An investigation into the complex formation of *Hs*ApoL1 and *Tbr*SRA through protein-protein docking and dynamic residues network (DRN) analysis.

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INTRODUCTION

Human African trypanosomiasis (HAT) is a neglected tropical disease (NTD) caused by two subspecies of the parasite, namely *Trypanosoma brucei (Tb) gambiense* (g-HAT) and *rhodesiense* (r-HAT). HAT, which can be fatal when left untreated, is endemic in sub-Saharan countries where the tsetse fly vector breeds, affecting an estimated 70 million people.

Both g-HAT and r-HAT are responsible for widespread epidemics throughout sub-Saharan African history, budding from the complex molecular interplay between trypanosomes and humans that result in unique innate immunity evasion mechanisms. Of specific interest, the *Tbr* subspecies expresses the serum resistance-associated protein (SRA), which binds to a human serum lytic factor, apolipoprotein L1 (ApoL1), nullifying trypanocidal activity. In response, *Hs*ApoL1 variants (G1 and G2) prevalent in humans of sub-Saharan African descent have been cited to confer resistance to the r-HAT infection in an interaction that remains obscure. An understanding of the SRA-facilitated infections could provide a framework to further combat the r-HAT.

METHODS AND RESULTS

The aim of the study was to computationally generate a *Hs*ApoL1:*Tbr*SRA wild-type and variant complexes to advance understanding of the interaction.

To achieve this, *in silico* structure prediction was applied to calculate 3D models of *Hs*ApoL1 C-terminal variants, to be complexed with *Tbr*SRA. The *Hs*ApoL1 structures were inspected dynamically to identify the effect of the variants through molecular dynamics (MD) simulations.

Protein-protein docking was applied to calculate plausible *Hs*ApoL1:*Tbr* SRA wild-type complex structures. Through extended MD simulations, twelve *Hs*ApoL1:*Tbr*SRA dimeric structures were narrowed down from five to two energetically sound complexes.

Dynamic residue network (DRN) analysis of the MD trajectories was fundamental in identifying residues playing a vital role in the intra- and intermolecular communication of both proteins with the two feasible complexes exhibiting favourable communication, including the retaining key residues

identified in prior monomer calculations. Additional incorporation of the ApoL1 C-terminal variants (G0, G1, G1G/M, G2 and G1G2) into the final *Hs*ApoL1:*Tbr*SRA complexes aided in further analysis of complex dynamics.

The MD runs in this study were conducted in GROMACS, utilising the CHARMM36, on 240CPU cores of the Lengau cluster, with each production run comprising 500ns.

CONCLUSIONS

Two feasible *Hs*ApoL1:*Tbr*SRA complexes were determined through global and local structural analyses, with the identification of crucial SRA and ApoL1 communication residues in both monomeric and dimeric form. Furthermore, the identification of residues crucial to complex formation highlighted the minimal dissociative role of the ApoL1 G1 mutations, but compounding effect of the G2 deletion mutation.