PhD defence Vera Kühne (Online)

Alternative antigens for a point of care test for serodiagnosis of visceral leishmaniasis in East Africa

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Supervisors

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Abstract

Visceral leishmaniasis (VL) is a fatal disease if it is not correctly diagnosed and treated. It is caused by unicellular parasites of the Leishmania donovani complex. The endemic areas for VL are mostly low- and middle- income countries. However, the existing diagnostic tests for VL are either not adapted for use in resource poor settings or their diagnostic performance in East Africa is variable.

This thesis aims to contribute to the development of an alternative diagnostic test for VL in East Africa based on antibody detection. The goal is to identify novel antigens, that can be incorporated into an immunochromatographic or rapid diagnostic test. These tests are ideal as point-of-care tests for low- and middle income countries as they are fast, non-invasive and need no equipment and minimum training.

We started by an attempt to replace an existing antibody detection test for VL: the direct agglutination test (DAT) (Part 2). The DAT has a high sensitivity and specificity in all endemic regions but it is based on entire parasites, which makes it difficult to standardize and to incorporate into an RDT. We analysed the existing literature on the nature of the DAT Ag (Chapter 4). From the retrieved evidence we concluded that the DAT Ag is composed of a mixture of Leishmania specific antigens. We first aimed to select so-called mimotopes - peptides that mimic the epitopes of the DAT Ag using a phage display approach (Chapter 5). We found peptides that have a diagnostic potential. Unfortunately, their reactivity with VL positive compared to VL negative sera was not sufficient to be incorporated in an RDT. We then used a more targeted approach and analysed hypotheses found in Chapter 4 experimentally. We reached the conclusion that lipophosphoglycan is part of the DAT Ag while carbohydrates alone are not (Chapter 6).

In Part 3 of this thesis, we analysed the pipeline of serodiagnostic tests for VL. We performed a systematic literature review (Chapter 7), which showed that most tests are not tested on sufficient specimens, especially from East Africa. Moreover, we did not find one non-native antigen (recombinant or synthetic) with a carbohydrate or lipid moiety. Based on this analysis we chose the most prominent glycoprotein of Leishmania – gp63 – and expressed it in a L. tarentolae expression system (Chapter 8). The recombinant glycoprotein has diagnostic potential and thus serves as a proof-of-concept for the use of glycoproteins in the serodiagnosis of VL.

To develop alternative diagnostic tests for VL in East Africa, we propose to focus on the evaluation of mixtures of existing antigens and to investigate the diagnostic potential of a synthetic LPG core-anchor fragment and of differently glycosylated variants of gp63.