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Immune Responses to Animal Trypanosomosis: A Review

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Abstract

The aim of this document is to review the current knowledge on Trypanosome parasites of animals with emphasis on the immunological response and points to the wealth of information available for trypanosomiasis, in contrast to the numerous gaps in our understanding of immune responses to trypanosomal infections. African trypanosomes are pathogens for humans and livestock. They are single-cell, extra-cellular parasites that cause persistent infections of the blood and induce profound immune-suppression. The specific immune response to the infecting parasites is complex and involves both the humoral and cellular branches of immune systems. In trypanosomosis, parasite growth is primarily controlled through T-cell dependent antibody responses to the variable surface glycoproteins and possibly to other molecules embedded on the surface of the parasites. Cellular immune responses also occur but at the level of immune-suppression directed against B cells. Additionally, a variety of immune-modulatory cytokines like TNF-α, IFN-γ, IL-10, IL-4, IL-6, IL-12 and etc are produced during the course of infection. The center of the immune-pathology is the T-cell-independent production of antibodies to the variant surface glycoprotein of trypanosomes, the anti-VSG antibody-mediated phagocytosis of trypanosomes by macrophages, and the subsequent profound dysregulation of the macrophage system. It has, however, been demonstrated that a T-cell subset is critical in protective immunity.

Keywords: Animals, Cytokines, Immune responses, Immuno-pathogenesis, Trypanosoma.

INTRODUCTION

Trypanosomosis is among the well-known constraints to livestock production in Africa as it causes a serious and often fatal disease of livestock mainly in the rural poor community and rightfully considered as a root cause of poverty in the continent [1]. The overall economic loss due to the disease was estimated between US $1408 and 1540 million per annum [2]. The main parasites that cause disease in livestock are tsetse-transmitted *T.congolense* and *T.vivax* and to a minor extent *T.brucie.* Their distribution is restricted to Africa, although *T.vivax* has crossed the Atlantic and spreads in South America via mechanical transmission by biting flies. *Trypanosome evansi* is also transmitted by biting flies and infects a wide range of livestock, including camels and buffalo in parts of Asia. Cattle are also an epidemiologically important reservoir for the human-infective parasite *T.b.rhodesiens* [3].

African trypanosomes are extracellular parasitic protozoa, transmitted by the bite of the tsetse fly [4]. *Trypanosoma b.brucei*, *T.vivax* and *T.congolense* are the causative agents of Nagana, a cattle disease similar to sleeping sickness, caused in humans by *T.b.gambiense* and *T.b.rhodesiense*. All these parasites need to survive a long time exposure to the immune system of their mammalian host, as they multiply predominantly in the blood stream. Hence, well equilibrated growth regulation systems must exist, allowing the parasite to survive sufficiently long without killing its mammalian host, to ensure an effective transmission of the species. Such a system involves the variant-specific surface glycoprotein, which is the major surface antigen and acts as a protective coat for the parasite [5, 6].

In the mammalian host, the whole parasite is covered with a glycoprotein coat of a single molecular species, called the variant surface glycoprotein (VSG). The surface coat of one trypanosome consists of about 107 VSG molecules. The VSG is anchored into the cell membrane via glycosylphosphatidylinositol (GPI). The GPI lipid, a diacylglycerol (DAG) moiety consisting of two myristic acid chains linked to glycerol, is inserted into the outer leaflet of the trypanosomal cell membrane. The extracellular phosphoinositolglycan (PIG) moiety of the GPI links the DAG with the variant protein. The variability of the VSG is provided by the variable amino-acid sequence of its N-terminal portion. The capacity for antigenic variation in African trypanosomes is almost unlimited. There

is a surprisingly great turnover of the VSG on the surface of the parasite. The VSG cell-surface pool of *T.brucei* is recycled within 12 min [7].

During the ascending parasitaemia, the majority of the dividing parasites (e.g., long slender forms) belong to the same antigenic type, called the homotype. A peak of parasitaemia is reached when long slanders differentiate into non-dividing, short stumpy forms, which have a relatively short in vivo half-life of 24–36 hr and release VSGs in the circulation upon degeneration [8]. These degenerating parasites allow the host to develop an antibody response to the homotype [9]. Subsequently, the parasitaemia enters a descending phase as trypanosomes of the major variable antigen type are eliminated. In contrast to the homotype VAT, spontaneous arising minor VATs or heterotypes continue to multiply during the descending phase of the parasitaemia. One of these VATs will overgrow the others and become the new homotype, giving rise to a new peak of parasitaemia [10]. Although an effective anti-VSG response allows the host to regularly eliminate excessive numbers of parasites through phagocytosis of opsonized parasites [11].

