

# Immune Response of Cattle Infected with African Trypanosomes

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*Trypanosomosis is the most economically important disease constraint to livestock productivity in sub-Saharan Africa and has significant negative impact in other parts of the world. Livestock are an integral component of farming systems and thus contribute significantly to food and economic security in developing countries. Current methods of control for trypanosomosis are inadequate to prevent the enormous socioeconomic losses resulting from this disease. A vaccine has been viewed as the most desirable control option. However, the complexity of the parasite's antigenic repertoire made development of a vaccine based on the variable surface glycoprotein coat unlikely. As a result, research is now focused on identifying invariant trypanosome components as potential targets for interrupting infection or infection-mediated disease. Immunosuppression appears to be a nearly universal feature of infection with African trypanosomes and thus may represent an essential element of the host-parasite relationship, possibly by reducing the host's ability to mount a protective immune response. Antibody, T cell and macrophage/monocyte responses of infected cattle are depressed in both trypanosusceptible and trypanotolerant breeds of cattle. This review describes the specific T cell and monocyte/macrophage functions that are altered in trypanosome-infected cattle and compares these disorders with those that have been described in the murine model of trypanosomosis. The identification of parasite factors that induce immunosuppression and the mechanisms that mediate depressed immune responses might suggest novel disease intervention strategies.*

Key words: trypanosomosis - *Trypanosoma congolense* - bovine - immunodepression - T cell - monocyte - cytokines

African trypanosomes are intravascular, extra-cellular parasites of livestock, humans and wild animals. Within the mammalian host, their cell membrane is covered by a variant surface glycoprotein (VSG) coat; termed variable because each parasite has an estimated 1000 VSG genes (Van der Ploeg et al. 1982), each encoding an antigenically distinct surface coat. Cattle immunized with irradiated trypanosomes or purified VSG are protected against a homologous (trypanosomes expressing the same antigenic repertoire), but not a heterologous, challenge (Wellde et al. 1975, Morrison et al. 1982). Thus, the potential of African trypanosomes to express different VSG coats reduces the likelihood of an effective VSG-based vaccine. As a result, vaccine design strategies are now focused on invariant trypanosome molecules that mediate pathogenesis (Authié 1994). It is clear that antigen selection and vaccine design will require knowledge of the immune responses provoked by infection and defini-

tion of the mechanisms involved in either parasite or disease control.

Immunodepression is a well-documented feature of trypanosomosis in cattle, humans and mice (Mansfield 1989, De Baetselier 1996, Taylor 1998). There is evidence that infection-related immunodepression compromises the ability of animals to control trypanosomosis (Sternberg et al. 1994), as well as secondary infections (Scott et al. 1977, Rurangirwa et al. 1978). Therefore identification of host factors that induce immunodepression and the immune mechanisms involved might provide a rational approach for vaccine design aimed at improved disease control and thus increased livestock productivity.

The majority of research on African trypanosomosis has focused on murine infections with *Trypanosoma brucei* subsp. as models of human disease. In contrast, research on trypanosomosis of livestock has centred mainly on infections of cattle with *T. congolense*. Besides the obvious fact that murine and bovine hosts are immunologically distinct, it is important to remember that *T. congolense* and *T. brucei* subsp. are also biologically distinct. The most important difference may be that *T. congolense* is a strictly intravascular parasite, while infection with *T. brucei* subsp. has ex-

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travascular foci, particularly within the central nervous system. The sum effect of these differences limits the value of comparisons between the two experimental models. Nonetheless, research on trypanosomosis of livestock has often followed in the path of that on human trypanosomosis and thus comparisons can not be avoided.

