African sleeping sickness: causes and effects

Trypanosomiasis, commonly known as African sleeping sickness, is a vector-borne parasitic disease (World Health Organization, 2011). The parasitic protozoans that cause this disease are called trypanosomes from the genus Trypanosoma, and are transmitted by the bite of tsetse fly. Tsetse flies are about the size of a housefly, and are extremely aggressive. The tsetse fly is endemic in regions of sub-Saharan Africa. Trypanosomes are classified as part of the Phylum Euglenozoa and subphylum Kinetoplasta. The kinetoplastans are known by their characteristic flagellum (Hickman, 2008). Trypanosomes are a large group of protozoans, but the specific trypanosome that causes African sleeping sickness is Trypanosoma brucei. This can come in two forms depending on the specific parasite: Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense. The more common form, responsible for over 95% of reported cases is T. b. gambiense (World Health Organization, 2011). The two forms also differ in the region in which they are popular; T. b. gambiense is found in West Africa in areas of heavy vegetation, forests and rivers, whereas the fly responsible for transmitting T. b. rhodesiense is found in East Africa in regions of woodlands and savannah (Public Health Agency of Canada, 2005).

African sleeping sickness has two life cycles: a stage in humans and a stage in tsetse flies. A human becomes infected when a tsetse fly takes a blood meal and injects metacyclic trypomastigotes (the parasites) into the skin, where they then go into the lymphatic system and finally pass into the blood stream. Once in the blood stream, the trypomastigotes are able to go to other sites in the body. They rapidly proliferate by binary fission, and spread throughout the whole body. When another tsetse fly takes a blood meal from

an already infected human, the life cycle of the trypomastigote continues. In this way, the disease can spread quite quickly in populated areas with this type of fly. In the midgut of the fly, the bloodstream trypomastigote transforms into a procyclic trypomastigote which also divides by binary fission. The next stage in the life cycle is transformation of the procyclic trypomastigote into an epimastigote. The epimastigotes multiply in the salivary gland of the tsetse fly and transform into metacyclic trypomastigotes which are the form of the parasite that is injected into the human skin. The life cycle in the fly takes approximately three weeks from start to finish (DPDx, Division of Parasitic Diseases, Center for Disease Control, 2011).

When a parasite enters the human body, the innate immune system is the first response to the foreign body. There are many cells that take part in the immune response in the body such as B-cells, T-cells, Natural killer cells, and macrophages. When T. brucei comes into the body, all these cells take part in reacting toward it.

The first barrier and protective system of the human body is the skin. After the bite of tsetse fly, the skin reacts due to the proliferation of the trypanosomes now in the body, by producing a chancre. After a few days, B-cells and T-cells go to the site of the chancre, and begin responding to the antigen. It is during this stage of the disease that the trypanosomes actually are able to evade the body’s innate immune system by expressing Variable Antigen Types which change after a few days in order to hide from the immune system (Vincendeau, 2006). In a sense, the trypanosomes change their coat of armor, so they are not destroyed by the body’s attack.

Even with mechanisms of defense such as the skin, and B and T-cells, the Trypanosome parasites are able to escape the host's innate immune system by a mechanism of switching antigen (Hunt, 2010), and they also have variant surface glycoproteins (VSG) which create some problems for the immune system (Vincendeau, 2006).

B-cells are known apart from other cells in the immune response as they are the cells on which antibody molecules (membrane-bound immunoglobin) are bound. B-cells that encounter an antigen that matches its Ig bind to the antigen and proceed to proliferate and divide rapidly into plasma cells and memory cells for future encounters. There are five isotypes of immunoglobin (IgM, IgA, IgD, IgG, and IgE), and these different Igs have different functions in the immune response (Kuby, 2007). Concerning T. brucei, immunoglobin M plays a key role. IgM increases rapidly after the initial onset of T. brucei as it is typically the first immunoglobin on the scene in the innate immune response, including both antibodies that are specific to T. brucei, and non-specific immunoglobins. The specific antibodies are induced by both the variant epitopes and invariant epitopes of the VSG on T. brucei. By binding to the surface of the antigen, these specific antibodies (VSG-specific IgM) are able to decrease the amount of parasitemia (parasites in the blood) by lysis of the parasites (Vincendeau, 2006).