Recently it has become clear that growth control of trypanosomes involves specific immune regulatory molecules. Both EGF [3] and interferon gamma (IFN-γ) were shown to enhance the growth of *Trypanosoma brucei*. As IFN-γ synthesis was shown to be induced during trypanosomiasis, this growth regulation can be considered as active. Another cytokine shown to be induced during trypanosome infections is tumor necrosis factor-α (TNF-α) [13], a cytokine mainly produced by activated macrophages [14]. Although the name of this cytokine is derived from its capacity to cause hemorrhagic necrosis of certain parenchymal organs and certain tumors, the molecule was initially isolated from the serum of *T.brucei* infected rabbits as a factor called “cachectin,” responsible for systemic suppression of lipoprotein lipase activity and trypanosome induced cachectia [15, 16]. In recent years TNF-αwas found to be involved in the pathology of several parasitic diseases, including trypanosomiasis [17], Chagas’ disease [18], leishmaniasis [19], Schistosomiasis [20], and malaria [21], and in many of these cases this cytokine plays a bidirectional role [22].

The modulation of host immunity during infection is highly diverse, both in regard to the spectrum of infectious agents involved and in the immune functions which can be affected. Experimental systems, and to a lesser extent clinical studies, have illustrated immune dysfunction in infections by viruses [23], bacteria [24] and metazoan and protozoan parasites [25, 26]. Particularly acute immunological changes are seen in mice infected with the extracellularly replicating African trypanosomes [27]. The activity of almost all lymphoid cell subpopulations is affected by *T.brucei* infection. T and B cell responses to antigens and mitogens are suppressed within a few days of virulent infection [28, 29, 30]. A strong polyclonal mitogenic pressure acts on splenic lymphocytes [28] while the cells do not respond to antigen selection. Infection with less virulent clones leads to an early, but transient, enhanced immune responsiveness [28, 31].

The nature of the interaction between the parasite and the immune system is still not clearly understood, but the host's normal homeostatic control mechanisms are disturbed. Macrophages after uptake of parasites can mediate immune-suppression and thus serve at least as one key target cell for parasite action [32]. These cells play a key role in controlling B and T cell function [33] and in trypanosomiasis they are activated, undergoing major changes in phenotype and mediator release [34]. Since soluble mediators such as the interleukins (IL), prostaglandins (PG) and interferons (IFN) appear to influence immune activity, changes in their production may represent a means by which micro-organisms can alter immune competence. IFNs are no longer considered to be produced only during virus infections, but are increased by many non-viral agents such as bacteria, foreign and neoplastic cells, synthetic polyribonucleotides and some intracellular protozoa [35] and can induce changes in immunological function [36]. Therefore, the objective of this paper is to review on the immunological response to trypanosome infection.

TRYPANOSOMOSIS

Trypanosomes

Trypanosomes are flagellated protozoa, which belongs to the family trypanosomatidae. The family consists of several genera and many species. The species which parasitize vertebrates require a vector for transmission [37]. Trypanosomes live and multiply in the blood stream, lymphatic vessels and tissues, including the cardiac muscle and the central nervous system. There are many species of Trypanosome. Three species, *T.congolense*, *T.vivax* and *T.brucei* cause animal African trypanosomiasis or nagana disease. Only two subspecies of *T.brucei*; *T.b.gambiense* and *T.b.rhodesiense*, which are morphologically indistinguishable, but have different epidemiological features and measuring 20-30µm by 1.5-3.5µm are infectious to humans. They can be differentiated by molecular methods not parasitological ones. The third subspecies, *T.brucei brucei* is not infectious to humans or a subset of catarrhine primates. Because of their innate protection, which in tsetse flies, Trypanosoma infection rates are various. *T.vivax* species has the highest and *T.brucei* species has the lowest infection rates [38].

Figure 1: *Trypanosoma brucei* in a blood smear (Source; [38])

Trypanosomes can infect all domesticated animals; clinical cases have been described in cattle, water buffalo, sheep, goats, camels, horses, donkeys, alpacas, llamas, pigs, dogs, cats and other species. The host preferences of each trypanosome species may differ, but *Trypanosoma congolense*, *T.vivax* and *T.brucei brucei* have a wide host range among domesticated animals. *T.godfreyi* and *T.suis* occur in pigs. *T.simiae* appears to be most important in pigs, but it has also been reported by PCR in camels, horses and cattle. In parts of Africa, cattle are the main species affected, due to the feeding preferences of tsetse flies; in effect, they can shield other domesticated animals such as goats and pigs from the effects of trypanosomiasis. More than 30 species in the wild or zoos, including ruminants such as white-tailed deer, duikers, antelope and African buffalo, as well as wild Equidae, lions, leopards, warthogs, capybaras, elephants, nonhuman primates and various rodents are also known to be susceptible to infection. *T.vivax* deoxyribonucleic acid (DNA) has been found by PCR in crocodiles and monitor lizards (*Varanus ornatus*) in Africa, but whether this organism can become established in reptiles or it is merely inoculated transiently by insect

remains to be determined. Experimental infections can be established in laboratory animals including mice, rats, guinea pigs and rabbits [39].

