Immunoinformatics of Placental Malaria Vaccine Development - DTU Orbit (23/10/2018)

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Malaria is an infectious disease caused by a protozoan parasite of the genus Plasmodium, which is transferred by female Anopheles mosquitoes. WHO estimates that in 2012 there were 207 million cases of malaria, of which 627,000 were fatal. People living in malaria-endemic areas, gradually acquire immunity with multiple infections. Placental malaria (PM) is caused by P. falciparum sequestering in the placenta of pregnant women due to the presence of novel receptors in the placenta. An estimated 200,000 infants die a year as a result of PM. In 2004 the specific protein responsible for the pathogenesis of PM was identified as the P. falciparum Erythrocyte Membrane Protein 1 (PFEMP1) variant VAR2CSA. VAR2CSA is the leading candidate for a vaccine against PM.

The thesis is divided into 4 parts, where part I provide the reader with an introduction and background for the subjects covered in the thesis. Part II presents the first paper: "SigniSite: Identification of residue-level genotype-phenotype correlations in protein multiple sequence alignments". SigniSite is based on a non-parametric statistical evaluation of the positional distribution of amino acid residues in a multiple sequence alignment (MSA), thereby quantifying residue association to MSA phenotype. SigniSite was found to outperform comparable state-of-the-art methods. Furthermore part II addresses the issue of controlling type I and type II error probabilities in multiple testing scenarios and lastly the Dissertation advisor: Prof. Ole Lund Leon Eyrich Jessen analysis of the MHCI:peptide binding interaction by application of the SigniSite method. Part III presents the second paper: "Insight into Antigenic Diversity of VAR2CSA-DBL5ε Domain from Multiple Plasmodium falciparum Placental Isolates". The data consisted of 70 VAR2CSA-DBL5ε sequences each with associated phenotypes. Immunity towards PM is gradually acquired, therefore if a given sequence motif can be phenotype-correlated then the motif may be involved in VAR2CSA immunogeneity. Motifs defining VAR2CSA immunogeneity are naturally interesting in vaccine development context. The motif 'TFKNI' was found to be correlated with the birth weight of the child. Part IV presents the development of two methods for analysis of high-throughput data from a novel High Density Peptide Microarray (HDPMa) chip technology. Subsequently the HDPMa chip is applied for the discovery of linear B-cell VAR2CSA epitopes. Peptides 'GMDEFKNTFKNIKE' and 'SCGSARTMKRGYKNDNYELCKYC' were identified as linear B-cell epitopes. The latter subsequently experimentally found to be highly immunogenic, but not capable of blocking VAR2CSA:receptor interaction. In summary, the work described in this thesis centres around the development and application of bioinformatics tools for in silico analysis of VAR2CSA, with an emphasis on statistical methodology. It is the hope of the author that the tools, developed, presented and applied in this thesis, may serve as an offset for further research and development in the field of placental malaria vaccine development.

**General information**

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