T-cells (T lymphocytes) are an important part of the body's immune response as they express antigen binding molecules on their membranes, and are able to recognize antigen that is presented to them via cell membrane proteins called major histocompatibility complexes (MHCs). Once T-cells recognize the antigen, they release cytokines that activate other B-cells, T-cells,

macrophages, and other cells associated with the immune response so that the antigen can be destroyed by phagocytosis, lysis, or other means (Kuby, 2007). The T-cells that appear during the immune response of T. brucei are mostly helper T-cells (those with surface markers of CD4) as opposed to cytotoxic T-cells (which have surface markers of CD8). There are two types of helper T cells that have been found in research, Th1 and Th2. During the first response to the onset of T. brucei, IL-12 plays a major role in T cell shift towards a Th1 response. Th1 cells tend to be VSG specific when in association with T. brucei and cause cytokine responses with IL-2 and IFN-γ (Vincendeau, 2006). Macrophages in the immune response rely on IFN-γ stimulation before they respond to the soluble VSG. One study done showed that the inflammatory response to T. brucei was dependent on the mediated activation of the immune system by an intracellular adapter molecule by the name of MyD88. The study showed that macrophages with a deficiency in this molecule did not respond to the soluble or the membrane bound glycoproteins (VSGs). The Th1 response is induced by being associated with the MyD88 dependent activation of the innate immune system. A decrease in this response of the Th1 causes a susceptibility to the parasitic disease of Trypanosoma brucei (Drennan, 2005).

Similar to the aforementioned cytokine activities, IL-1 and TNF-α also play a role when the body tries to rid itself of T. brucei. These two cytokines are released by macrophages, and TNF-α in particular, helps eliminate the pathogen either indirectly by activating other cells or directly with its cytotoxic properties (TNF-α is also stimulated to be produced by IFN-γ). IFN-γ can actually help parasitic growth, showing one interaction between

cytokines and the parasitic T. brucei that is not effective for destroying the pathogen (Vincendeau, 2006).

It has been found that there are two Trypanolytic factors (TLF) in human serum, both identified as high-density lipoproteins (Vincendeau, 2006). These factors cause lysis to occur on trypanosome species in human serum (Wheeler, 2010). TLF2 has a high molecular weight and is not inhibited by haptoglobin, a protein produced by the liver that connects certain types of hemoglobin in the blood. This is different from TLF1 which is inhibited by haptoglobins, and is a high density lipoprotein. Due to this difference, it is thought that TLF2 causes the main trypanolytic effect on trypanosomes (Vincendeau, 2006).

Trypanosoma brucei has two stages that have different clinical symptoms and signs. The first stage is called the haemolymphatic stage and is when the protozoan multiplies in the subcutaneous tissue, the blood and lymph. This stage shows signs such as fever, headaches, joint aches, and itching (World Health Organization, 2011). This stage is also the stage in which a chancre may appear on the skin. This stage is treatable with medications such as pentamidine and suramin. These drugs are safe and effective for the first stage of this disease, but are not effective at all for the second stage (Lejon, 2007).

The second stage, known as the encephalitic stage is when the parasite has made its way past the blood-brain barrier and into the central nervous system. It is during this stage that the symptoms for which the disease is named appear: malaise and fatigue. Along with these signs also appear

neurologic signs, as the disease has reached the brain and due to the trypanosomes in the brain, there is responsive inflammation caused by leukocytes, causing the neurologic problems (Masocha, 2006). There are drugs that can be used for this stage of the disease just as for the first stage. The drugs that are used are Melarsoprol and Eflornithine. Eflornithine is only effective against Trypanosoma brucei gambiense, and follows a strict regimen which can be difficult to follow. Just recently in 2009, a combination therapy was discovered using the drug Nifurtimox in combination with Eflornithine. This therapy is simpler than the regiment with Eflornithine; however, it is not effective against Trypanosoma brucei rhodesiense. Nifurtimox is used by itself against Trypanosoma cruzii but is not effective alone against T. brucei (World Health Organization, 2011).