Biology and lifecycle of trypanosomes

The life cycle of the African trypanosome begins when a tsetse fly feeds from an infected mammalian host. The non-proliferating, stumpy-form parasites that are pre-adapted for life in the fly rapidly undergo structural and metabolic transformation to insect-stage cells (procyclic form) in the gut lumen. Within several days, trypanosomes are reported in the ectoperitrophic space of midgut between the peritrophic matrixes and gut epithelial cells [40]. The development of different trypanosome species in site of the fly is different. Blood streams forms (trypomastigates) ingested by the fly undergo considerable changes, in morphology as well as in their metabolism. They change in to long slender forms called epimastigotes, which multiply and finally give rise to the infective metatrypanosome [41]. The life cycle of trypanosome is complex in both the tsetse fly vector and the mammalian host. Trypanosomes undergo a series of transformation into different forms [42].

The infective metatrypanosomes undergo development and multiplication at the site of infection where a swelling or chancre may be detected in the skin; and finally the mature blood trypanosomes (typeomastigotes) are released via lymph vessels and lymphnodes in to blood circulation. Reproduction in the mammalian host occurs through a process of binary division. Trypanosomes feed by absorbing nutrients through their outer membrane, from the body fluids of the host [41].

Epidemiology

The transmission of trypanosomiasis is either cyclically by tsetse flies or mechanically by hemathophagus flies. So, the distribution of tsetse transmitted trypanosomosis is limited to the continent where the tsetse vectors are found. Mechanically transmitted trypanosomes are found in Africa, Asia, Middle East and South America [43]. Among the salivarian group only *T.vivax* and *T.evansi* are found beyond the tsetse belt areas by mechanical transmission [44].

Tsetse transmitted trypanosomosis affects 37 Sub-saharan countries; an estimate of 160 million cattle and 260 million sheep and goats are kept in this area of risk extending over 10 million km^2 of land [45]. In Ethiopia, the potential area of tsetse infestation has been variously estimated at 66,000km^2 based on a 1500m above sea level breeding limit [46] 98, 025km^2 based on 1600m above sea level breeding limit [47] and between 135,000- 220,000km^2, based on maximum dispersals up to 1700m above sea level and 2000m [48]. Table one shows the species of tsetse flies found in Ethiopia and the region in which they are found.

Host-Parasite interaction and pathogenesis

Interaction refers to inter dependent operation of factors to produce effect [49]. The outcome of disease occurrence depends on the interplay of the host, the agent (the parasite) and environmental factors. By adding or modifying the factors the frequency of the occurrence of the disease can be changed [49]. Upon the bite of the mammalian host by a trypanosome infected tsetse fly, the parasites multiply locally in the skin and elicit a local host response that manifests itself as an indurated skin lesion called the chancre. Eventually, the parasites enter the blood circulation via lymph vessels and can survive in the blood circulation throughout the infection of the host [50, 51]. Thus, they remain continually exposed to the host's immune system. *T.brucei* species have the ability to penetrate the walls of capillaries, invade interstitial tissues, but always remain extracellular. *T.congolense* is an extracellular, intravascular blood parasite that is unable to leave the circulation. *T.congolense* has a tendency to bind to walls of capillaries and small vessels of infected cattle and mice, the mechanism of which is unknown [52, 53]. African trypanosomes have evolved very sophisticated evasion mechanisms to survive in the chronically infected host. Well-documented evasion mechanisms include antigenic variation of the VSG [54] and the induction of alterations in the host's defense system, such as excessive activation of the complement system leading to persistent hypocomplementemia, down regulation of nitric oxide production, polyclonal B-lymphocyte activation and marked immune-suppression [55, 56, 57, 58]. Most likely African trypanosomes induce other, yet undiscovered, changes in the physiology of the infected host, which might interfere with effective control of the parasite [59].

The pathogenesis of tsetse transmitted trypanosomosis can be described according to the site of host- parasite interaction. In addition, the pathogenesis of the disease differs according to the species causing the infection. For example *T.vivax* and *T.congolense* appear to be parasites of the blood plasma and produce tissue injury. The first interaction between trypanosomes and host occur in the skin following a successful feed by an infected tsetse fly. Within a few days of bite, animal develop a raised cutaneous swelling called a chancre, caused as a result of the reaction of multiplying trypanosomes [60]. According to [61] the pathogenesis of trypanosomosis includes; chancre, lymphadenopathy, anemia and tissue damage.