#### T CELL AND MONOCYTE/MACROPHAGE RESPONSES

T cell proliferative responses are depressed during infection in both murine and bovine hosts. In mice, T cell proliferation to mitogens and parasite antigens is either blocked or reduced. Reduced proliferative responses are associated with decreased interleukin-2 (IL-2) production and IL-2 receptor (IL-2R) expression in infected mice (Sileghem et al. 1986, 1987); nevertheless, cells retain the ability to secrete IFN- $\gamma$  (Sileghem et al. 1987, Bakhiat et al. 1990, Olsson et al. 1991, Schleifer et al. 1993). The mechanisms controlling T cell suppression in trypanosome-infected mice are not only site-specific, but also differ during the acute and chronic phases of infection (Beschin et al. 1998, Mabbott et al. 1998). In the lymph node, prostaglandins and nitric oxide secreted by activated macrophages inhibit IL-2 production (Sileghem et al. 1989b) and proliferation (Beschin et al. 1998), respectively, during the acute phase of infection in murine hosts. Decreased IL-2R expression is prostaglandin-independent and is reversed by anti-IFN- $\gamma$  antibodies (Darji et al. 1993, 1998), as is decreased proliferation (Beschin et al. 1998). In addition, the administration of anti-TNF- $\alpha$  antibodies to infected mice partially restores T cell proliferative responses in the lymph node (Darji et al. 1992). During the chronic stages of infection nitric oxide does not mediate T cell unresponsiveness in the lymph node; although IFN- $\gamma$  is involved, so are other factors that have not yet been identified (Beschin et al. 1998).

Both TNF- $\alpha$  and IFN- $\gamma$  are involved in increased secretion of macrophage-derived nitric oxide and prostaglandins in the peritoneal cavity and spleen of *T. brucei*- and *T. b. rhodesiense*-infected mice. These products in turn mediate T cell suppression (Sternberg & Mc Guigan 1992, Schleifer & Mansfield 1993), but apparently only during the very early days of infection (Beschin et al. 1998, Mabbott et al. 1998). The addition of nitric oxide- and prostaglandin-inhibitors to cells derived from the spleen and peritoneal cavity of *T. b. rhodesiense*-infected mice restored trypanosome antigen-specific and mitogen-triggered proliferation (Schleifer & Mansfield 1993). Similarly, nitric oxide production was suppressed and proliferation was restored in cultures treated with anti-IFN- $\gamma$  (Beschin et al. 1998) or anti-TNF- $\alpha$  mAb

(Darji et al. 1996), as well as in IFN- $\gamma$ -receptor null mutant mice (Mabbott et al. 1998). Moreover, mice treated with a substrate analog inhibitor of nitric oxide controlled parasitaemia and anaemia better than untreated mice did (Sternberg et al. 1994, Mabbott & Sternberg 1995). This suggests that the animals were capable of a more effective response if nitric oxide-mediated suppression was reversed. However, depressed T cell responses in the spleens of chronically infected mice are not sensitive to either nitric oxide inhibitors or anti-IFN- $\gamma$  (Beschin et al. 1998, Mabbott et al. 1998). In addition, although *T. b. rhodesiense*-infected IFN- $\gamma$  receptor knock out mice controlled anaemia better over the first ten days of infection, these same mice experienced more severe anaemia than wild type mice later in infection (Mabbott et al. 1998).

Recent studies have suggested that TNF- $\alpha$  and IFN- $\gamma$  play opposing roles in regulation of parasite growth. *T. brucei* release factors that induce murine CD8 T cells to secrete IFN- $\gamma$  which was shown to be a parasite growth factor (Olsson et al. 1991). Similarly, *T. brucei* induces production of TNF- $\alpha$ , which, in contrast to IFN- $\gamma$  has trypanolytic activity (Magez et al. 1993, 1997). However, it is not yet known how these cytokines interact *in vivo* to influence parasite numbers. The challenge now is to understand the contribution of these two cytokines to direct control of parasite numbers balanced with their influence on downstream immunological responses.

In summary, macrophages of trypanosome-infected mice produce immunosuppressive factors such as prostaglandins, nitric oxide, and TNF- $\alpha$ . During the early acute phase of infection these factors are involved in reduced T cell responses in the spleen and, to a lesser extent, the lymph node of *T. brucei* subsp.-infected mice. In addition, production of IFN- $\gamma$  by T cells appears to be a common feature in murine trypanosomosis. However, the factors that mediate suppressed T cell proliferative responses in chronically infected mice are not fully understood. More importantly, it is not clear how these responses relate to either protection or immunopathology.

In cattle, mitogen-induced proliferation, IL-2 production and IL-2R expression by cells derived from the lymph node draining the site of infection are transiently depressed (Flynn & Sileghem 1991, Lutje et al. 1996, Taylor et al. 1996a). While trypanosome-specific proliferative responses can be detected in the draining lymph node during the second week of infection, they are not associated with significant IL-2 production and are nearly absent by one month post-infection (Lutje et al. 1995, 1996, Taylor et al. 1996a).

