Second RUFORUM Biennial Meeting 20 - 24 September 2010, Entebbe, Uganda

Research Application Summary

Involvement of oligopeptidase B in the establishment of a central nervous system infection by *Trypanosoma brucei brucei*

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Abstract

African trypanosomiasis is a major disease in several countries in eastern Africa, Uganda inclusive. This study is examining the role of oligopeptidase B (opB) in virulence of the vector *Trypanosoma brucei rhodesiense* and *T. brucei gambiense*. Preliminary results are discussed.

Key words: African trypanosomiasis, central nervous system, *oligopeptidase*

Résumé

La trypanosomiase africaine est une maladie importante dans plusieurs pays d'Afrique de l'Est, l'Ouganda inclusivement. Cette étude examine le rôle de *oligopeptidase* B (opB) dans la virulence du vecteur *Trypanosoma brucei rhodesiense* et *T. brucei gambiense*. Les résultats préliminaires sont discutés.

Mots clés: La trypanosomiase africaine, le système nerveux central, *oligopeptidase*

Background

African trypanasomiasis is a major health concern in the tsetse fly infested areas and affects both humans and animals. *Trypanosoma brucei rhodesiense* and *T. brucei gambiense* are the causes of Human African trypanosomiasis (HAT), a disease characterized by acute and chronic infections.

In the late stage of the disease, trypanosomes invade the central nervous system (Barrett *et al.*, 2003). The crucial step leading to central nervous system (CNS) colonization is the process of traversing the blood brain barrier by the trypanosomes (Masocha *et al*., 2006). However, the mechanism of this movement remains unclear. It is assumed that there is a direct role by the parasites in damaging of the blood brain barrier. The dysfunctions in the nervous system are probably as a result of molecules released either directly from the parasites or from host cells that respond to the infection (Masocha *et al.*, 2004). From the latter category, oligopeptidase B (opB) appears to be involved in this phenomenon.

Literature Summary

Human African trypanosomiasis, also known as sleeping sickness, is caused by *T. brucei gambiense* and *T. brucei rhodesiense* (Barrett *et al*., 2003; Croft *et al*., 2005). HAT manifests in two forms, the acute (early) and the chronic (late) form. They are transmitted to humans by tsetse fly (*Glossina* spp) bites which have acquired their infection from human beings or from animals harboring the human pathogenic parasites (Matovu *et al*., 1997; Matovu *et al*., 1998; WHO, 2006). The disease generally occurs in remote rural areas where health systems are weak or non-existent, characterized by displacement of populations, war and poverty.

Oligopeptidase B (opB) is a member of the prolyl oligopeptidase family of serine peptidases (Rawlings *et al*., 2006). It is present in Gram-negative bacteria, spirochetes and some unicellular eukaryotes like trypanosomes and leishmania. The physiological role of opB is unclear, and its substrates have not been identified. However, it is documented to play role in the pathogenesis of South American and African trypanosomiasis. According to Thibault (1985) OpB appears to be directly involved in the virulence of *T. brucei*, the causative agent of African sleeping sickness. During infection, *T. brucei* opB is released into the host bloodstream, where it is free to cleave regulatory peptides present in the host serum (Morty *et al.*, 2001).

Research Approach

Trypanosoma brucei opB knock-outs are being generated with subsequent study of the phenotypes of the generated knockout parasites, especially ability to establish CNS infections.

Research Application

The study investigates opB as a potential drug target against HAT. This is based on the likelihood that parasite invasive strategies can potentially be targeted as therapeutic targets. Therefore it will form a basis for further research in drug development against the disease.

Preliminary results indicate partial success in development of the deletion constructs. The 5' and the 3' un-translated regions of the gene have been successfully amplified and cloned in their respective vectors, however the deletion construct is currently under development.

Acknowledgement

Thanks are due to the Regional Universities Forum for Capacity Building in Agriculture for funding this study.

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