Chancre which is the first interaction between the trypanosome and the host; is a raised cutaneous inflammatory swelling produced within few days at the site of inoculation of trypanosomes when the metacyclic forms multiply locally as typical blood forms [62]. This local response in the skin corresponds to the first protection developed by the host. Following inoculation of Trypanosomes (it can be *T.brucei*, *T.vivax* and *T.congolense*) into mammalian hosts, by the tsetse fly, a local skin reaction is induced by trypanosome proliferation and appears a few days after inoculation. In efferent lymphatic vessels, trypanosomes have been detected in lymph 1-2 days before the chancre. Their number declined during development of the chancre (6 days) and later increased. They are detected in the blood 5 days after inoculation. In *T. congolense* infected sheep, neutrophils predominate in the early days and then T and B lymphocytes infiltrate the chancre. Later, T lymphocytes predominate, especially $CD8^+$ T cells [63, 64]. An early response due to an increase in CD4+ and CD8+ T cells was revealed by flow cytometry in the afferent lymph draining the chancre. As the chancres regressed there was an increase in lymphoblasts and surface immunoglobulin bearing cells [65, 64]. During this first stage, trypanosomes expressed Variable Antigen Types (VATs) found characteristically in the tsetse fly, which changed after few days. An antibody response specific to these VATs appeared in the lymph and then in the plasma [66, 64]. Generally all the three cyclically transmitted species eventually undergo a chancre [67]; although the local skin reaction is less sever with *T.vivax* infections [43].

Following the chancre, enlargement of the lymph node (lymphadenopathy) characterized by, generalized enlargement of lymph nodes and splenomegaly develop. This is associated with marked proliferation of lymphoid cells in the organs. In the medullar cords of lymph nodes and splenic red pulp there are increases in plasma cells and numerous large active germinal centers are also present [68]. In addition, the red pulp of the spleen, there is an increase in the number of activated macrophages, some of which are engaged in erythro- phagocytosis. Like other infectious diseases, trypanosomes start with an increase of body temperature (hyperthermia). This is the result of the contact between the trypanosomes multiplying in the host and the defense system of the host [41]. In general the pathogenicity of the strain, the animal hosts, breed,

genotype, age, sex, skin type and most importantly, on the method by which the infection was induced that is natural or artificial [68].

The onset and severity of anemia is directly related to the appearance of the parasite in the blood and to the level of the parasitaemia. According to [69] the development of anemia is a well-recognized and inevitable consequence of trypanosome infection in domestic animals. In addition [70, 71] indicated that principal factor involved in the pathology of African trypanosomosis in humans and animals is anaemia; although the mechanisms through which the anaemia occurs remain open. However, haemolysis is involved in the early stage of the infection as a result of erythrophagocytosis by the mono nuclear phagocyte (monocyte-macrophage) system [72, 69]. Immunologic mechanisms also play a role in the trypanosomosis induced anaemia, which renders the erythrocytes more susceptible to phagocytosis [73]. Trypanosomes produce sialidase, which is a potent enzyme that cleaves off the membrane surface sialic acid of erythrocytes which results in a shortened life-span of erythrocytes by exposing the galactose of the cell membrane which readily binds to lectin on the surface of Kupffer cells and other macrophages, resulting in erythrophagocytosis [74, 73].

The initial fall in packed cell volume is associated with the first wave of parasitaemia in the blood. During this period anemia is extra vascular and is possibly the result of increased red blood cell destruction by erythrophagocytosis in the spleen, lungs haemal nodes and bone marrow as a result of direct traumatic effect on red cells thereby increasing red cell fragility [43]. According to [75] in those cattle subjected to a single fly challenge, the packed cell volume (PCV) progressively decreases by about 40-50% over the first 4-6 weeks. The figure below shows the pathophysiology of anemia as a result of infection with trypanosome parasite.

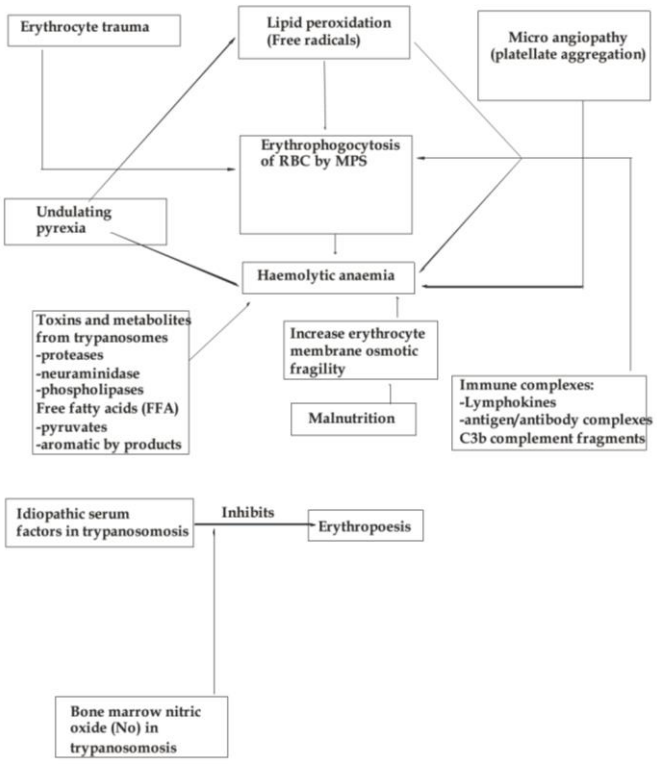

Figure 2: Pathophysiology of anaemia in African trypanosomosis (Source: [76])