Efforts to characterise the regulation of IFN- $\gamma$  in *T. congolense*-infected cattle have been incon-

clusive. While mitogen-induced IFN- $\gamma$  secretion by lymph node cells was shown to increase in infected cattle (Sileghem & Flynn 1992, Lutje et al. 1996), in another study, no significant change was detected (Taylor et al. 1996a). In addition, no increase in IFN- $\gamma$  mRNA is observed in lymph node or peripheral blood mononuclear cells (PBMCs) of infected cattle (Taylor et al. 1996a, 1998). Nonetheless, expression of IFN- $\gamma$  mRNA was higher in the spleen of two infected calves compared with their uninfected identical twin (Taylor et al. 1996a). These differences suggest that bovine trypanosomiasis produces highly compartmentalized immune responses, similar to those seen in mice (De Baetselier 1996, Beschin et al. 1998).

Unlike those of the mouse, bovine monocyte and macrophage effector functions do not appear to be activated during trypanosomiasis. *Ex vivo* secretion of TNF- $\alpha$  from monocytes of *T. congolense*-infected cattle is not increased, however, a small but transitory increase is observed in *T. vivax*-infected cattle (Sileghem et al. 1994). In keeping with this observation, TNF- $\alpha$  mRNA expression did not increase in the PBMC of *T. congolense*-infected cattle (Taylor et al. 1998, Mertens et al. 1999). Moreover, nitric oxide production is not elevated during infection of cattle and neither nitric oxide nor prostaglandins are responsible for reduced T cell proliferation of lymph node cells (Sileghem & Flynn 1992, Taylor et al. 1996a).

More recent research suggests that IL-10, a macrophage de-activating cytokine, might be related to the apparent failure of monocytes and macrophages of trypanosome-infected cattle to produce inflammatory products. IL-10 mRNA transcripts are elevated in the peripheral blood, lymph node and splenic leukocytes of *T. congolense*-infected cattle (Taylor et al. 1996a, 1998). A pleuripotent cytokine, IL-10 is associated with T<sub>H</sub>2 type responses and can suppress macrophage effector and costimulatory functions (Moore et al. 1993).

IL-10 is known to suppresses the activation of inducible nitric oxide synthase, IL-1 $\alpha$ , IL-6, TNF- $\alpha$  and, possibly, IL-12, at the level of transcription in murine macrophages (deWaal Malefyt et al. 1991, Fiorentino et al. 1991, Kennedy et al. 1994). Coincident with the observed increase in IL-10 mRNA expression in PBMC, lymph node and spleen, monocytes of trypanosome-infected cattle became desensitized to IFN- $\gamma$ -induced secretion of nitric oxide (Taylor et al. 1996a, 1998). Furthermore, recombinant human IL-10 blocks both IFN- $\gamma$ -induced nitric oxide and TNF- $\alpha$  production by monocytes derived from healthy cattle (Taylor et al. 1998). This, combined with the evidence that TNF- $\alpha$  production (Sileghem et al. 1994, Taylor et al. 1998, Mertens et al. 1999) does not increase during infection, suggests that macrophage

monokines are not activated during bovine trypanosomiasis and that IL-10 may be involved in this lack of response. Indeed, recent experiments have demonstrated that anti-IL-10 antibodies partially restored IFN- $\gamma$ -induced nitric oxide production by monocytes derived from *T. congolense*-infected cattle (unpublished data).

IL-10 also acts to downregulate expression of the B7 costimulatory molecules on murine antigen-presenting cells (Willems et al. 1994), which may lead to T cell anergy and in some cases apoptosis (Dubois et al. 1994). Anergic T cells do not proliferate or produce IL-2, but retain the ability to produce other cytokines such as IFN- $\gamma$  (Jenkins et al. 1990). IL-10 has been associated with the induction of parasite antigen-specific T cell anergy in asymptomatic microfilaremic filariasis patients (King et al. 1993), schistosomiasis (King et al. 1996), leishmaniasis (Ghalib et al. 1993) and toxoplasmosis (Candolfi et al. 1995). Suppressed costimulatory signalling has also been proposed as the cause of anergy of T<sub>H</sub>1 cells that leads to apoptosis during HIV infection (Clerici et al. 1994) and leprosy (Sieling et al. 1993).

