammation aids in keeping the parasite population under control, it is also responsible for the induction of inflammation-associated pathologies. Acute anemia and possibly B cell destruction are direct consequences of the over-activated state of the immune system. These pathologies weaken the host but ensure parasite survival by enhancing infection chronicity and transmission potential (Figure 1).

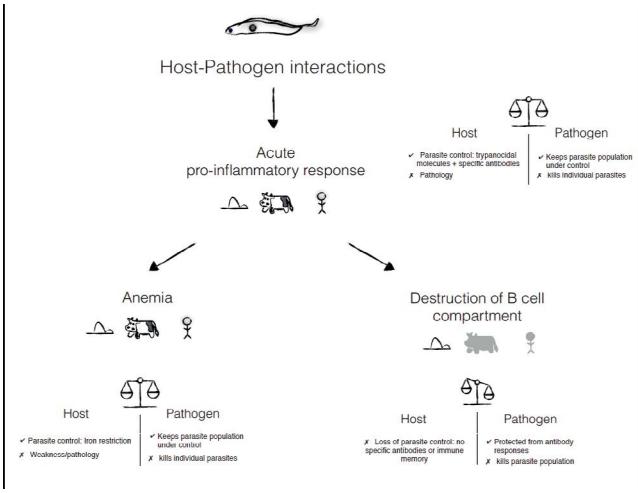

Figure 1: Overview of the host pathogen interactions during African trypanosomosis in mice, cattle and humans. Three phenomenon's are depicted: acute pro-inflammatory response, Anemia and Destruction of the B cell compartment. When the phenomenon has been described for a specific host the symbol is depicted. If not, the symbol is greyed out. Advantages and disadvantages for parasite and host are listed in a table accompanying each phenomenon. The tipping of the scale indicates whether the phenomenon is in favor of host or parasite. If the scale is balanced, the characteristic favors both host and parasite.

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