DEVELOPMENT OF IMMUNITY AGAINST TRYPANOSOMES

Trypanosome antigens and exposure to host's immunity

African trypanosomes causing morbidity and mortality in both man and livestock are unusual among the protozoan parasites in that they never enter the host's cells and yet persist for extended periods of time in mammalian blood and tissues. In the mammalian host, these parasites are completely surrounded by a dense immunogenic surface coat (12–15 nm thick) of a single polypeptide species referred to as the variant surface glycoprotein (VSG) [5, 77] that shields invariant surface antigens from immune recognition. Moreover, trypanosomes constantly modify their VSG by the process of antigenic variation, resulting in the fluctuating waves of parasitaemia that characterizes African trypanosomosis [78, 79].

During their development in the invertebrate and vertebrate hosts, African trypanosomes pass through several morphologically distinct phases [10, 4]. For example In the case of *Trypanosoma brucei*, the infection is initiated by a haematophagous arthropod, the tsetse fly (Glossina species), depositing metacyclic trypanosomes in the mammalian host's dermal connective tissue, leading to local inflammatory reaction called the 'chancre', characterized by accumulation of macrophages, granulocytes and lymphocytes [66]. The parasites rapidly reach lymph and blood circulation and may traverse the walls of blood and lymph capillaries into connective tissues, but always remain extracellular. At a later stage, the parasites may cross the choroid plexus to reach the brain and the cerebro-spinal fluid. In all these sites, the parasites multiply by mitosis as long slender trypomastigotes with a doubling time of 5–10hrs [80].

In contrast, *T.congolense* is an extracellular intravascular blood parasite that is unable to leave the circulation but tends to bind to walls of capillaries and small vessels of infected cattle and laboratory rodents [81, 52, 53]. During the descending phase of the parasitaemic wave, the slender trypomastigotes are replaced by non-dividing short stumpy trypomastigotes which can only continue their life cycle in the tsetse vector. Once ingested by the vector during a blood meal, the stumpy trypomastigotes transform into actively dividing procyclic trypanosomes; and the vicious cycle continues [10, 4].

During the course of African trypanosomosis, a complex interaction between the host immune responses and parasite survival strategies occurs. As such, natural selection has enabled African trypanosomes to develop very sophisticated mechanisms to evade immune killing to survive in the chronically infected host and hence allow transmission to the next host, via the tsetse vector. Well-documented evasion mechanisms include antigenic variation of the VSG [75] and the induction of alterations in the host's defense system [82, 83, 84, 85, 86, 87]. Antigenic variation remains one of the most spectacular adaptive mechanisms exhibited by African trypanosomes and is the central most important immune escape mechanism by these parasites [88, 78]. Trypanosomes contain up to 1000 different genes in their genome which afford them extensive opportunities to escape host adaptive immune responses by displaying new coat antigens. The parasite has intrinsic mechanisms that ensure that only one VSG gene is transcribed at any one given time. By switching VSG genes and expressing a new variant antigenic type, trypanosomes evade B- and T-cell mediated immune

responses. Furthermore, expression of VSG is central to the process of antigenic variation that eventually leads to exhaustion of the host immune system for the benefit of the trypanosome [78, 79, 75].

During infection of a mammalian host, African trypanosomes are in constant contact with the host's immune system. Because of the strong selection pressure from continuous contact with the host's immune system, the trypanosomes seem to have developed several ways of evading immune killing through alteration of the host's natural and adaptive immune responses. For instance, *T.congolense* and *T.b.brucei* have been documented to induce a generalized state of immunosuppression following infection of cattle or mice [82]. The mechanisms of such immune depression seem to be mediated by both MFs [82, 89] and T cells [82] with suppressive phenotypes. In the case of MFs, the suppressive phenotype may be exhibited by both classically and alternatively activated cells (caMFs and aaMFs, respectively) [90, 91, 92]. These MF subsets are antagonistically regulated, and their development is influenced by the cytokine environment. Whereas caMFs are induced by type I cytokines (TNF-α, IL-12, IFN-c) and inhibited by type II cytokines (IL-4, IL-10, IL-13), the reverse is true for aaMFs [93]. Furthermore, whereas caMFs mediate pro-inflammatory responses and are microbicidal, aaMFs are anti-inflammatory and actively participate in tissue healing and contribute to peripheral tolerance [94].

Host responses to trypanosomes

The inoculation of trypanosomes into their mammalian hosts triggers a series of events involving, at first, innate immunity and, secondarily, specific immunity. The latter requires an efficient presentation of parasitic antigens, activation of T and B cells implying specific antigen receptor recognition, and the development of effector cells and molecules. These mechanisms are highly regulated by multiple signals delivered through a large number of receptors transduced across the plasma membrane and processed. During co-evolution with their hosts, trypanosomes have learnt to cope with host immune systems, by penetrating, diverting, and altering the numerous steps leading to the generation of an effective immune response. Major modifications of immune systems have been observed in trypanosomiasis: lymphadenopathy, splenomegaly (up to thirty times the normal size) with destruction of lymphatic tissue architecture and hypergammaglobulinemia. However, their effectiveness is limited as, most of the time, parasites cannot be eliminated and immunopathological phenomena, which induce tissue alterations [64].