A number of observations are consistent with the loss of antigen-specific proliferation and IL-2 production in the lymph node of trypanosome-infected cattle arising from IL-10-mediated T cell anergy. First, the antigen-specific hypo-responsiveness of lymph node cells is preceded by a period of responsiveness, at which time IL-10 mRNA transcripts are normal (Taylor et al. 1996a, 1998). Second, that T cell suppression in the lymph nodes of infected cattle is related to suppression of macrophage accessory cell function is consistent with the finding that "macrophage-like" cells are responsible for depressed mitogen-triggered proliferation of lymph node cells (Flynn & Sileghem 1991). Third, recombinant human IL-10 suppresses proliferation of antigen-specific bovine T cell clones and down-regulates expression of IL-2R and IFN- $\gamma$  mRNA (Chitko-McKown et al. 1995). Interestingly, BALB/c mice, which are highly trypanosusceptible, produce significantly more IL-10 when infected with *T. congolense* than relatively trypanoresistant C57Bl/6 mice. Addition of anti-IL-10 antibodies in cultures of mitogen-stimulated spleen cells from infected mice completely restored proliferation (Uzonna et al. 1998). In this study, BALB/c mice treated with anti-IL-10 antibodies and infected with *T. congolense* exhibited slightly longer survival times than untreated mice. Efforts are currently underway to test the role of IL-10 in mitogen and antigen-specific T cell responses during trypanosomiasis in cattle directly.

There is conflicting evidence regarding the integrity of macrophage costimulatory functions during murine trypanosomiasis. IL-1 secretion and

antigen-presentation function are depressed in *T. b. rhodesiense*-infected mice (Paulnock et al. 1988) and in both resistant and susceptible strains of *T. congolense*-infected mice (Mitchell et al. 1986). Similarly, Ia<sup>+</sup> macrophages are depleted during murine *T. b. rhodesiense* infection (Bagasra et al. 1981). No increase in IL-1 mRNA transcription was observed in the PBMC of *T. congolense*-infected trypanotolerant or trypanosusceptible cattle (Mertens et al. 1999), again suggesting that costimulatory functions are not elevated. It should be noted, however, that increased IL-1 production was observed in *T. brucei*-infected mice (Sileghem et al. 1989a).

Analysis of cytokine mRNA expression confirms that neither T<sub>H</sub>1 cytokines nor inflammatory monokines are increased during *T. congolense* infection of either trypanosusceptible or trypanotolerant cattle (Mertens et al. 1999). However, transcription of the T<sub>H</sub>2 type cytokine IL-4 was increased in trypanotolerant cattle, but not trypanosusceptible cattle, one month post-infection (Mertens et al. 1999). As IL-4 is an important regulatory molecule for isotype switching from IgM to IgG1 (Estes 1996), perhaps it is not coincidental that trypanotolerant cattle produce more IgG1 to a number of trypanosome antigens than do trypanosusceptible cattle (Taylor et al. 1996b).

## CONCLUSIONS

A crucial question is whether depressed macrophage and T cell responses tip the balance of infection in favour of the host or the parasite during bovine trypanosomosis. Down-regulation of monokines and other T<sub>H</sub>1 type cytokines by IL-10 has been shown to protect against immunopathology in mice infected with a variety of parasites (Flores-Villanueva et al. 1996, Gazzinelli et al. 1996) but can also lead to ineffective parasite killing (Heinzel et al. 1991, Silva et al. 1992, Gazzinelli et al. 1992). In this context, it is important to recognise the distinction between trypanotolerant and trypanosusceptible cattle. Trypanotolerant breeds of cattle are not refractory to infection. In fact, they are just as "susceptible" to primary infection as so-called trypanosusceptible breeds. There is little or no difference in parasitaemia between trypanotolerant and trypanosusceptible cattle during the early stages of infection. Despite this, trypanotolerant cattle maintain higher packed-cell volumes throughout infection and eventually control parasite numbers during the chronic stages of infection (Paling et al. 1991a, b). That antigen-specific and mitogen-driven T cell responses appear to be equally depressed in both trypanotolerant and trypanosusceptible breeds of cattle, suggests that these responses are not required to control disease.

However, loss of these responses may be necessary for the successful establishment of parasites, as well as their continued presence, in both the acutely- and chronically-infected animal. In contrast, specific antibody responses and an upregulation of IL-4 in trypanotolerant cattle may be involved in these animals ability to control disease, despite the presence of parasites.

Our laboratory is currently devoted to understanding the role of IL-4 and isotype switching in trypanotolerance. In addition, efforts to determine the contribution of depressed T<sub>H</sub>1 and macrophage effector functions to the establishment and maintenance of infection continue. Development of improved strategies for the control of trypanosomosis will depend heavily on an understanding of the balance between protective and pathogenic immune responses in the face of infection.

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