HUMAN AFRICAN TRYPANOSOMIASIS; POSSIBLE TREATMENT WITH ANTILYMPHOCYTE SERUM

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ABSTRACT

Trypanosoma brucei is a protozoan parasite that causes Trypanosomiasis (Sleeping Sickness). This has become a major problem in sub-Saharan Africa. The second and terminal stage of the disease involves the migration of the parasite across the blood-brain barrier. Recent research suggests that the Trypanosome uses the patient’s own T cells to make a passage into the brain, exploiting the ability of the lymphocyte to create a hole in Laminin 4, and Laminin 2.

This remarkable cooperation provides a therapeutic option, the use of anti-lymphocyte serum to block the signaling and close physical proximity needed by the parasite and lymphocyte for the brain invasion to succeed. In addition the significance of this occurrence is discussed in the context of the possible evolution of lymphocytes from protozoa.

Keywords: Human African Trypanosomiasis, Lymphocytes, Anti-lymphocyte Serum.

INTRODUCTION

The re-emergence of West African sleeping sickness constitutes an immense problem in sub-Saharan Africa, with as many as 500,000 people condemned to die if left untreated. (Stich A et al, 2002). The tsetse fly is responsible for biting the human victim and transmitting the protozoan pathogen Trypanosoma brucei. As the disease progresses from the trypanosomal chancre to a generalized infection, lymphadenopathy and fever are common signs. Finally in the second stage of the disease, the trypanosome crosses the blood-brain barrier, resulting in a terminal somnolent state.

The work of Masocha et al, 2004, suggests that the protozoan parasite uses the patient’s T cells to gain entrance to the brain, crossing the endothelium of the post capillary venules. The parasite exploits the ability of the T cell to penetrate the laminin component of the basement membrane. This remarkable cooperation supports in a general way, the concept that vertebrate lymphocytes may have an evolutionary connection to protozoa, but more importantly suggests a therapeutic approach, namely the use of anti-lymphocyte serum to block the signaling between the lymphocyte and the protozoan pathogen by coating the lymphocyte receptor sites, and by making it more difficult for the Trypanosome to bond with its escort.

STUDIES ON ANIMAL BRAINS

Masocha and Kristensson, 2012, and Philip et al, 1994, summarized the series of elegant experiments demonstrating the need for T cells to clear a path for the Trypanosoma through the basement membrane. Laminin 4 is a component of the basement membrane and resists the protozoan parasite. However, T cells are able to gain entry to the brain by physically destroying the laminin and then widening the hole by enzyme digestion, (Harrison-Brown et al, 2016).

In the course of Trypanosomiasis, large numbers of T cells accumulate with the parasite at designated post capillary venules, then commence to cross the endothelium, in close physical proximity to the protozoan. (Nikolskaia et al, 2006) (FIGURES 1 through 5). This results in the terminal stage of the disease.
The T cell must precede the Trypanosome in order to make the hole in the laminin, and then enlarge it to permit the passage of the parasite. In turn this indicates a synchronization of cell movement, and in order to accomplish this, a number of cell signals would be required.

**ANTI-LYMPHOCYTE SERUM**

Anti-lymphocyte serum has been used since the 1960's in transplant patients (Thiyagarajan et al, 2013), and although its mechanism of action is still not fully understood it has proven to be a very effective immunosuppressant.

This is also important in the treatment of Trypanosomiasis as it has been found that immunosuppression hinders the effectiveness of T cells in their cooperation with the parasite. (Masocha et al, 2004).

Non specific coating of the lymphocytes would also create a barrier to the close proximity needed for the effective “towing” of the parasite to the correct place in the basement membrane, where the hole had been made (FIGURE 6).

In addition a Coombs type second coating of antibody could be added by injecting goat anti-rabbit globulin, (FIGURE 7).

**Bridging T Cells**

In addition to its immunosuppression activity, anti-lymphocyte...
serum may also block key signal receptor sites, in a way similar to the blockade suggested for the antigen recognition site by Coulson, (1969). (FIGURE 8)

**Figure 8 - O: Signal Communication Center on Lymphocyte Surface, P: Antibody Blocking the Center**

**SIGNALING BETWEEN TRYPANOSOMES AND LYMPHOCYTES**

The complex choreography involved in the T cell assisting the Trypanosome to enter the brain indicates a close almost preternatural connection between these two cells, one which might support a common ancestry, (Coulson, 2013).

In addition the sequence of operations probably requires an as yet undiscovered class of protein signals, cerebropenetrins. The first message would instruct the lymphocytes to assemble at a specific postcapillary venule, this would be essential as there are literally miles of vascular tubing in the brain; secondly, the lymphocytes would need to be instructed to start the process of “towing” the Trypanosome through the endothelial cell, and then to make a hole big enough in the Laminin 4, to permit the passage of the Trypanosome. A third instruction would tell the lymphocyte to make a similar opening in the Parenchymal Basement Membrane, employing matrix metalloproteinases to negotiate Laminin 1 and 2 in the process, and a fourth signal involves the release of CXCL 10 (Owens et al, 2008).

**DISCUSSION AND CONCLUSIONS**

In the course of searching for clues that might support the general theory that lymphocytes evolved as endosymbionts from protozoa, we came upon this remarkable example of cooperation between lymphocytes and a deadly pathogen, wherein what should be protecting cells for the mammalian host, actually assists the protozoan to invade the host’s brain. While this process protects the Trypanosome from serum factors, by effectively converting the blood-brain barrier into a blood-Trypanosome barrier, it necessarily results eventually in lethal consequences to the host, and to the loss of habitat to its erstwhile lymphocyte population.

Since this process has absolutely no evolutionary survival value to the mammalian host, it raises questions as to how and why this disconnect occurs, and why it persists. If lymphocytes did evolve from marine protozoan parasites, then it makes some kind of sense; possibly certain aspects of lymphocyte behavior can be induced to revert back to their original protozoan status, after receiving and obeying signals from what would be their very distant cousins. It is as if the lymphocytes’ destructive “power of membrane penetration” has been retained in a prelapsarian fashion, and can be unmasked and unleashed as part of an assaultive alliance to destroy its host when appropriately stimulated by protozoan relatives.

It then occurred to us that anti-lymphocyte serum might be a useful therapeutic tool for various reasons: by coating the lymphocyte with a foreign protein it would make it more difficult for the lymphocyte to bind to receptors on the endothelium needed as a preliminary to penetration of that cell, namely the tethering and integrin binding; and subsequently make it more difficult for the lymphocyte to traverse the endothelial cell. It would also provide a barrier to the linkage with the Trypanosome. Finally, immunosuppression makes the T cells less effective as escorts for the parasite. (Masocha, 2004)

**REFERENCES**