VSG constitutes an important molecular interface between trypanosomes and the host immune system (Figure 3). VSG prevents trypanosome lysis by complement alternative pathway, and, above all, enables them to avoid the specific immune response via the phenomenon of antigenic variation (trypanosomes sequentially express antigenically distinct VSG). VSG also has several effects on immune elements such as induction of autoantibodies and cytokines, in particular tumor necrosis factor (TNF)-α [87]. Other trypanosome components and soluble factors, such as a trypanosome-released triggering factor (TLTF) which triggers interferon (IFN)-γ production by T cells, are also involved in modulation of the immune system by acting on the synthesis of immune elements [12], (Figure 4). Elaboration of escape mechanisms to host immune defenses and induction of parasite growth factor production are well developed by trypanosomes. In a recently discovered escape mechanism, host arginase induction, trypanosomes decrease immune response efficiency and increase the production of L-ornithine, an essential growth factor [95].

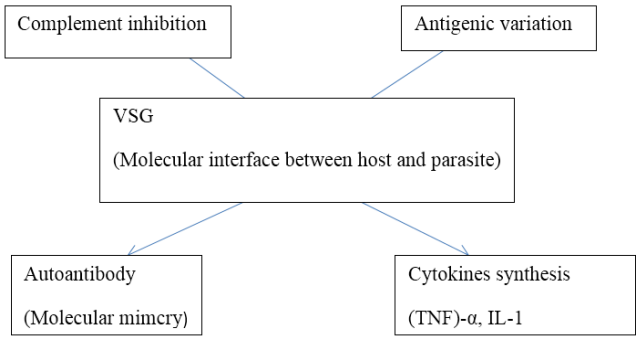

Figure 3: Variable surface glycoprotein (VSG), the major surface component of trypanosomes, is also released in host fluids (Source: [64]).

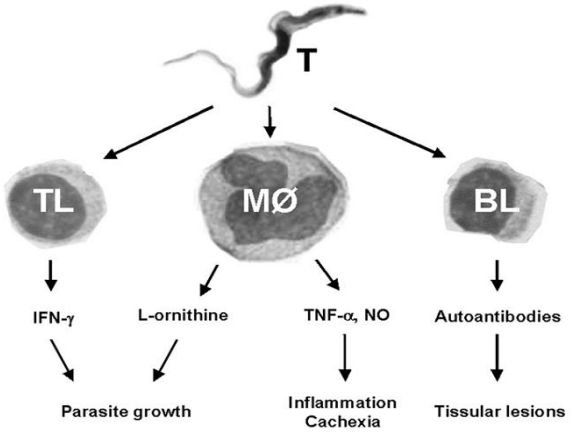

Figure 4: Secretion of various components from immune cells induced by trypanosomes. (T: trypanosome; Mø: macrophage; TL: T lymphocyte; BL: B lymphocyte) (Source: [64])

Understanding of the immune response was recently advanced by the discovery of the T and B subpopulations and, especially, of the T helper (Th) subsets, as well as the cytokines synthesized by each Th1 and Th2 subset. These factors control different aspects of the immune response, in peculiar the synthesis of nitric oxide, which is probably involved in several steps in the immune mechanisms [64].

Antibodies to VSG

The production of antibodies to the VSG of *T.brucei* or *T.congolense* is the major early immune response. The first antibody to the VSG is of immunoglobulin M (IgM) class and is produced independently of T cells [96]. Antibodies to the VSG are able to mediate control of the parasitaemia. There are three known mechanisms of anti-VSG-mediated control of parasitaemia [97]. These are:

i) antibody/complement-mediated immune lysis,
ii) phagocytosis by macrophages, and
iii) cytotoxic effect of induced nitric oxide

Although anti-VSG antibodies can mediate some degree of complement-mediated immune lysis, the parasites have developed mechanisms to evade an effective lysis [98]. Considering that anti-VSG antibody can induce shedding of soluble VSG (sVSG) into the circulation and mediate the formation of soluble complexes of sVSG covalently bound to degradation products of complement component C3, immune lysis might be more harmful than beneficial. In fact, *T.congolense* infected complement C5-deficient mice have about the

same survival time as infected wild type mice, indicating that immune lysis of trypanosomes is not an efficient control of infection [99].

