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Introduction of tryptophan residues towards the cytoplasmic end of the *Trepanosoma brucei* Aquaporin

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African Trepanosoma brucei cause sleeping sickness in humans, a disease that is typically fatal without chemotherapy. Unfortunately, drug resistance is common and our understanding of the underlying mechanisms remains incomplete. In Trypanosoma, three aquaporins genes, AQP1-3, have been identified. Recent studies have shown that loss of AQP2, a channel with an unusual selectivity filter, is specifically responsible for MPXR, leading to the hypothesis that some of the clinical trypanocides, specifically pentamidine and the melaminophenyl arsenicals enter through these aquaporins. In T. brucei, the TbAQP2 protein was found to be a highly efficient transporter for pentamidine and melarsoprol and introduction of the corresponding gene into Leishmania mexicana made these parasites more than 1000-fold more sensitive to melarsoprol, and 40-fold more sensitive to pentamidine. Therefore, an understanding of the mechanisms of AQP2-mediated drug uptake in African trypanosomes will facilitate the advancement of diagnostic tools and perhaps at the same time the improvement of enhanced treatments. We report here the construction of several genetic mutations (single amino acid substitutions) in AQP2 to investigate their effects on the ability of the gene for drug sensitivity and drug transport. As part of this strategy, leucine residues were replaced by tryptophan in three suggested sites in the Tb AQP2 gene. The results of introducing tryptophan residues in L84 and L118 in the TbAQP2 showed some loss of pentamidine susceptibility compared to the wild-type cells, whereas L218 showed equal sensitivity to pentamidine compared to the wild-type cells.

Keywords: African *trypanosomiasis*, drug resistance, *Leishmania spp*, *Trepanosoma brucei*

Biography

Ali Efan Alghamdi is currently a PhD student of the Genetics of Leishmania at the Institute of Infection, Immunity and Inflammation College of Medical, Veterinary and Life Sciences, University of Glasgow. He studied his Master degree in Biotechnology from Macquarie University, School of Science in Australia, and his B.Sc. in the Department of Biology, Albaha University, Albaha, Saudi Arabia.

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