Macrophages

Macrophages play a central role in immunity and immune deviation after phagocytosis of trypanosomes. Peripheral blood mononuclear cells and monocytes of resistant N'Dama cattle were found to produce more nitric oxide (NO) but less IL-10 than those of susceptible Boran cattle [100]. Peritoneal and bone marrow derived macrophages pulsed with opsonized *T.congolense* in vitro, in the presence of interferon-γ (IFN-γ), produced NO which was found to be cytotoxic for the parasite. *T.congolense* pulsed macrophages derived from relatively resistant C57Bl/6 mice produced more NO than those from susceptible BALB/c mice [101]. Macrophages from highly susceptible BALB/c mice, when pulsed with *T.congolense*, produced more IL-10 and IL-6 but less TNF-αand IL-12 than did equally treated macrophages derived from C57Bl/6 mice [102].

For instance, the most important mechanism of clearance of *T.brucei* from the blood of infected mice is mediated by antibodies to the VSG via phagocytosis of trypanosomes by Kupffer cells of the liver [103]. Complement component C3 appears to be required for optimal phagocytosis. Susceptibilities of A/J mice to *T.congolense* infections and C3H mice to *T.brucei* infections were not associated with an inability of the mononuclear phagocyte system to clear the parasite [104].

IgM anti-VSG-mediated phagocytosis of *T.congolense* by macrophages enhances synthesis of tumor necrosis factor-α, but inhibits synthesis of nitric oxide (NO) by these macrophages [57]. Antibodies specific for the exposed epitopes of the VSG are lead to rapid clearance of trypanosomes by the liver and the spleen due to phagocytosis by macrophages [103, 83].

Cytokines

Most, if not all, cytokines are produced by more than one cell type and most, if not all, are pleiotropic. Thus, the effect of a cytokine is dependent on the micro-environment, dosage, and timing in the course of a disease. One of the major activities of IFN-γ is activation of macrophages by inducing synthesis of various cytokines, e.g. TNF-α and IL-12, enhancing the production of NO and inducing the expression of surface molecules on the macrophages, such as major histocompatibility complex (MHC) class-II, B7-1, B7-2, etc. On the other hand, IL-10 down regulates the macrophage activating effect of IFN-γ [105].

The effects of lipopolysaccharide (LPS) in inducing endotoxic shock in experimental animals have been studied extensively. Many cytokines are involved in endotoxic shock, such as IL-1, IL-12, TNF-α, IL-10, and IFN-γ [105, 106]. The result of sepsis leading to a multiple organ dysfunction has been termed systemic inflammatory response syndrome (SIRS), associated with high serum levels of IL-6 and high IL-6/IL-10 ratio [107, 108] showed that susceptible BALB/c mice infected with *T.congolense* succumb to the infection due to the development of SIRS within 10 days of infection. This inflammatory syndrome is associated with hyper activated macrophages, an outburst of cytokine release, enlarged capillary bed, and decreased blood pressure, drop of body temperature, hypo motility, and piloerection towards the terminal stage. SIRS also occurs in infected resistant C57BL/6 mice, when treated with antibodies blocking the IL-10 receptor (IL-10R). This early mortality is mediated by IFN-γ produced by MHC class II restricted CD4+ T cells. IL-10 appears to be crucial in controlling the lethal SIRS. It appears that IL-10 plays a dual role in African trypanosomiasis: it exerts a detrimental role in mediating immunosuppression, but it is beneficial by controlling excessive lethal cytokine release by macrophages [83].

Trypanosome induced professional antigen presenting cell defects

Macrophages and dendritic cells play a central role in the immune response as professional antigen-presenting cells. This function includes internalization of trypanosomes and⁄or their VSG through phagocytosis, processing of parasite antigens in the acidic compartment of the endocytic pathway, costimulation and presentation of the immunogenic trypanosome peptides to antigen-specific T-helper cells (Th cells) in the context of MHC Class II molecules [82, 83, 109]. Following activation, VSG-specific Th cells, through their secretory products, deliver a specific signal to both the innate and adaptive immune systems, aimed at destroying the infecting trypanosomes. Thus, through antigen presentation, Macrophages and dendritic cells modulate downstream events that impact on the development of adaptive anti-trypanosomal immunity [82, 109]. Modulation of antigen presentation function of macrophages and dendritic cells is an obvious way of the parasite to escape killing by immune cells and may contribute to global immune-suppression occurring during trypanosomosis. As such, selective pressure from the host immune system could have possibly induced the trypanosome to evolve several ways of altering the antigen presentation for its own survival [82, 57, 83, 109]. Several studies have reported alterations of antigen-presenting cell membrane phenotype at different time point post infection resulting in impaired antigen presentation [109]. Recently, [109] reported that *T.b.rhodesiense* clone LouTat 1 parasites induced a splenic dendritic cell depletion and down regulation of costimulatory molecules on splenic macrophages which contributed to their inability to elicit a significant VSG-specific T-cell response. Furthermore, peritoneal MFs from trypanosome-infected mice failed to activate naive Th cells in vitro and presented relatively low levels of VSG peptides to T cells in vivo.

Immunopathology

Infection by trypanosomes results in a rising parasitemia. Subsequently, a T-cell-independent antibody response to each VSG [96] leads to massive phagocytosis of trypanosomes by macrophages, especially in liver and spleen [103]. Most of the early produced anti-VSG is of IgM class. The phagocytosis of trypanosomes then leads to rapid activation of the Kupffer cells in the liver with release of monokines and enlargement of the Kupffer cells [83, 108] indicated that highly susceptible BALB/c mice infected intra peritoneal. With 10^3*T.congolense*clone TC13 die within 8 to 9 days after infection. Up to 5 days post-infection (p.i.), there is little trypanosomal antigen detectable in the liver, and the Kupffer cells are not visibly enlarged. At day 6, however, there is a dramatic accumulation of parasite antigen in Kupffer cells, and the Kupffer cells are greatly enlaMice were killed on days 0–7 post-infection. Immunocytochemical stain for trypanosomes (A–C): No trypanosomal antigen was detected on day 0 post infection (A). The earliest time of detection of trypanosomal antigen was on day 5 (B). Accumulation of parasite antigens dramatically increased on day 6 (C). Immuno-cytochemical stain with anti-F4/80 antibodies for Kupffer cells (D-F): Kupffer cells did not appear visibly enlarged up to day 5 (D, E). Kupffer cells were markedly enlarged on day 6 (Figure 5). An impressive fivefold increase in size of the Kupffer cells develops towards the terminal stage of infection, and about 10% of the Kupffer cells undergo apoptosis, indicating that a profound derangement of the macrophage system has occurred. Infection of mice with *T.congolense* is associated with an outburst of production of monokines [IL-1, TNF-α, IL-6, IL-12, monocyte chemotactic protein-1 (MCP-1), IL-10] (Shi *et al*., 2004) and T-cell cytokines [interferon-γ (IFN-γ), IL-10, IL-4] [83].

[108]; in his experimental study of mice indicate that, some of the cytokine production precedes the massive phagocytosis by Kupffer cells that is detectable at day 6 [83]. In fact, production of IL-10 and IFN-γin infected BALB/c mice, but not in infected C56BL/6 mice, is already elevated at 4 and 5 days post infectoin, at a time when there is no detectable difference between the parasitemias of infected BALB/c and C57BL/6 mice [110].

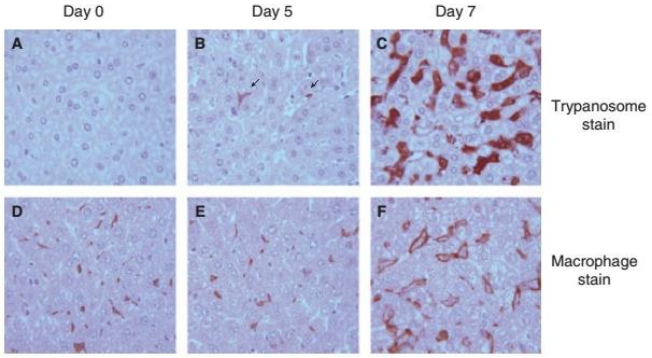

Figure 5: Accumulation of trypanosomal antigen in Kupffer cells of the liver (Source: [108])

CONCLUSION AND RECOMMENDATIONS

Animal trypanosomosis is associated with profound changes in the function of the immune system. In the mammalian host, the parasites establish controlled growth to ensure survival and optimal transmission. In order to escape the adaptive immune system, trypanosomes undergo antigenic variation by altering their major surface antigen, VSG. Beside this immune evasion mechanism, trypanosomes have been shown to modulate immune functions of macrophages, T lymphocytes, and B lymphocytes. The main host immune effectors involved in parasite control are considered to be trypanosome specific antibodies and the cytokine TNF. Concerning trypanosome-specific antibodies, increased VSG-reactive immunoglobulin M (IgM) antibody isotype have been associated with improved control of trypanosome infections. TNF, as a host cytokine, was released from activated macrophages in response to stimulation by soluble VSG (sVSG) and membrane-bound VSG. TNF was demonstrated to have trypanocidal properties for certain trypanosome stocks and to be associated with the occurrence of immune pathology in infected animals. As such, direct or indirect modulation of parasite-specific antibody induction and TNF release might influence trypanosome growth and the severity of infection. The T cells produce a variety of cytokines which, when bound to specific cell surface receptors, modulate the growth, differentiation or function of the receptor-bearing cells. IL-2 and IFN-γ are secreted by the proliferative lymph node cells during infection. IFN-γ is known to stimulate macrophage activity and to promote surface expression of major histocompatibility complex (MHC) class I and II on various cell types. However, the role of IFN-γ and other cytokines in immunity to Animal trypanosomosis remains unclear. Therefore, the following points are forwarded for future studies:

- Identifying the molecules responsible for the induction of protective immune responses which can greatly facilitate the development of an effective vaccine against trypanosomosis.
- Most likely African trypanosomes induce other, yet undiscovered, changes in the physiology of the infected host, which might interfere with effective control of the parasite and this undiscovered changes in the physiology of the infected host must be investigated.

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